RADIOTHERAPY

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High-dose intensity-modulated radiation therapy as primary treatment of prostate cancer: genitourinary/gastrointestinal toxicity and outcomes, a single-institution experience

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Abstract

Purpose Prostatectomy, radiotherapy and watchful waiting are the main therapeutic options available for local stage of prostate cancer (PCa). We report our experience on 394 patients affected by prostate cancer primarily treated with high-dose, image-guided, IMRT, focusing on gastrointestinal, genitourinary toxicities and biochemical control.

Methods From July 2003 to August 2014, 394 patients were treated with radical high-dose radiotherapy (HDRT) for prostate cancer; the mean total radiation dose was 79 Gy in standard fractions. Hormonal therapy (HT) was administered to 7.6% of low-risk patients, to 20.3% of intermediate-risk patients and to 72% of high-risk patients. Patients were evaluated for biochemical failure, local recurrence (LR) and metastases.

Results Ninety-seven patients (26.65%) developed acute GU toxicity at the medium dose of 25.4 Gy, grade 1 (G1) or grade 2 (G2) in 94 cases. Only 16 patients (4.06%) reported chronic GU toxicity (G1 or G2), and one case developed G3 cystitis. No G3 GI acute and late toxicity were detected. Fifty-six (14.2%) patients experienced LR, 26 (6.6%) developed metastases and 70 patients (17.8%) were deceased. Gleason sum score > 7 was predictive for worse overall survival (GS = 7 was borderline) and for metastasis. No factors resulted predictive for local relapse. HT pre-RT had been demonstrated as a negative predictor for OS and DFS-DM.

Conclusions Data confirm the safety of HDRT for PCa. Treatment was efficient with low toxicity profile. Moreover, continued technologic advancements, as image-guided radiotherapy, could lead to further reduction in toxicity, thus increasing the therapeutic index.

Keywords Prostate cancer · Intensity-modulated radiation therapy (IMRT) · Genitourinary toxicity · Gastrointestinal toxicity

Introduction

Prostate cancer is the second most common cancer and the sixth leading cause of death among men [1]. In Italy, it is the most frequent tumor in people over 50 years of age [2]. Radical prostatectomy (RP), radiotherapy (RT) and watchful waiting/active surveillance in selected cases are the main available therapeutic options for early-stage disease.

Therapeutic decision making should be tailored to individual patient' characteristics, yet the treating center's expertise and the availability of RT technologies are also critical considerations. Since the end of the 1980s, all major clinical guidelines proposed surgery and RT as oncological equivalent alternatives for localized prostate cancer. Biochemical control and survival rates obtained with either treatment are comparable, at least in localized prostate cancer [3].

Randomized trials supported the indication of higher doses of RT in the treatment of prostate cancer [4, 5], associated with better results and higher biochemical disease control [6–9]. Acute and chronic toxicities depend on total radiation doses and treatment techniques. Exclusive

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RT provides acceptable outcomes, but unfortunately, dose escalation could be associated with a higher risk of acute and late toxicity [10]. In fact, the proximity of the rectum and bladder has been a limiting factor in safe dose escalation both in 2D and in 3D treatment planning era [6, 11]. Nevertheless, the technological evolution and improvements led to spare organs at risk (OARs) and to limit their exposure: intensity-modulated radiotherapy (IMRT) in association with image-guided radiation therapy (IGRT) allowed to lower rates of severe toxicity, as well as a better quality of life [12], often respecting normal tissue-sparing goals since IGRT allows to correct target and OARs movement immediately. In particular, IMRT is associated with a significant reduction in acute G2 + gastrointestinal (GI) toxicity with a trend for a decrease in late G2 + GI toxicity [13]. Moreover, many publications investigated the volumes and dose parameters correlated with GI and urinary toxicities [13–15]. The occurrence of acute GI toxicity and large (> 15%) volumes of rectum > 70 Gy are associated with late rectal toxicity. Obviously, some immobilization devices or strategies (endorectal balloon and standardized bladder filling) reduce organs motion [16]. We, herein, report our institutional experience in 394 patients with localized prostate cancer treated with definitive high-dose, image-guided-intensity-modulated radiotherapy (IG-IMRT). We primarily sought to evaluate the acute/late gastrointestinal (GI) toxicities and the acute/late genitourinary (GU) toxicities. We have also reported disease outcomes, in terms of loco-regional recurrence (LR) and distant metastasis occurrence (DM).

