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Assessment of rectal toxicities after radiation therapy for localized prostate cancer: experience of the Akanda Cancer Institute in Gabon

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ABSTRACT

Background: The purpose was to evaluate the incidence of acute and late rectal toxicities and their correlation with the clinical and dosimetric parameters of patients who underwent curative radiotherapy for localized prostate cancer at the Akanda Cancer Institute, Gabon.

Materials and methods: Between 2013 and 2021, a cohort of 46 patients with clinically localized stage cT1c–T4 prostate cancer was treated with three-dimensional conformal radiation therapy (3D-CRT) at the national cancer institute with doses ranging from 66 to 80 Gy. Post-radiation gastrointestinal (GI) toxicities were classified and graded according to the Common Terminology Criteria for Adverse Events CTCAE v4.0.

Results: In our study, 17.4% (8/46) developed acute GI. Grades 1 and 3 acute GI complications were seen in 13.0% (6/46) and 4.3% (2/46), respectively. No patient developed acute grade 2 or grade higher than 3 complications. Late GI side effects were limited. The median time to the development of late GI Grade ≥ 1 toxicities was 12 months (range: 9-19 months). 10.9% (5/46) had experience late GI. Among them, grade 1 and 2 were seen in 6.5% (3/46), and 4.3% (2/46), respectively. There was no grade 3 or higher complications. Statistically, we did not find any correlation between the presence of rectal toxicity and clinical factors or the presence of comorbidity. On the dosimetric level, the Mann-Whitney statistical test found a correlation between the presence of late GI toxicity and rectal volume irradiated at the prescribed dose ($p = 0.02$).

Conclusion: Despite the high radiation doses involved, our results showed an acceptable complication rate.

Key words: 3DCRT; conformal radiotherapy; dose evaluation

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Introduction

Radiation therapy is an integral part of the treatment of patients inflicted with cancer. Prostate cancer is one the most frequent tumors affecting men in the world [1]. External beam radiotherapy (EBRT), more particularly the 3D-CRT, represents one of the standard treatment modality for localized and advanced prostate cancer allowing the delivery of highly "conformed" (focused) radiation to the cancer cells, while significantly reducing the amount of radiation received by surround-

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ing healthy tissue [2]. Radiation therapy affects both tumor cells and uninvolved normal cells. High radiation doses are often related to high local control rates. However, the clinical effect of these high doses on normal tissue toxicities is generally overlooked [3–5]. Radiotherapy is therefore one of the reference treatments alongside hormone therapy and surgery in the management of prostate cancer. During the last decade, radiotherapy has experienced technological innovations to improve treatment ballistic. Despite these technological innovations, it remains a provider of deleterious effects, particularly in terms of acute and late toxicity [6].

Rectal toxicity is one of the main side effects arising when treating prostate cancer with radiotherapy [7]. Odrazka et al. [8] underlined that the rectum and bladder are the crucial organs at risk for curative radiation therapy of localized prostate cancer. Indeed, irradiation of the prostate gland leads to irradiation of healthy tissues surrounding the bladder, the femoral heads, the small intestine and the rectum, and, therefore, leads to toxicities in these organs.

Gastrointestinal toxicities, acute or late, can occur after radiotherapy (RT) for localized prostate cancer, altering the quality of life of up to 50% of patients. The rectum, in most instances, tends to be the structure that limits the overall prescribed dose due to potential toxicities. Early rectal toxicities develop during the course of radiation therapy and typically persist for < 90 days after the completion of treatment. These symptoms include loose stools or diarrhea, tenesmus, urgency, anorectal pain, irritation of hemorrhoids, and bleeding. Chronic rectal bleeding is one of the most common complications of radiation therapy for prostate cancer. These side effects are typically self-limited. Late RT-induced rectal toxicities are defined as those persisting or developing > 90 days after the completion of therapy [9–11].

These toxicities can be more or less intense for each patient, the tolerance profile being patient dependent. An association has been reported between late rectal toxicities and various clinical parameters. Although several clinical parameters were evaluated, most did not show a statistically significant association, except for the presence of acute rectal toxicities [12].

