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FULL PAPER

No increase in toxicity of pelvic irradiation when intensity modulation is employed: clinical and dosimetric data of 208 patients treated with post-prostatectomy radiotherapy

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Objective: To compare the toxicity of image-guided intensity-modulated radiotherapy (IG-IMRT) to the pelvis or prostate bed (PB) only. To test the hypothesis that the potentially injurious effect of pelvic irradiation can be counterbalanced by reduced irradiated normal tissue volume using IG-IMRT.

Methods: Between February 2010 and February 2012, 208 patients with prostate cancer were treated with adjuvant or salvage IG-IMRT to the PB (102 patients, Group PB) or the pelvis and prostate bed (P) (106 patients, Group P). The Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria were used to evaluate toxicity.

Results: Median follow-up was 27 months. Toxicity $G \geq 2$ in Group PB: in the bowel acute and late toxicities were 11.8% and 10%, respectively; urinary acute and late toxicities were 10.8% and 15%, respectively. Toxicity $G \geq 2$ in Group P: in the bowel acute and late toxicities were

both 13.2%; urinary acute and late toxicities were 13.2% and 15.1%, respectively. No statistical difference in acute or late toxicity between the groups was found (bowel: $p = 0.23$ and $p = 0.89$ for acute and late toxicity, respectively; urinary: $p = 0.39$ and $p = 0.66$ for acute and late toxicity, respectively). Of the clinical variables, only previous abdominal surgery was correlated with acute bowel toxicity. Dosimetric parameters that correlated with bowel toxicity were identified.

Conclusion: The toxicity rates were low and similar in both groups, suggesting that IG-IMRT allows for a safe post-operative irradiation of larger volumes. Further investigation is warranted to exclude bias owing to non-randomized character of the study.

Advances in knowledge: Our report shows that modern radiotherapy technology and careful planning allow maintaining the toxicity of pelvic lymph node treatment at the acceptable level, as it is in the case of PB radiotherapy.

INTRODUCTION

The role of adjuvant post-prostatectomy irradiation in prostate cancer has been recently established in three large randomized trials.¹⁻⁴ Adjuvant post-operative radiotherapy should be offered to patients with adverse pathologic findings at prostatectomy (*i.e.* seminal vesicle invasion, positive surgical margins and extraprostatic extension), while salvage radiotherapy should be proposed to patients with a prostatic-specific antigen or local recurrence after prostatectomy (with no adjuvant irradiation), in whom there is no evidence of distant metastatic disease.¹⁻⁴

Recent research also suggests the benefit of post-operative pelvic irradiation in patients with positive lymph nodes.⁵⁻⁷ While the radiotherapy volume in patients with pN1 will always include the pelvic lymph node area, the optimal volume [prostate bed (PB) only or pelvis and prostate bed (P)] in case of adjuvant or salvage irradiation in pN0 or pNx has not been established.¹ The ongoing Radiation Therapy Oncology Group (RTOG) 0534 trial will help in clarifying this issue, at least for salvage therapy. The potential benefit, *i.e.* improvement of tumour control by inclusion of regional lymph node areas, should

exceed the risk of increased normal tissue injury with larger irradiated volumes.

With the advent of new high-precision radiotherapy technologies such as image-guided radiotherapy or intensity-modulated radiotherapy (IMRT), the irradiated volume of the normal tissue might be reduced and, in consequence, the treatment toxicity can be kept at an acceptable level. Although no randomized controlled trial of IMRT vs three-dimensional conformal radiotherapy (3DCRT) in prostate cancer is available, at least 13 non-randomized studies comparing IMRT with 3DCRT were found.⁸ These comparative series showed that IMRT reduces late rectal toxicity in patients with prostate cancer, allowing safe dose escalation.^{8–11} However, the findings in favour of IMRT over 3DCRT regard the radical treatment of localized prostate cancer where doses >70 Gy are required.¹² There are insufficient data comparing IMRT with 3DCRT in the post-operative setting.¹² In daily practice, decision-making for patients referred for post-prostatectomy irradiation is based on the assessed risk of pelvic lymph node involvement, risk of normal tissue injury and available technology.

In our department, since the installation of RapidArc® (Varian Medical Systems, Palo Alto, CA) in February 2010, IMRT is routinely proposed for patients with prostate cancer. In case of post-prostatectomy irradiation, the decision regarding treatment volume (PB vs P) is based on physician judgment, according to general institutional guidelines.

The aim of this study was to retrospectively compare the toxicity of pelvic image-guided intensity-modulated radiotherapy (IG-IMRT) with PB IG-IMRT. Namely, our intent was to test the hypothesis that the potentially injurious effect of pelvic irradiation can be counterbalanced by reduced irradiated normal tissue volume using IG-IMRT.

METHODS AND MATERIALS

Inclusion criteria

The inclusion criteria for this retrospective study were as follows: (1) patients referred for post-operative (adjuvant or salvage) irradiation after surgery for prostate cancer between February 2010 and February 2012; and (2) written informed consent for radiotherapy. The study was notified to the Ethical Committee of the European Institute of Oncology (IEO), Milan, Italy (notification regarding the clinical and dosimetric aspects of image-guided radiotherapy for the prostate, IEO N79).

Surgery and radiotherapy

Surgery consisted of an open or robot-assisted laparoscopic retropubic approach including radical prostatectomy with or without pelvic lymph node dissection. In all cases, the indication for irradiation was established within a multidisciplinary tumour board.

Institutional guidelines for simulation CT and contouring were employed.¹³ The planning 3-mm-slice CT scan (High Speed, GE Healthcare) was acquired with patients in supine position using a leg immobilization device (Combifix™, CIVCO, Kalona, IA). Patients were asked to have an empty rectum and full bladder for

the planning CT and for each treatment session, in order to minimize daily variations in PB location.

PB and pelvic lymph node clinical target volumes (CTVs) were contoured according to the guidelines of the European Organization for Research and Treatment of Cancer and RTOG.^{14–16} The presacral area was not included. Pelvic volume was added in case of pN1 or cN0/pNx, if the estimated risk of lymph node involvement was >30%, with the calculation based on available Memorial Sloan Kettering Cancer Centre nomogram.¹⁷ In case of pN1 disease, two nodal CTVs were contoured, namely negative and positive lymph node areas, respectively.