Materials and methods

From our institutional database, we retrospectively reviewed the clinical data of 394 patients, treated between July 2003 and August 2014 with radical high-dose RT for localized prostate cancer. The main eligibility criteria were added which include: untreated histologically confirmed adenocarcinoma of the prostate and stage cT1c-T4 N0 M0 according to the sixth edition American Joint Committee on Cancer staging system. Prognostic risk groups' stratification was made based on D'Amico criteria. Hormonal therapy was administered mainly in intermediate- and high-risk groups. Data that were extracted from our medical records included age and tumor characteristics like Gleason score and pretreatment PSA.

Staging

Staging of pelvic lymph node and bone metastases was performed by computed tomography (CT) scan and bone scan, as indicated, and these were negative for all examined patients. All patients underwent a pretreatment prostate magnetic resonance imaging (MRI) to evaluate for extraprostatic extension of disease. MRI fused with the planning CT for target volume delineation.

Radiotherapy

All treatment plans were generated by using inverse planning and IMRT technique. The planning CT scan was performed with 3-mm slices in the supine position with leg immobilization system (Combifix-Sinmed, Civco, Kalona, IA, USA). RT was delivered in all cases with a 5-fields approach using 10 MV photons. The clinical target volume (CTV) was limited to the prostate in low-risk patients, while in high-risk patients the entire seminal vesicles were included in the CTV.

The planning treatment volume (PTV) was generated by adding an 8-mm isotropic expansion to the CTV excepting 6 mm posteriorly. The median prescribed dose was 80 Gy (range 76–80 Gy), in 1.8–2 Gy per fraction. The dose was prescribed at the isocenter according to the International Commission of Radiation Units and Measurements recommendations. For treatment planning, the dose–volume constraints for the bladder were V65 < 50% and a maximum dose < 65 Gy; for the small bowel V15 < 120 ccs and V45 ≤ 195 ccs; for the rectum: V50 Gy ≤ 50%, V60 Gy ≤ 35%, and V70 Gy ≤ 20%. Dose constraints for the organs at risk (OAR) were selected based upon Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data [17]. All patients were treated using bowel- and bladder-filling protocols [18, 19]. Before each delivery, KV images and cone beam-CT (CBCT) scan were obtained. Shifts were performed by aligning finally to soft tissue on CBCT.

Hormonal therapy

Patients were stratified according to D'Amico risk groups [20]. Hormonal therapy (HT) consisted of a monthly subcutaneous injection of luteinizing hormone-releasing hormone analogue. HT was administered to 7.6% of low-risk patients (subgroup treated in the earlier period), 20.3% of intermediate-risk patients and 72% of high-risk patients. Two hundred and forty-three patients received neoadjuvant, concurrent and adjuvant HT for a total of 6-month duration in intermediate risk and for a total of 2 years in high-risk disease. During RT, patients were visited at least once weekly by a physician.

Follow-up and toxicity evaluation

From the end of the RT, a regular follow-up (FU) was performed. An assessment of toxicity, a digital rectal examination and a prostatic-specific-antigen (PSA) test were

performed every 3 months for the first 2 years, every 6 months until the fourth year and every year thereafter. Acute side effects were delineated as those developing during treatment or within 3 months following completion of RT. The grade of acute toxicity was rated according to the National Cancer Institute Expanded Common Toxicity Criteria (NCI-CTC), version 2.0. Late toxicities were delineated as those developing 3 months after completion of RT and were assessed according to the Radiation Therapy Oncology Group (RTOG) scale. Radiological assessments were performed only as indicated by symptomatology or in case of biochemical failure according to ASTRO criteria [21].