The aim of this study was to retrospectively evaluate the incidence of acute and late rectal toxicities and their correlation with the clinical and dosimetric parameters of patients who underwent curative radiotherapy for localized prostate cancer at the Akanda Cancer Institute (ICA), Gabon.

Materials and methods

Patient selection

Between 2013 and 2021, a cohort of 46 patients with clinically localized stage cT1c-T4 prostate cancer was treated at the ICA, Gabon. The pre-treatment median prostate-specific antigens (PSA) were 48.41 ng/mL (range: 4.71–422 ng/mL). The median age at the start of the treatment was 67 years (range: 50-79 years). The clinical characteristics of the cohort are shown in Table 1.

Table 1. Patient and disease characteristics

Items	Number	%
Age at diagnosis [y]		
≤ 70	29	63.0
> 70	17	37.0
Commorbidity		
Hypertension	27	58.7
Diabetes	8	17.4
TNM stage		
T1c	1	2.2
T2a	3	6.5
T2b	6	13.0
T2c	16	34.8
T3a	2	4.3
T3aN1	1	2.2
T3b	11	23.9
T3bN1	5	10.9
T4	1	2.2
D'Amico risk		
High risk	41	89.1
Intermediate risk	5	10.9
Low Risk	0	0.0
Median pre-treatment PSA [ng/mL]	48.41 (range = 4.71–422)	
Prescription dose [Gy]		
≤ 72	5	10.9
> 72	41	89.1
Median follow-up [months]	57.5 (range = 39–88)	

PSA — prostate-specific antigen

This is a longitudinal retrospective study based on the study of patient records. At the start, 72 patient files were selected because they had benefited from curative radiotherapy for a histologically proven and non-metastatic prostate adenocarcinoma after extension assessment combining a pelvic MRI, a chest-abdomen-pelvis CT scan and bone scintigraphy. Patients for whom the medical file was incomplete or who had not been followed up at the ICA were excluded from the study.

Delineation of organs at risk

CT images were acquired using Phillips Big Bore. Before the CT scan, patients were asked to empty bladder and drink a comfortable volume of water not exceeding 1.5 L. The patient was in the treatment position, supine position, arms crossed on the chest, thighs apart with a knee rest and a footrest. 3 mm tomography slices were acquired. Rectal delineation was defined from the rectosigmoid flexture to the anus. Bladder, small bowel, sigmoid colon and femoral heads were delineated separately.

Target volume

The definition of the target volumes was made according to the extension assessment and in case of negativity of the latter, the risk of lymph node invasion and seminal vesicles were determined by the Roach formula.

Intermediate risk

The clinical target volume (CTV) was defined as the prostate + seminal vesicles, if lymphadenectomy and/or risk of lymph node invasion < 15%. It was defined as the prostate + seminal vesicles + pelvic lymph nodes, if lymphadenectomy is not performed and with a risk of lymph node invasion > 15%.

High risk

The CTV was defined as the prostate + seminal vesicles + pelvic lymph nodes.

The planning target volume (PTV) was created by adding 10 mm margin with 5 mm in posterior.

In postoperative

The CTV was defined as the prostatic bed. The PTV was created by adding a margin from 5 mm to 10 mm.

Treatment planning

The treatment plan was calculated by the CMS-Xio treatment planning system (TPS). The treatment procedure was divided into two or three sequences. Namely, irradiation to PTV1, PTV2 and PTV3. In the first sequence, a dose of 46 Gy in twenty-three fractions was delivered to PTV1 using the four beams, from the left (270°), right (45°), anterior (0°) and posterior (180°) direction. In the second sequence, a median dose of 11 Gy (range: 8–14 Gy) was delivered to PTV2 using six beams in (225°; 270°; 315°; 45°; 90°; 135°) field directions. In the third sequence, a median dose of 18 Gy (range: 12–22 Gy) was delivered to the PTV3 using six beams in the same orientation as sequence 2. A total median dose of 74 Gy (range: 66–80 Gy) was prescribed. The daily dose fraction was 2 Gy. The irradiation schedule was 5 days/week. Prescription point was set to the isocenter. The treatment plan was intended to encompass the PTV with 95% of the prescribed isodose line if a rectal dose was acceptable for the criteria. For the rectum, the treatment plan was designed and optimized so that dose-volume histogram (DVH) constraints would not exceed V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, V75 < 15%.