The margin between CTV and planning target volume was 5 mm. Dose–volume histograms (DVHs) were computed. Institutional DVH constraint guidelines have been established based on our own data and the Quantitative Analysis of Normal Tissue Effects in the Clinic Recommendation.^{18,19} For the peritoneal cavity, we recommended that the dose of 45 Gy be given to <195 cm⁻³ of the delineated volume. All patients were treated with IG-IMRT using volumetric-modulated arc therapy technologies (RapidArc). The plans were created using an Eclipse™ treatment planning system v. 8.6.0 AAA (Varian, UT) with 6-MV photon beams and a maximum dose rate of 600 MU/min. The Varian Trilogy® System equipped with a Millennium multileaf collimator with 120 leaves (Varian Medical System, Palo Alto, CA) was employed for treatment delivery.

The prescribed dose depended on the radiotherapy intent (adjuvant or salvage in case of detectable PSA) and followed the International Commission on Radiation Units and Measurements 83 recommendations.²⁰ The dose prescribed to the PB was 66 or 69 Gy in 30 fractions for adjuvant and salvage irradiation (2.2–2.3 Gy/fraction, 5 fractions/week), respectively. Pelvic doses were 51 Gy and 54 Gy in 30 fractions (1.7–1.8 Gy/fraction) to the negative and positive lymph nodes areas, respectively. In patients with more than one planning target volume, simultaneous integrated boost technique was employed.

The institutional target-positioning guidelines based on the cone-beam CT manual soft-tissue registration were followed. All patients were imaged for the first 3 fractions and weekly thereafter. A preliminary match between the cone-beam CT data set and planning CT scans was obtained by automatic image registration and then manually refined by a radiation oncologist for improved target alignment (manual soft-tissue registration). Detected misalignments were corrected by couch motion. In case of unacceptable misalignment in the patient setup or variation in hollow organ filling, the patient was repositioned and/or corrective measures (such as filling or emptying of the rectum and bladder) were undertaken in order to reproduce the planning situation as much as possible.

During radiotherapy, the patients were seen by a radiation oncologist once a week (no preventive measures were given before radiotherapy and only symptomatic therapy was prescribed when side effects occurred). After the treatment, the patients were seen by a radiation oncologist or urologist every 6–9 months, or more frequently if clinically indicated.

Table 1. Patient, tumour, treatment and follow-up data

Characteristic	All patients	Prostate bed only	Prostate bed and pelvis	p-value
Number of patients	208	102	106	na
Median age at surgery (range) (years)	65 (49–78)	65 (51–78)	65 (49–78)	0.84
Concomitant disorders	188	92	96	0.95
Diabetes mellitus	27	14	13	
Cardiomyopathy	19	11	8	
Arterial hypertension	72	32	40	
Peripheral vasculopathy	8	3	5	
Colon diverticulosis	20	9	11	
Dyslipidaemia including hypercholesterolemia	26	14	12	
Prior abdominal surgery	26	13	13	
Type of surgery				
Open	121	61	60	0.75
Robot-assisted laparoscopic approach	87	41	46	
Extent of surgery				
Prostatectomy	55	18	37	<0.01
Pelvic lymph node dissection + prostatectomy	153	84	69	
iPSA, median (range) (ng/ml)	8.28 (0.02–346)	8.6 (0.02–346)	7.4 (0.48–67)	0.4
PSA at the beginning of RT, median (range) (ng/ml)	0.18 (0–18.1)	0.13 (0–18.1)	0.19 (0–8.6)	0.35
Tumour stage after surgery ^a				
pT2	66	38	28	0.14
pT3a	77	38	37	
pT3b	59	21	38	
pT3c	1	0	1	
pT4	4	2	2	
Missing	1	1	–	
pN0	101	81	20	<0.0001
pN1	34	0	34	
pNx	71	20	51	
Missing	2	1	1	
cM0	107	102	105	0.38
M1	1	–	1	
Gleason score after surgery, median (range)	7 (5–10)	7 (5–10)	7 (5–10)	0.97
Margin status				
R0	81	43	38	0.1
R1	109	47	62	
R0/R1	1	–	1	
Missing/na	17	12	5	
Time interval surgery—RT, median (range) (months)	4.5 (1.7–217.3)	4.8 (1.7–217.3)	4.4 (2.1–168.8)	0.22
ADT added to RT				
No	130	77	53	<0.001
Yes ^b	78	25	53	

(Continued)

Table 1. (Continued)

Characteristic	All patients	Prostate bed only	Prostate bed and pelvis	p-value
RT intent				
Adjuvant	113	53	60	0.28
Salvage (detectable PSA)	95	49	46	
RT dose (Gy)				
Tumour bed, median (range)	67.1 (45–69)	68.2 (45–69)	66.3 (54–69)	0.47
Pelvis				
Positive lymph node areas, median (range)	54 (51–56.1)	–	54 (51–56.1)	na
Negative lymph node areas, median (range)	51 (45–61)	–	51 (45–61)	na
Overall RT duration, median (range) (days)	44 (32–67)	44 (37–67)	44 (32–59)	0.70
RT interruption	3	2	1	1
Acute RT toxicity ^f				
Gastrointestinal (bowel)				
Grade 0	107	59	48	0.23
Grade 1	75	31	44	
Grade 2	25	12	13	
Grade 3	1	0	1	
Genitourinary				
Grade 0	131	68	63	0.39
Grade 1	52	23	29	
Grade 2	21	8	13	
Grade 3	4	3	1	
Follow-up ^d median (range) (months)	27 (9–47)	27 (9–47)	27 (11–46)	0.33
Late RT toxicity ^c (evaluated in 206 patients with follow-up less than 3 months)	206	100	106	–
Gastrointestinal (bowel)				
Grade 0	154	77	77	0.89
Grade 1	28	13	15	
Grade 2	11	4	7	
Grade 3	10	5	5	
Grade 4	3	1	2	
Genitourinary				
Grade 0	120	63	57	0.66
Grade 1	55	22	33	
Grade 2	17	8	9	
Grade 3	12	6	6	
Grade 4	2	1	1	

ADT, androgen deprivation therapy; iPSA, initial PSA; na, not available; PSA, prostate-specific antigen; RT, radiotherapy.

In case of ADT concomitant to RT, pre-ADT PSA was registered.

p-value was calculated with χ^2 test for categorical data and with *t*-test (two tails) for numeric data.

^aAccording to TNM 2009.

^bLuteinizing hormone-releasing hormone agonist alone or combined with bicalutamide.

^cAccording to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria.²³

^dCalculated from the last day of RT to the last contact.

Table 2. Evaluation of late toxicity at first, second and third year of follow-up

Late RT toxicity		Grade	TOT	Pelvis and prostate bed	Prostate bed only	χ^2 test
First year	GI	0	148	81	66	p -value = 0.59
		1	21	11	10	
		2	9	3	6	
		3	7	4	3	
		4	1	1	0	
	GU	0	122	63	59	p -value = 0.47
		1	45	28	16	
		2	16	8	8	
		3	3	1	2	
		4	0	0	0	
Second year	GI	0	107	64	43	p -value = 0.07
		1	21	8	10	
		2	9	6	1	
		3	7	2	6	
		4	1	2	0	
	GU	0	92	50	42	p -value = 0.28
		1	45	21	8	
		2	16	7	5	
		3	3	3	5	
		4	0	1	0	
Third year	GI	0	55	24	30	p -value = 0.66
		1	6	3	3	
		2	1	1	0	
		3	2	1	1	
		4	1	1	0	
	GU	0	49	20	29	p -value = 0.08
		1	7	6	1	
		2	2	2	0	
		3	5	2	3	
		4	1	0	1	

GI, gastrointestinal; GU, genitourinary; RT, radiotherapy; TOT, total number of patients.

Clinical and dosimetric potential predictive factors
For each patient, clinical and dosimetric data were collected. Bowel toxicity and its potential correlation with dosimetric parameters was investigated. For each patient, DVHs of the peritoneal cavity and rectum were obtained and analyzed. Normal tissue complication probability (NTCP) was calculated from the rectum DVH, based on the Lyman–Kutcher–Burman model. Late toxicity \geq G2 was chosen as the end point. Radiobiological parameters published by Michalski et al²¹ were used ($n = 0.09$; $m = 0.13$; $TD_{50} = 76.9$ Gy, where n describes the volume effect, m describes the curve steepness and TD_{50} is the dose for 50% complication probability). The correlation between single points of DVH and NTCP was previously analyzed by our

group.²² Analysis was performed in MATLAB® environment (MATLAB and Statistics Toolbox Release 2008a, MathWorks, Inc., Natick, MA).

Statistical analysis

RTOG/European Organization for Research and Treatment of Cancer criteria were used to evaluate clinically acute and late treatment toxicity.²³ Sexual dysfunction was not analyzed. Late toxicity was evaluated in patients with follow-up longer than 3 months.

Acute and late bowel and urinary toxicity were compared in the two groups (PB or P) with χ^2 test. Stratification of the clinical

Table 3. Correlation between comorbidities and toxicity. Prior abdominal surgery is correlated with worse acute bowel toxicity

Factor	Toxicity	Characteristic	G0	G1	G2	G3	G4	<i>p</i> -value
Prior abdominal surgery	Acute GI	Yes	12	6	8	0	0	0.02
		No	95	69	17	1	0	
	Acute GU	Yes	17	6	3	0	0	0.87
		No	107	42	13	3	0	
	Late GI	Yes	19	4	0	3	0	0.39
		No	135	24	11	7	3	
Late GU	Yes	20	5	1	0	0	0.27	
	No	100	50	16	11	3		
Bowel diverticulosis	Acute GI	Yes	11	5	4	0	0	0.56
		No	96	70	21	1	0	
	Acute GU	Yes	13	4	3	0	0	0.76
		No	118	48	18	4	0	
	Late GI	Yes	15	2	0	2	1	0.34
		No	139	26	11	8	2	
Late GU	Yes	14	5	0	1	0	0.61	
	No	106	50	17	10	3		
Diabetes mellitus	Acute GI	Yes	16	7	4	0	0	0.66
		No	91	68	21	1	0	
	Acute GU	Yes	15	6	6	0	0	0.14
		No	116	46	15	4	0	
	Late GI	Yes	21	4	0	1	1	0.58
		No	133	24	11	9	2	
Late GU	Yes	14	8	3	1	1	0.76	
	No	106	47	14	10	2		
High blood cholesterol	Acute GI	Yes	26	11	6	0	0	0.40
		No	81	64	19	1	0	
	Acute GU	Yes	25	13	3	2	0	0.22
		No	107	42	13	3	0	
	Late GI	Yes	33	4	4	1	0	0.42
		No	121	24	7	9	3	
Late GU	Yes	16	6	3	1	0	0.88	
	No	95	42	14	9	3		
Cardiac disorders	Acute GI	Yes	11	6	2	0	0	0.94
		No	96	69	23	1	0	
	Acute GU	Yes	13	4	2	0	0	0.89
		No	118	48	19	4	0	
	Late GI	Yes	13	1	1	3	1	0.08
		No	141	27	10	7	2	
Late GU	Yes	14	2	2	1	0	0.50	
	No	106	53	15	10	3		

(Continued)

Table 3. (Continued)

Factor	Toxicity	Characteristic	G0	G1	G2	G3	G4	<i>p</i> -value
High blood pressure	Acute GI	Yes	40	24	7	1	0	0.94
		No	67	51	18	0	0	
	Acute GU	Yes	14	3	3	0	0	0.57
		No	117	49	18	4	0	
	Late GI	Yes	55	8	2	6	0	0.86
		No	99	20	9	4	3	
Late GU	Yes	45	19	5	2	0	0.47	
	No	75	36	12	9	3		
Peripheral vasculopathy	Acute GI	Yes	3	3	2	0	0	0.68
		No	104	72	23	1	0	
	Acute GU	Yes	5	2	1	0	0	0.98
		No	126	50	20	4	0	
	Late GI	Yes	5	2	1	0	0	0.68
		No	149	26	10	10	3	
Late GU	Yes	5	1	2	0	0	0.40	
	No	115	54	15	11	3		
Androgen deprivation therapy	Acute GI	Yes	31	22	7	0	0	0.94
		No	76	53	18	1	0	
	Acute GU	Yes	35	18	6	1	0	0.76
		No	96	34	15	3	0	
	Late GI	Yes	49	5	3	2	0	0.42
		No	105	23	8	8	3	
Late GU	Yes	41	13	4	1	0	0.20	
	No	79	42	13	10	3		

GI, gastrointestinal; GU, genitourinary.