Treatment

The treatment planning was delivered with an Elekta Precise 15 MV Linear Accelerator (LINAC). After verification of the patient's identity, the patient was fixated using immobilization shell. Two-dimensional orthogonal X-ray images (anterior and left or right) were used for the patient setup with bone matching. Patients underwent treatment with a comfortably full bladder and an empty rectum.

Follow-up

During treatment, patients were evaluated weekly and questioned for acute GI complaints. After 3D-CRT, patients were followed every 3 months during the first two years and once per semester thereafter, with serial PSA and physical examination. Image studies were done when specific complaints occurred. Acute complication was defined as that occurring within 3 months post radiation therapy and late complication as that occurring from the third month on [13, 14]. GI complications

were graded according to the Common Terminology Criteria for Adverse Events CTCAE v4.0

Statistical analysis

Data were analyzed using SPSS 21 software. Qualitative data were compared using Pearson's Chi^2 test or Fisher's exact test. Quantitative data were compared using the Mann-Whitney non-parametric test or Student's t-test in case of a normal quantitative variable. For univariate analysis, the Wilcoxon test was applied. The statistical significance level considered was (p-value < 0.05).

Results

A total of 46 eligible patients were evaluated, clinical and dose volume data were collected. Patients and disease characteristics are summarized in Table 1. Treatments were well tolerated. The median follow-up time after radiotherapy was 57.5 months (range: 39–88 months). No local recurrences were observed at the prostate floor. All patients were on remission during the follow up. Randomized trials have indeed shown excellent long-term biochemical recurrence-free survival with high radiation doses [15]. No deaths related to prostate cancer were observed during follow-up. Overall survival is therefore 100% in all of our patients, as is recurrence-free survival. Note, however, that, since 2013 until 2021, only 8.7% (4/46) patients died due to other pathologies. 91.3% (42/46) of them are still alive.

The combination of EBRT and androgen deprivation therapy (ADT) remains a standard definitive treatment option for men with prostate cancer. However, EBRT has been found to portend long-term risks of GI toxicities [16]. In our study, most patients 82.6% (38/46) did not experience any acute GI complications. 17.4% (8/46) had developed acute GI. Grades 1 and 3 acute GI complications were seen in 13.0% (6/46) and 4.3% (2/46), respectively. No patient developed acute grade 2 or grade higher than 3 complications. Late GI side effects were limited. The median time to the development of late GI grade ≥ 1 toxicities was 12 months (range: 9–19 months). As underlined by Bosset et al. [17] late rectal morbidity has been observed in 2–25% of patients treated with radiotherapy using curative doses for prostate. In our study 10.9% (5/46) had experienced late GI. Among them, grade 1 and 2 were seen in 6.5% (3/46), and 4.3% (2/46), respectively. There were no grade 3 or higher complications. Acute rectal effects occur during or soon after RT and typically include softer or diarrhea-like stools, pain, a sense of rectal distention with cramping, and frequency and rectal bleeding is usually self-limited [18]. Following the range of toxicities listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The incidence of toxicities with grade and side effects are presented in Table 2.

After listing the incidence of acute and late GI toxicities, we sought to find out if the latter were linked to several factors such as age, Gleason score, Tumor–Nodes–Metastases (TNM) stage of the tumour, the risk of d'Amico, the prescribed dose or certain comorbidities. The results are listed in Table 3.

After analysis, the occurrence of these toxicities does not depend significantly on any of these parameters. On the other hand, we also investigated whether the occurrence of acute and late GI toxicities was related to dosimetric parameters: mean

Table 2. Acute and late gastrointestinal (GI) side effects

Side effects	Acute GI toxicity		Late GI toxicity	
	Grade	N (%)	Grade	N (%)
Diarrhea				
	1	3 (6.5)	1	0(0.0)
	3	2 (4.3)	3	0(0.0)
Proctitis				
	1	1 (2.2)	1	0(0.0)
Bleeding				
	1	3 (6.5)	1	3 (6.5)
	2	0(0.0)	2	2 (4.3)

Table 3. Incidence of acute and late gastrointestinal (GI) grade ≥ 1 with patient and clinical characteristics

		Acute GI toxicity		p-value	Late GI toxicity		p-value
		Grade 0	Grade ≥ 1		Grade 0	Grade ≥ 1	
	N (%)	38 (82.6)	8 (17.4)		41 (89.1)	5(10.9)	
Clinical parameters							
Age at diagnosis [y]				1.000			0.691
≤ 70	29 (63.0)	23 (50.0)	6 (13.0)		26 (56.5)	3 (6.5)	
> 70	17 (37.0)	15 (32.6)	2 (4.3)		15 (32.6)	2 (4.3)	
Comorbidity							
Hypertension	27 (58.7)	24 (52.2)	3 (6.5)	0.246	26 (56.5)	1 (2.2)	0.144
Diabetes	8 (17.4)	6 (13.0)	2 (4.3)	0.613	7 (15.2)	1 (2.2)	1.000
Clinical stage				0.898			0.660
T1c	1 (2.2)	1 (2.2)	0 (0.0)		1 (2.2)	0 (0.0)	
T2a	3 (6.5)	2 (4.3)	1 (2.2)		3 (6.5)	0 (0.0)	
T2b	6 (13.0)	6 (13.0)	0 (0.0)		6 (13.0)	0 (0.0)	
T2c	16 (34.8)	12 (26.1)	4 (8.7)		14 (30.4)	2 (4.3)	
T3a	2 (4.3)	2 (4.3)	0 (0.0)		1 (2.2)	1 (2.2)	
T3aN1	1 (2.2)	1 (2.2)	0 (0.0)		1 (2.2)	0 (0.0)	
T3b	11 (23.9)	9 (19.6)	2 (4.3)		9 (19.6)	2 (4.3)	
T3bN1	5 (10.9)	4 (8.7)	1 (2.2)		5 (10.9)	0 (0.0)	
T4	1 (2.2)	1 (2.2)	0 (0.0)		1 (2.2)	0 (0.0)	
Gleason Score (GS)				0.091			0.097
GS ≤ 6	8 (17.4)	8 (17.4)	0 (0.0)		8 (17.4)	0 (0.0)	
GS 7a (3 + 4)	4 (8.7)	2 (4.3)	2 (4.3)		2 (4.3)	2 (4.3)	
GS 7b (4 + 3)	26 (56.5)	21 (45.6)	5 (10.9)		24 (52.2)	2 (4.3)	
GS 8 (4 + 4; 3 + 5; 5 + 3)	6 (13.0)	6 (13.0)	0 (0.0)		5 (10.8)	1 (2.2)	
GS 9 (4 + 5; 5 + 4; 5 + 5)	2 (4.3)	1 (2.2)	1 (2.1)		2 (4.3)	0 (0.0)	
D'amico risk				1.000			0.631
High risk	41 (89.1)	34 (73.9)	7 (15.2)		36 (78.2)	5 (10.9)	
Intermediate risk	5 (10.9)	4 (8.7)	1 (2.2)		5 (10.9)	0 (0.0)	
Low risk	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Prescription dose [Gy]				1.000			0.453
≤ 72	5 (10.9)	4(8.7)	1 (2.2)		4 (8.7)	1 (2.2)	
> 72	41 (89.1)	34 (73.9)	7 (15.2)		37 (80.4)	4 (8.7)	

Pre-treatment prognostic groups for D'Amico risk: high risk — T2c or Gleason Score greater than or equal to 8 or prostate-specific antigen (PSA) greater than 20 ng/mL or T3-T4; intermediate risk — T2b or Gleason score equal to 7 or PSA greater than 10 ng/mL and less than or equal to 20 ng/mL; low risk — those with a PSA less than or equal to 10, a Gleason score less than or equal to 6, or are in clinical stage T1–T2a [19]

dose, maximum dose, volume dose constraints to the rectum, volume of the contoured rectum, and volume of the rectum irradiated at various doses. The results are listed in Table 4.