variables among the two groups was investigated with χ^2 test for categorical data and *t*-test for numeric data. The correlation between related clinical variables and toxicity was investigated with χ^2 test. Concomitant disorders [diverticulosis, diabetes mellitus, cardiac disorders, high blood pressure, high cholesterol level, peripheral vasculopathy, prior abdominal surgery other than prostatectomy and androgen deprivation therapy (ADT) with bicalutamide or luteinizing hormone-releasing hormone analogue or a combination of both] and correlation between age and

toxicity were investigated with linear correlation coefficient. The correlation between treatment-related variables and toxicity was investigated with χ^2 test for categorical data and with linear correlation coefficient, Spearman's ρ and Kendall's τ rank correlation coefficients for quantitative data. Intent of radiotherapy (salvage *vs* adjuvant), type of surgery (open *vs* robotic *vs* laparoscopic), extent of surgery (prostatectomy *vs* prostatectomy and lymph node dissection), the interval between surgery and radiotherapy and radiotherapy duration were also investigated.

Table 4. Correlation between patient age and toxicity

Factor	Toxicity	Correlation coefficient <i>r</i>	<i>p</i> -value
Patient age	Acute GI	0.02	0.73
	Acute GU	0.06	0.41
	Late GI	0.1	0.17
	Late GU	-0.09	0.19

GI, gastrointestinal; GU, genitourinary.

Table 5. Correlation between treatment characteristics and toxicity

Factor	Toxicity	Characteristic	G0	G1	G2	G3	G4	<i>p</i> -value
Type of surgery	Acute GI	Laparotomy	59	50	12	0	0	0.38
		Laparoscopy	4	4	1	0	0	
		Robotic	44	21	12	1	0	
	Acute GU	Laparotomy	84	25	11	1	0	0.29
		Laparoscopy	6	2	1	0	0	
		Robotic	41	25	9	3	0	
	Late GI	Laparotomy	85	18	8	6	2	0.07
		Laparoscopy	4	3	2	0	0	
		Robotic	65	7	1	4	1	
	Late GU	Laparotomy	67	36	6	10	1	0.14
		Laparoscopy	5	2	2	0	0	
		Robotic	48	17	9	1	2	
Lymph node dissection	Acute GI	Yes	81	55	17	0	0	0.25
		No	26	20	8	1	0	
	Acute GU	Yes	97	37	15	4	0	0.83
		No	34	15	6	0	0	
	Late GI	Yes	116	17	8	7	3	0.44
		No	38	11	3	3	0	
	Late GU	Yes	88	39	13	9	3	0.39
		No	32	16	4	2	0	
Intent of RT	Acute GI	Adjuvant	59	43	10	1	0	0.36
		Salvage	48	32	15	0	0	
	Acute GU	Adjuvant	76	22	12	3	0	0.21
		Salvage	55	30	9	1	0	
	Late GI	Adjuvant	81	19	5	4	2	0.46
		Salvage	73	9	6	6	1	
	Late GU	Adjuvant	63	29	11	7	1	0.76
		Salvage	57	26	6	4	2	

GI, gastrointestinal; GU, genitourinary; RT, radiotherapy.

The systematic analysis of DVH parameters was performed with Fisher's exact test. The correlation between volume (in cubic centimetre) receiving X Gy and toxicity was investigated. Doses were varied between 1 and 70 Gy (with steps of 1 Gy), volume thresholds were varied between 1 and 3000 cm³ for the peritoneum (with steps of 1 cm³) and between 1 and 100% for the rectum (with steps of 1%). Acute and late toxicities with a cut-off at grade G > 0, 1 and 2 were examined. This is a simple and novel approach that allows examining a large amount of data in an automated way. Six matrices of *p*-values were generated for the rectum DVH and six for the peritoneum DVH. Each matrix represents a different toxicity threshold (G1, G2 or G3) for acute and late toxicity. DVH regions of potential interest, where *p*-values were <0.05, were identified. A tentative DVH constraint was

selected as the set of dose–volume points with minimum *p*-values.

RESULTS

Study population

Between February 2010 and April 2012, 208 patients with prostate cancer were treated with post-prostatectomy IG-IMRT at the Division of Radiotherapy of the IEO (Table 1). The PB and P were treated in 102 and 106 patients, respectively. The two groups (PB and P) were well balanced with regard to age, concomitant disorders, type of surgery (open vs robotic or laparoscopic), tumour stage (T), Gleason score and margin status, intent of radiotherapy (adjuvant vs salvage), interval between surgery and radiotherapy, radiotherapy dose and duration (Table 1). The two groups were not balanced regarding the

Table 6. Correlation between treatment characteristics and toxicity

Factor	Toxicity	Correlation coefficient <i>r</i>	<i>p</i> -value
Interval between surgery and RT	Acute GI	-0.05	0.51
	Acute GU	-0.04	0.59
	Late GI	0.09	0.19
	Late GU	-0.03	0.65
RT duration	Acute GI	0.08	0.26
	Acute GU	0.0	0.90
	Late GI	0.03	0.67
	Late GU	0.08	0.26

GI, gastrointestinal; GU, genitourinary; RT, radiotherapy.

extent of surgery, lymph node staging (pN) and concomitant ADT. This finding is indeed expected, as patients with evidence of lymph node involvement were more likely to receive lymph node dissection, to be staged as pN1 and to receive pelvic irradiation and ADT.

Radiotherapy toxicity

Radiotherapy was well tolerated. All but three patients completed IG-IMRT. Median follow-up was 27 months (range 9–47 months). Two patients were lost at follow-up (they have follow-up longer than 3 months). Late toxicity was evaluated in 206 patients with follow-up longer than 3 months. Both acute and late toxicities were limited. No G4 acute events were observed. Five G4 late events were reported (three urinary events: two acute urine retention and one haematuria; two bowel events: one enterovesical fistula requiring temporary colostomy and one intestinal bleeding from angiodysplasia treated with argon plasma coagulation complicated by post-argon plasma coagulation bowel perforation). No statistical difference in toxicity between Groups PB and P was found with *p*-values as follows: acute bowel toxicity with *p*-value = 0.23, late bowel toxicity with *p*-value = 0.89, acute urinary toxicity with *p*-value = 0.39 and late urinary toxicity with *p*-value = 0.66.

A vast majority of patients never reported any toxicity at all during follow-up [74% always had G0 gastrointestinal (GI) toxicity and 58% always had G0 genitourinary (GU) toxicity]. Among those who did report some toxicity, the most common

pattern was a stable toxicity level G1–G2 with, in rare cases, episodes of higher grade toxicity. In this series, there was no patient with progressive worsening toxicity or with permanent G3–G4 toxicity. A minority of patients (15% for GI and 27% for GU) had isolated episodes of G1–G2 toxicity that lasted less than 6 months and resolved completely.

We analyzed the two groups (PB and P), trying to assess late toxicity evolution over time and focusing on toxicity at 1, 2 and 3 years; the difference was not significant at any point in time. Results are summarized in Table 2. For the rest of the analysis, we considered late toxicity as the higher reported toxicity during follow-up.

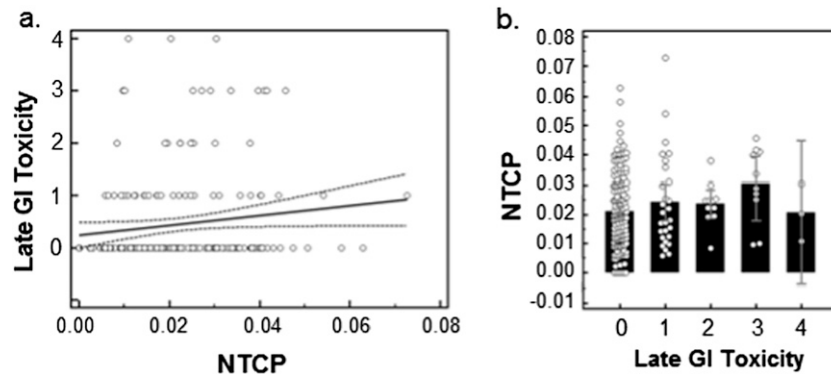
The correlation between clinical variables and toxicity is shown in Tables 3 and 4. A statistically significant (*p*-value = 0.02) correlation between prior abdominal surgery (other than prostatectomy) and acute bowel toxicity was found; interestingly, there was no correlation between previous surgery and late bowel toxicity. No other correlation between clinical variables and toxicity was found. The correlation between treatment-related parameters and toxicity is shown in Tables 5–7. The only correlation found was the one between intent of radiotherapy and GU toxicity, with patients treated post-operatively showing worse acute and late GU toxicity than those treated at time of recurrence. There was a strong correlation (*p*-value < 0.01) between acute and late bowel toxicity, whereas no correlation was found for urinary toxicity.

Table 7. Correlation between acute and late toxicity. Acute bowel toxicity was predictive of late bowel toxicity

Correlation	Statistics	Value	<i>p</i> -value
Acute vs late GI toxicity	Correlation coefficient <i>r</i>	0.19	0.005
	Spearman's ρ	0.3	<0.0001
	Kendall's τ	0.27	<0.0001
Acute vs late GU toxicity	Correlation coefficient <i>r</i>	-0.04	0.005
	Spearman's ρ	-0.02	0.73
	Kendall's τ	-0.02	0.67

GI, gastrointestinal; GU, genitourinary.

Figure 1. (a) The regression line of normal tissue complication probability (NTCP) to the measured toxicity is shown. As can be observed, data are rather sparse. The R correlation coefficient is 0.134 (95% confidence interval: -0.03 to 0.266). (b) NTCP distribution in patients developing late bowel [gastrointestinal (GI)] toxicity of increasing grade is shown.



Dosimetric predictors

Late G2 bowel NTCP varied between 0 and 7.3%. The mean and standard deviation (SD) of NTCP were 2.0% and 1.3% in the PB group and 2.3% and 1.3% in the P group. The difference was not statistically significant (Welch's test p -value = 0.06). As expected, a significant correlation was found between NTCP and late bowel toxicity. Patients developing late bowel toxicity $<G2$ had a mean NTCP of 2.1% with SD of 1.3%, whereas patients with late bowel toxicity $\geq G2$ had a mean NTCP of 2.7% with SD of 1.0% (Welch's test p -value = 0.04). This correlation is shown in Figure 1.

No single peritoneal cavity DVH point was correlated with probability of developing acute or late bowel toxicity.

Rectal DVH was correlated with bowel toxicity. The portion of rectum DVH between 32 and 51 Gy was strongly (p -value < 0.01) correlated with acute bowel toxicity $G \geq 1$ (a curve between 51 Gy to 20% of the volume and 32 Gy to 53% of the volume was identified). Moreover, the portion of rectum DVH between 48 and 68 Gy was strongly (p -value < 0.01) correlated with late bowel toxicity $G \geq 2$ (a curve between 68 Gy to 4% of the volume and 48 Gy to 27% of the volume was identified). These potential DVH constraints are shown in Figure 2. In multivariate analysis, using a logistic model, none of the variables selected (NTCP and rectum DVH centred around 58 Gy for late GI toxicity and previous surgery and rectum DVH centred around 42 Gy for acute toxicity) retained significance.

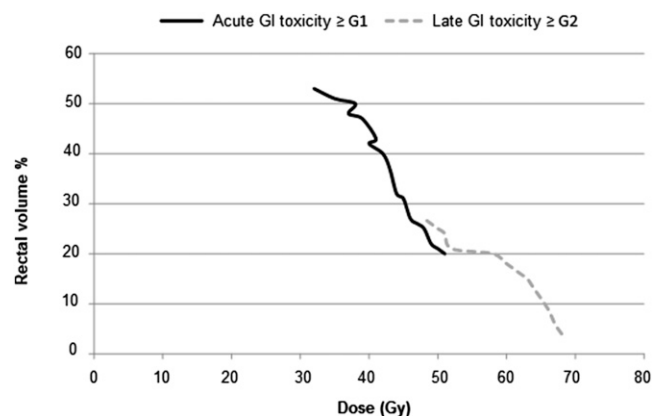
DISCUSSION

Our study including the clinical and dosimetric data of 208 patients treated with post-prostatectomy IG-IMRT showed no increase in toxicity in patients treated to the whole pelvis compared with those irradiated only on the PB. Toxicity in both groups was low. Our findings suggest that IG-IMRT allows safe post-operative irradiation of large volumes.