After analysing the aforementioned results of the Mann-Whitney test, it appears that the occurrence of late toxicity depends on the volume of the rectum irradiated at the prescribed dose with a statistically significant ($p = 0.020$).

In univariate analysis, according to the Wilcoxon test, the rectal bleeding that occurs both in acute and late GI toxicities depends on the volume of the irradiated rectum, with $p < 0.001$ which is statistically significant (Tab. 5).

The rectal volume: V_{50}, V_{60}, V_{65}, V_{70}, V_{75} in the patients with grade ≥ 1 rectal bleeding were significantly larger than in the non-bleeding patients by the Wilcoxon rank sum test.

Table 4. Incidence of acute and late gastrointestinal (GI) toxicity as a function of dose and rectal volume

		Acute GI toxicity		p-value	Late GI toxicity		p-value
		Grade 0	Grade ≥ 1		Grade 0	Grade ≥ 1	
	N = 46	38 (82.6)	8 (17.4)		41 (89.1)	5(10.9)	
Doses-volume parameters							
D_{mean} [Gy]	56.5 ± 4.3	56.5 ± 4.5	56.6 ± 3.5	0.787	56.4 ± 4.7	57.2 ± 3.6	0.607
D_{max} [Gy]	75.7 ± 3.1	75.7 ± 2.7	75.3 ± 4.8	0.831	75.8 ± 2.7	74.6 ± 6.1	0.706
V_{50}	66.6 ± 15.1	66.8 ± 15.8	65.6 ± 12.2	0.809	66.3 ± 15.3	69.6 ± 15.3	0.537
V_{60}	39.9 ± 14.3	39.7 ± 14.9	41.2 ± 11.0	0.618	39.4 ± 14.3	44.0 ± 14.6	0.470
V_{65}	27.6 ± 12.3	27.8 ± 12.3	26.6 ± 12.9	0.809	27.7 ± 11.7	30.4 ± 17.8	0.316
V_{70}	15.0 ± 9.9	16.9 ± 8.1	17.4 ± 8.2	0.599	16.8 ± 7.8	18.6 ± 10.9	0.370
V_{75}	05.3 ± 11.3	3.2 ± 3.4	5.2 ± 5.3	0.456	3.4 ± 3.6	5.2 ± 4.9	0.388
V [cm^3]	87.3 ± 39.9	87.2 ± 34.0	87.6 ± 63.3	0.211	89.1 ± 42.0	73.0 ± 8.9	0.471
$D_{46,V}$ [cm^3]	74.8 ± 39.8	74.6 ± 33.2	75.5 ± 66.2	0.223	76.2 ± 41.9	63.5 ± 10.9	0.732
$D_{70,V}$ [cm^3]	15.0 ± 9.9	14.0 ± 7.0	19.5 ± 18.4	0.989	14.4 ± 9.1	19.6 ± 15.5	0.300
$D_{T,V}$ [cm^3]	03.2 ± 5.5	2.3 ± 2.5	7.3 ± 11.7	0.146	2.9 ± 5.8	5.3 ± 2.1	0.020

D_{mean} — mean dose; D_{max} — maximum dose; V_x — rectal volume receiving x Gy; V — total rectal volume; $D_{x,V}$ — rectal volume irradiated at x dose, $D_{T,V}$ — rectal volume irradiated at the prescribed dose

Table 5. Comparison of grade ≥ 1 rectal bleeding and non-rectal bleeding per the rectal volume (rV)

Parameters	Volume [cm^3]		p-value
	Bleeding	Non-bleeding	
V_{50}	69.3 ± 13.7	66.2 ± 15.5	< 0.001
V_{60}	45.0 ± 13.3	39.2 ± 14.4	< 0.001
V_{65}	31.8 ± 16.3	27.0 ± 11.7	< 0.001
V_{70}	19.8 ± 10.2	16.6 ± 7.8	< 0.001
V_{75}	4.3 ± 4.9	3.5 ± 3.6	< 0.001

V_x — rectal volume receiving x Gy

Discussion

The combination of external beam radiation therapy and androgen deprivation therapy remains a standard definitive treatment option for men with prostate cancer. However, EBRT has been found to portend short and-long-term risks of GI toxicities [20]. In this study, we showed the incidence of acute and late GI toxicities in 46 patients treated with a high dose 3D-CRT for prostate cancer and analyzed the associated clinical and dosimetric parameters.