To the best of our knowledge, this is one of the first studies comparing the toxicity of radiotherapy to the pelvis vs PB only in the era of high technology.^{24,25} There are several reports regarding pelvic irradiation in the radical setting with an intact prostate^{26–28} or comparing pelvic IMRT with pelvic 3DCRT.^{29–32}

In radical series, the majority of the retrospective analyses showed some increase in acute toxicity (principally GI rather than GU) with pelvic radiotherapy.^{26,33} Some studies, however, did not show any statistically significant increase in toxicity in patients treated to the pelvis.^{26,34–36} In a recent study from Norway, males treated for high-risk or locally advanced prostate cancer with IMRT including the prostate and pelvis had more acute side effects at 3 months than those treated with 3DCRT to the prostate only.²⁸ Interestingly, at 12-month follow-up, the observed urinary and bowel function and bother were similar in both groups. In the post-prostatectomy setting, Van Praet et al²⁴ compared pelvic IMRT (48 patients) with PB only (239 patients) in a matched case analysis. The differences between the groups were similar to those observed in our study (ADT, N-stage etc.). Pelvic volumes were bigger than those in our study; the presacral lymph node area was included (increasing the dose to organs at risk). This difference may at least partially explain the results of Van Praet et al's study:²⁴ acute and late lower intestinal toxicity was significantly higher following pelvic IMRT (acute G2 toxicity is 42% in whole pelvis vs 15% in PB-only irradiation; late G2 toxicity is 30% in the whole pelvis vs 15% in PB-only

Figure 2. The dose-volume histogram (DVH) constraint for acute bowel [gastrointestinal (GI)] toxicity $\geq G1$ (solid black line) and the DVH constraint for late GI toxicity $\geq G2$ (dotted grey line) are shown. Gy, gray.



irradiation), while acute and late urinary toxicity was similar in both groups (acute toxicity $G \geq 2$ is 40% in whole pelvis vs 29% in PB-only irradiation; late toxicity $G \geq 2$ is 50% in whole pelvis vs 35% in PB-only irradiation). Deville et al²⁵ in their retrospective study on 67 patients found a significant increase only in acute bowel toxicity (61% vs 29% $G \geq 2$ toxicity in whole pelvis irradiation and PB-only irradiation, respectively), and no difference in late bowel toxicity (3% vs 0%) or acute (22% vs 7%) and late (17% vs 13%) urinary events, when pelvic IMRT was compared with PB-only IMRT. As in our study, the presacral area was not included. In a multi-institutional retrospective analysis of 959 patients, adjuvant radiotherapy, ADT and PB-only radiotherapy were statistically significantly predictive for $G2$ (or higher) late GU toxicity.³⁷

We are well aware of the limitations of our study, including its retrospective character and the length of median follow-up. A retrospective study carries the risk of selection bias (decision between PB vs pelvic irradiation) and may suffer from missing data and lack of baseline and regular follow-up information. An inadequate follow-up length may result in missing tardive events such as, for this kind of therapy, late GU toxicity that may appear even 5–8 years after the end of treatment. Indeed, some studies reported late rectal toxicity of 11% and urinary toxicity of 16% after a median follow-up of 70 months³⁸ or 5-year freedom from late rectal and urinary toxicity ($\geq G2$) rates of 95% and 88%, respectively.³⁹ However, few data are available about longer toxicity follow-up after whole pelvic IMRT, thus prompting the need for further studies to better characterize these very late toxicities and help physicians prevent and manage them.⁴⁰ However, in our study, the two groups were well balanced, apart from the known factors correlated with indication for pelvic irradiation (pelvic lymph node dissection showing positive lymph nodes). All the procedures including indications for radiotherapy volume, radiotherapy simulation, planning and delivery and patient monitoring are well standardized in our institution. The post-treatment follow-up radiotherapy or urology appointments are scheduled with 6–9-month intervals, which could lead to underevaluation of late toxicity; however, the patients are instructed to inform the clinician about any clinically significant event in the interval between appointments. Therefore, we do believe that our study may represent a solid basis for further investigation on the impact of volume in the era of high-precision prostate cancer radiotherapy.

Our data confirm the utility of NTCP with the Lyman–Kutcher–Burman model. Most treatment planning systems do not optimize biological parameters, but require DVH constraints. Our data-mining approach could detect the potentially significant DVH region. These data suggest that low-grade acute toxicity is mainly due to medium doses delivered to a large volume of the

rectum, whereas higher grade late toxicity is mainly due to high doses delivered to a small volume of the rectum. Data mining without an underlying physiopathological model has to be considered as “hypothesis generating”, and these findings need to be confirmed prospectively. Only rectal DVH was correlated with bowel toxicity. The peritoneal cavity was delineated instead of single bowel loops, as this method was considered safer against bowel movement. It is relevant to acknowledge that a better investigation of the dose–response relationship for the small bowel would demand an evaluation of accumulated dose as achievable with daily volumetric imaging and reliable deformable registration. However, this information was not available for this study. Therefore, the peritoneal cavity DVH was selected as a more reliable surrogate with respect to bowel loop DVH, as the latter could be strongly influenced by the position of the bowel loop in the planning CT scan. For the same reason, we did not investigate the correlation between inhomogeneous spatial distributions of dose and the aetiopathogenesis of radiation-induced GI toxicity.⁴¹

No point in the peritoneal cavity DVH correlated significantly with GI toxicity. This of course does not mean that dose to the peritoneal cavity is not toxic but rather that the IMRT technique employed and the dose constraint used allowed the treatment of pelvic lymph nodes without exceeding the threshold of clinically detectable toxicity. Correlation between previous abdominal surgery and bowel toxicity is well known in prostate and gynaecological radiotherapy.^{42,43} It is, however, interesting to point out that the group with previous surgery had an increase of $G1$ – $G2$ scores, but not of $G3$ toxicity. Correlation between acute and late toxicity was also expected.^{44,45} Genetic features are involved in toxicity; however, this aspect was not investigated in our series.^{46,47}

The fact that the significance of DVH parameter, NTCP and previous surgery was not confirmed in multivariate analysis is probably owing to the underlying assumption of logistic multivariate regression, whereas more general models could be used in univariate analysis.

In conclusion, our study has not demonstrated any increase in acute or late bowel or urinary toxicity when IG-IMRT was administered to the pelvic lymph node area when compared with IG-IMRT to the prostate bed only. Further investigation is warranted to exclude bias due to non-randomized character of the study.