Despite the use of high-dose radiotherapy, our patients tolerated well the treatment and the incidence of acute and late GI toxicity was very low. In the study cohort, the incidence of acute GI was 17.4% (8/46). More specifically, 13% (6/46) of patients presented with grade 1 acute toxicity, 4.3% (2/46) presented with grade ≥ 2 acute toxicity. The incidence of late GI was 10.9% (5/46), 6.5% (3/46) on grade 1 and 4.3% (2/46) of grade ≥ 2. This incidence is particularly low compared to other studies as shown in Table 6 below.

This low incidence of GI toxicities can be explained by the fact that, for the clinical validation of our treatment plans, we use QUANTEC dose constraints (V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, V75 < 15%) [25]. Michalski et al. [18] pointed out, on the one hand, that the use of these dose constraints is the starting point in three-dimensional dosimetric planning treatment and, on the other hand, that this should limit Grad ≥ 2 late rectal toxicity to < 15% and the probability of Grad ≥ 3 late rectal toxicity to < 10% for prescriptions up to 79.2 Gy in standard 1.8 to 2 Gy fractions. In the present study, Grade ≥ 2 was 4.4%,

Table 6. Incidence of gastrointestinal (GI) toxicity for curative prostate cancer treated with three-dimensional conformal radiation therapy (3D-CRT)

Authors [reference]	Endpoint	Time period/RT technique	Incidence, % (n)	Total prescribed dose [Gy]/fraction size [Gy]
Delobel et al. [21]	CTCAE V3.0, Acute* Grade 1	2000–2012	35.9 (314/874)	
	Grade ≥ 2	3D-CRT	22.2 (194/874)	75 (70–80)/2
	Late§, Grade ≥ 2		15.3 (134/874)	
Huang et al. [22]	RTGO, Late§	1992–1999		
	Grade 1,	3D-CRT	31.9 (52/163)	74–78/2
	Grade ≥ 2		23.3 (38/163)	
Vranova et al. [4]	RTOG and LENT-SOMA	2004–2009		
	Acute* grade ≥ 2	3D-CRT	58.6 (68/116)	< 71 and ≤ 74/1.8–2.0
	Late§ grade ≥ 2		6.9 (8/116)	
Taleb et al. [23]	RTOG, Acute*	2010–2014		
	Grade 1	3D-CRT	8.9 (8/90)	≤ 70 and > 70/2
	Grade ≥ 2		7.8 (7/90)	
	Late§ grade 1		7.8(7/90)	
	Late§ grade ≥ 2		2.2 (2/90)	
D'avino et al. [24]	RTOG/EORTC, Acute*			
	Grade 1	3D-CRT	31 (26/84)	76/2
	Grade ≥ 2		11 (9/84)	
	Late§ grade 1		25 (21/84)	
This study	CTCAE V4.0, Acute* Grade 1	2013–2021 3D-CRT	13.0 (6/46)	74 (66–80)/2
	Grade ≥ 2		4.3 (2/46)	
	Late§ grade 1		6.5 (3/46)	
	Late§ grade ≥ 2		4.3 (2/46)	

RTOG — Radiation Therapy Oncology Group; CTCAE — Common Terminology Criteria for Adverse Events; LENT-SOMA — Late Effects Normal Tissues-Subjective, Objective, Management, Analytic; *Acute toxicity was defined as toxicity from the start of treatment up to 90 days; §Late toxicity was defined as from 90 days after start of treatment up to five years after treatment

which is less than 15% for late rectal toxicity. No grade 3 rectal toxicity was observed. Fuentes-Rapall et al. [26] reported late toxicity in relation with 3D-CRT for prostate cancer that showed an incidence between 5% and 20%, with 9.3% of cases in their own group of patients.