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REFERENCES

- Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol* 2013; **190**: 441–9. doi: <http://dx.doi.org/10.1016/j.juro.2013.05.032>
- Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Post-operative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* 2012; **380**: 2018–27. doi: [http://dx.doi.org/10.1016/S0140-6736\(12\)61253-7](http://dx.doi.org/10.1016/S0140-6736(12)61253-7)
- 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**: 956–62. doi: <http://dx.doi.org/10.1016/j.juro.2008.11.032>
- Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, et al. Phase III post-operative 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* 2009; **18**: 2924–30. doi: <http://dx.doi.org/10.1200/JCO.2008.18.9563>
- Da Pozzo LF, Cozzarini C, Briganti A, Suardi N, Salonia A, Bertini R, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. *Eur Urol* 2009; **55**: 1003–11. doi: <http://dx.doi.org/10.1016/j.eururo.2009.01.046>
- Briganti A, Karnes RJ, Da Pozzo LF, Cozzarini C, Capitanio U, Gallina A, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2–4 pN+ prostate cancer: results of a matched analysis. *Eur Urol* 2011; **59**: 832–40. doi: <http://dx.doi.org/10.1016/j.eururo.2011.02.024>
- Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol* 2014; **32**: 3939–47. doi: <http://dx.doi.org/10.1200/JCO.2013.54.7893>
- Hummel S, Simpson EL, Hemingway P, Stevenson MD, Rees A. Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. *Health Technol Assess* 2010; **14**: 1–108, iii–iv. doi: <http://dx.doi.org/10.3310/hta14470>
- Staffurth J; Radiotherapy Development Board. A review of the clinical evidence for intensity-modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010; **22**: 643–57. doi: <http://dx.doi.org/10.1016/j.clon.2010.06.013>
- Latorzeff I, Mazurier J, Boutry C, Dudouet P, Richaud P, de Crevoisier R. Benefit of intensity modulated and image-guided radiotherapy in prostate cancer. [In French.] *Cancer Radiother* 2010; **14**: 479–87. doi: <http://dx.doi.org/10.1016/j.canrad.2010.06.013>
- Ohri N, Dicker AP, Showalter TN. Late toxicity rates following definitive radiotherapy for prostate cancer. *Can J Urol* 2012; **19**: 6373–80.
- Bauman G, Rumble RB, Chen J, Loblaw A, Warde P; Members of the IMRT Indications Expert Panel. Intensity-modulated radiotherapy in the treatment of prostate cancer. *Clin Oncol (R Coll Radiol)* 2012; **24**: 461–73. doi: <http://dx.doi.org/10.1016/j.clon.2012.05.002>
- Jerezek-Fossa BA, Zerini D, Fodor C, Santoro L, Cambria R, Garibaldi C, et al. Acute toxicity of image-guided hypofractionated radiotherapy for prostate cancer: nonrandomized comparison with conventional fractionation. *Urol Oncol* 2011; **29**: 523–32. doi: <http://dx.doi.org/10.1016/j.urolonc.2009.10.004>
- Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, et al. Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. *Radiother Oncol* 2007; **84**: 121–7. doi: <http://dx.doi.org/10.1016/j.radonc.2007.07.017>
- Michalski JM, Lawton C, El Naqa I, Ritter M, O'Meara E, Seider MJ, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for post-operative conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2010; **76**: 361–8. doi: <http://dx.doi.org/10.1016/j.ijrobp.2009.02.006>
- Lawton CA, Michalski J, El-Naqa I, Buyyounouski MK, Lee WR, Menard C, et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009; **74**: 383–7. doi: <http://dx.doi.org/10.1016/j.ijrobp.2008.08.002>
- Prostate cancer nomograms. [Cited 29 April 2016.] Available from: <http://www.mskcc.org/nomograms/prostate>.
- Greco C, Mazzetta C, Cattani F, Tosi G, Castiglioni S, Fodor A, et al. Finding dose-volume constraints to reduce late rectal toxicity following 3D-conformal radiotherapy (3D-CRT) of prostate cancer. *Radiother Oncol* 2003; **69**: 215–22. doi: <http://dx.doi.org/10.1016/j.radonc.2003.08.003>
- Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010; **76**(Suppl. 3): S3–9. doi: <http://dx.doi.org/10.1016/j.ijrobp.2009.09.040>
- International Commission on Radiation Units and Measurements. ICRU Report 83: Prescribing, recording and reporting photon-beam-intensity modulated radiation therapy (IMRT). *J ICRU* 2010; **10**(1). doi: <http://dx.doi.org/10.1093/jicru/ndq002>.
- Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 2010; **76**(Suppl. 3): S123–9. doi: <http://dx.doi.org/10.1016/j.ijrobp.2009.03.078>
- Cambria R, Jerezek-Fossa BA, Cattani F, Garibaldi C, Zerini D, Fodor C, et al. Evaluation of late rectal toxicity after conformal radiotherapy for prostate cancer: a comparison between dose-volume constraints and NTCP use. *Strahlenther Onkol* 2009; **185**: 384–9.
- 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**: 1341–6. doi: [http://dx.doi.org/10.1016/0360-3016\(95\)00060-C](http://dx.doi.org/10.1016/0360-3016(95)00060-C)
- Van Praet C, Ost P, Lumen N, De Meerleer G, Vandecasteele K, Villeirs G, et al. Postoperative high-dose pelvic radiotherapy for N+ prostate cancer: toxicity and matched case comparison with postoperative prostate bed-only radiotherapy. *Radiother Oncol* 2013; **109**: 222–8. doi: <http://dx.doi.org/10.1016/j.radonc.2013.08.021>
- 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 intensity-modulated radiation therapy after prostatectomy. *Int J Radiat Oncol Biol Phys* 2012; **82**: 1389–96. doi: <http://dx.doi.org/10.1016/j.ijrobp.2011.04.041>