On a clinical level, Giodano et al. [3] showed in their study that the treatment with hormone therapy was a significant predictor of GI diagnoses. Although several studies have shown a correlation between clinical factors (age, previous abdominal surgery), comorbidity (androgen deprivation therapy, diabetes mellitus, hypertension) and the augmentation of the risk or the presence of rectal toxicities [3, 4, 14, 20, 24, 27]. In this study, we did not statistically find any correlations between the presence of rectal toxicity and clinical factors or the presence of comorbidity. This observation is shared by several authors, in particular Faure et al. [19] did not observe any statistically significant difference in terms of incidence and toxicity between patients over 70 and those under 70. The age of the patients, the use of concomitant hormone therapy, and the medical history did not seem to influence the occurrence of acute and late anorectal sequelae. It is also the case for Lee et al. [28] who did not find a statistical correlation between the pre-treatment clinical factors (e.g. diabetes) with incidence of late rectal toxicity. In the same way, Huang et al. [22] did not find diabetes to be a significant risk factor for developing grade 2 toxicity. They underlined in their study that diabetes is an important predictor of late rectal toxicity. They thought that the difference may be due to the small

number of diabetes patients available for analysis. Regarding the correlation between late toxicity and diabetes, our results can be superimposed on those of Lee et al. [28] because in our study only 17.4% (8/46) of patients are diabetic with p = 1.000.

On the dosimetric level, the risk of developing late rectal complication grows exponentially as a greater volume of the rectum is irradiated to a defined dose [22]. With regard to late rectal toxicity, the relationships between doses and volumes irradiated, on the one hand, and risk of complication, on the other, are globally reproducible for prostatic doses varying from 70 to 80 Gy [27]. These observations agree with our results. Indeed, we found a statistically significant association between late GI toxicity and volume of the rectum irradiated at the prescribed dose (p = 0.020).

Lee et al. [28] underlined that the prescribed radiation dose and percentage of rectal volume treated with 60 or 70 Gy had statistically significant correlations with the increase of late rectal toxicity. Peeters et al. [29] in their study stated that a trend was found that a total radiation dose of 74 Gy resulted in a high incidence of severe rectal bleeding, and increasing the prostate dose from 68 Gy to 78 Gy resulted in a higher incidence of acute and late GI and GU toxicity. For Zelefsky et al. [30], when it comes to 3D-CRT, several reports have noted that when dose levels exceed 75.6 Gy, the increased risks of Grade ≥ 2 rectal related late toxicities are expected. For our study, despite a median prescribed dose of 74 Gy (range: 66–80 Gy), we found no statistically significant correlation (p = 1.000) between the prescribed dose and the occurrence of late toxicity.

De Crevoisier et al. [27] emphasized in their study that several randomized studies had shown that the risk of rectal toxicity was greater when a high dose of irradiation (78–80 Gy) was delivered to the prostate. Although no conclusion can be made on the basis of a single patient, we nevertheless point out that the only patient in our study who received a therapeutic dose of 80 Gy did not present any GI toxicity. They further stated that some studies have shown an association between acute rectal toxicity and late toxicity. This assertion is shared by Zelefsky et al. [30]: Patients with acute GI symptoms experienced a significantly increased likelihood for developing late rectal toxicity. In our study, only 6.5% (3/46) patients who presented with acute toxicities had late toxicities, mainly bleeding.

Conclusion

At the end of our study, it appears that only the occurrence of late toxicities is correlated to the volume of the rectum irradiated at the prescribed dose. Although our sample is small, we noted the absence of a significant correlation between the occurrence of toxicities and the other dosimetric parameters. This could reflect a good tolerance to radiation by the organ studied in our patients.

However, although very few patients in our sample presented both acute and late toxicities, it would be desirable to take into account not only the dose constraints to the organs at risk but also the patient's clinical parameters. That is the reason why, even if today these side effects can be treated, we still believe that the best way to treat them is not to create them. Hence, the necessity to implement new irradiation techniques such as intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT).

Conflict of interest

None declared.

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None declared.

Data availability statement

Research data are stored in our institutional repository and could be shared upon request.

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