26. Dirix P, Joniau S, Van den Bergh L, Isebaert S, Oyen R, Deroose CM, et al. The role of elective pelvic radiotherapy in clinically node-negative prostate cancer: a systematic review. *Radiother Oncol* 2014; **110**: 45–54. doi: <http://dx.doi.org/10.1016/j.radonc.2013.06.046>
27. Joo JH, Kim YJ, Kim YS, Choi EK, Kim JH, Lee SW, et al. Whole pelvic intensity-modulated radiotherapy for high-risk prostate cancer: a preliminary report. *Radiat Oncol J* 2013; **31**: 199–205. doi: <http://dx.doi.org/10.3857/roj.2013.31.4.199>
28. Lilleby W, Stensvold A, Dahl AA. Adding intensity-modulated radiotherapy to the pelvis does not worsen the adverse effect profiles compared to limited field radiotherapy in men with prostate cancer at 12-month follow-up. *Acta Oncol* 2014; **53**: 1380–9. doi: <http://dx.doi.org/10.3109/0284186X.2014.916042>
29. Gandhi AK, Sharma DN, Rath GK, Julka PK, Subramani V, Sharma S, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. *Int J Radiat Oncol Biol Phys* 2013; **87**: 542–8. doi: <http://dx.doi.org/10.1016/j.ijrobp.2013.06.2059>
30. Pinkawa M, Piroth MD, Holy R, Djukic V, Klotz J, Krenkel B, et al. Combination of dose escalation with technological advances (intensity-modulated and image-guided radiotherapy) is not associated with increased morbidity for patients with prostate cancer. *Strahlenther Onkol* 2011; **187**: 479–84. doi: <http://dx.doi.org/10.1007/s00066-011-2249-z>
31. Ashman JB, Zelefsky MJ, Hunt MS, Leibel SA, Fuks Z. Whole pelvic radiotherapy for prostate cancer using 3D conformal and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; **63**: 765–71. doi: <http://dx.doi.org/10.1016/j.ijrobp.2005.02.050>
32. Alongi F, Fiorino C, Cozzarini C, Broggi S, Perna L, Cattaneo GM, et al. IMRT significantly reduces acute toxicity of whole-pelvis irradiation in patients treated with post-operative adjuvant or salvage radiotherapy after radical prostatectomy. *Radiother Oncol* 2009; **93**: 207–12. doi: <http://dx.doi.org/10.1016/j.radonc.2009.08.042>
33. Lawton CA, DeSilvio M, Roach M 3rd, Uhl V, Kirsch R, Seider M, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007; **69**: 646–55. doi: <http://dx.doi.org/10.1016/j.ijrobp.2007.04.003>
34. Aizer AA, Yu JB, McKeon AM, Decker RH, Colberg JW, Peschel RE. Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2009; **75**: 1344–9. doi: <http://dx.doi.org/10.1016/j.ijrobp.2008.12.082>
35. Milecki P, Baczky M, Skowronek J, Antczak A, Kwias Z, Martenka P. Benefit of whole pelvic radiotherapy combined with neoadjuvant androgen deprivation for the high-risk prostate cancer. *J Biomed Biotechnol* 2009; **2009**: 625394. doi: <http://dx.doi.org/10.1155/2009/625394>
36. Pommier P, Chabaud S, Lagrange JL, Richaud P, Lesaunier F, Le Prise E, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol* 2007; **25**: 5366–73. doi: <http://dx.doi.org/10.1200/JCO.2006.10.5171>
37. Feng M, Hanlon AL, Pisansky TM, Kuban D, Catton CN, Michalski JM, et al. Predictive factors for late genitourinary and gastrointestinal toxicity in patients with prostate cancer treated with adjuvant or salvage radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; **68**: 1417–23. doi: <http://dx.doi.org/10.1016/j.ijrobp.2007.01.049>
38. Müller AC, Lütjens J, Alber M, Eckert F, Bamberg M, Schilling D, et al. Toxicity and outcome of pelvic IMRT for node-positive prostate cancer. *Strahlenther Onkol* 2012; **188**: 982–9. doi: <http://dx.doi.org/10.1007/s00066-012-0169-1>
39. Saracino B, Petrongari MG, Marzi S, Bruzzaniti V, Sara G, Arcangeli S, et al. Intensity-modulated pelvic radiation therapy and simultaneous integrated boost to the prostate area in patients with high-risk prostate cancer: a preliminary report of disease control. *Cancer Med* 2014; **3**: 1313–21. doi: <http://dx.doi.org/10.1002/cam4.278>
40. Liberman D, Mehus B, Elliott SP. Urinary adverse effects of pelvic radiotherapy. *Transl Androl Urol* 2014; **3**: 186–95. doi: <http://dx.doi.org/10.3978/j.issn.2223-4683.2014.04.01>
41. Munbodh R, Jackson A. Quantifying cell migration distance as a contributing factor to the development of rectal toxicity after prostate radiotherapy. *Med Phys* 2014; **41**: 021724. doi: <http://dx.doi.org/10.1118/1.4852955>
42. Lee TF, Huang EY. The different dose-volume effects of normal tissue complication probability using LASSO for acute small-bowel toxicity during radiotherapy in gynecological patients with or without prior abdominal surgery. *Biomed Res Int* 2014; **2014**: 143020. doi: <http://dx.doi.org/10.1155/2014/143020>
43. Budäus L, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol* 2012; **61**: 112–27. doi: <http://dx.doi.org/10.1016/j.eururo.2011.09.027>
44. Jereczek-Fossa BA, Zerini D, Fodor C, Santoro L, Serafini F, Cambria R, et al. Correlation between acute and late toxicity in 973 prostate cancer patients treated with three-dimensional conformal external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; **78**: 26–34. doi: <http://dx.doi.org/10.1016/j.ijrobp.2009.07.1742>
45. Jereczek-Fossa BA, Zerini D, Vavassori A, Fodor C, Santoro L, Minissale A, et al. Sooner or later? Outcome analysis of 431 prostate cancer patients treated with post-operative or salvage radiotherapy. *Int J Radiat Oncol Biol Phys* 2009; **74**: 115–25. doi: <http://dx.doi.org/10.1016/j.ijrobp.2008.07.057>
46. De langhe S, De Meerleer G, De Ruyck K, Ost P, Fonteyne V, De Neve W, et al. Integrated models for the prediction of late genitourinary complaints after high-dose intensity modulated radiotherapy for prostate cancer: making informed decisions. *Radiother Oncol* 2014; **112**: 95–9. doi: <http://dx.doi.org/10.1016/j.radonc.2014.04.005>
47. Valdagni R, Rancati T, Ghilotti M, Cozzarini C, Vavassori V, Fellin G, et al. To bleed or not to bleed. A prediction based on individual gene profiling combined with dose-volume histogram shapes in prostate cancer patients undergoing three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 2009; **74**: 1431–40. doi: <http://dx.doi.org/10.1016/j.ijrobp.2008.10.021>