Statistical analysis

Loco-regional recurrence disease-free survival (LR-DFS) was defined as the time from the end of radiation therapy to the date of the first event, between loco-regional recurrence and biochemical failure. Biochemical failure was defined according to the ASTRO criteria. Loco-regional recurrence was defined as the appearance of a new lesion in the prostate bed or in the pelvis lymph nodes detected by CT scan or by choline-PET. Distant metastasis disease-free survival (DM-DFS) was defined as the time from the end of radiation therapy to the date of the first event of appearance of distant lesions, detected by CT scan, choline-PET or bone scintigraphy. Cox regression models were employed to identify predictive factors for disease recurrence and toxicity. Hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) are reported. Statistical comparisons were considered significant at a p value ≤ 0.05.

Results

A total of 394 patients were analyzed. The average age of the cohort was 72 years (range 56–85). Two hundred and eighty-four patients (72.1%) were defined as high risk. Fifty-nine (14.9%) of these presented with seminal vesicles invasion. Eighty patients (20.3%) were defined as intermediate risk and thirty (7.6%) as low risk. Mean pretreatment PSA was 10.66 ng/ml (range 1.73–99.6) (Table 1).

At a median follow-up of 6.7 years (range 0.6–12.8), 56 (14.2%) patients had a local recurrence and 26 (6.6%) developed distant metastases. Meantime-to-LR occurrence was 4.7 years (range 1.2–10.4). Meantime-to-DM occurrence was also 4.7 years (range 1.1–10.3). Seventy patients (17.8%) died during follow-up. In 38 cases (9.6% of the entire cohort, 54.3% of all deaths), death was deemed to be cancer related.

The treatment was overall well tolerated, and all patients completed the prescribed course. Acute GU toxicity was

Table 1 Patient's characteristics

Sample size, n	394
Age (years)	
Median	72
Range	56–85
Gleason score, n (%)	
<7	208 (52.8)
7	97 (24.6)
>7	89 (22.6)
Pre-RT PSA (ng/ml)	
<10	223 (56.6)
10–20	113 (28.7)
>20	58 (14.7)
D'Amico risk group, n (%)	
Low	30
Medium	80
High	284
HT pre-RT, n (%)	
No	151 (38.3)
Yes	243 (61.7)
Time HT pre-RT	
≤3 months	29
>3 months	195
HT adjuvant, n (%)	
No	246 (62.4)
Yes	148 (37.6)
Time HT adjuv.	
≤6 months	42
>6 months	95
Tumor stage, n (%)	
I	31 (7.9)
II	185 (47,2)
III	176 (44.9)

encountered in 243 (61.7%) patients, at a median dose of 24 Gy. In general, this was $\leq$ G2, with only 17.6% of patients requiring alpha blockers and/or anti-inflammatory medications. Two patients (0.5%) developed G3 acute urinary toxicity and were hospitalized for bleeding.

Significant acute GI toxicity was also uncommon. One hundred and fifty patients (38.1%) experienced $\leq$ G2 GI toxicity (G1 in 49 (12.4%) and G2 in 101 (25.6%) cases). There were no G3 + GI toxicities. The most common GI complaints were diarrhea, rectal burning and anal fissure. These were generally treated with anti-inflammatory therapy with complete resolution.

GU late toxicity was reported in 16 patients (4.1%): G1 in 3 (0.8%), G2 in 12 (3%) and G3 only in 1 (0.2%).

Table 2 Acute and late toxicities

Toxicity	n (%)	Mean dose (Gy)
Acute GU	243 (61.7)	25.14
G1	37 (9.4)	(range 0–80)
G2	204 (51.8)	
G3	2 (0.5)	
Late GU	16 (4.1)	
G1	3 (0.8)	
G2	12 (3.1)	
G3	1 (0.2)	
Acute GI	150 (38.1)	
G1	49 (12.5)	17.82
G2	101 (25.6)	(range 0–80)
G3	0 (0)	
Late GI	21 (5.3)	
G1	8 (2)	
G2	13 (3.3)	
G3	0 (0)	

GU genitourinary, *GI* gastrointestinal, *G1* grade 1, *G2* grade 2, *G3* grade 3

Only 21 patients (5.3%) developed chronic proctitis which was G1 in 8 cases (2.0%) and G2 in 13 cases (3.3%). No late G3 + GI toxicities were detected (Table 2).

The statistical analysis was performed to investigate whether acute toxicities were predictive of late complications: No significant association between them, either in GU ($p = 0.55$) or in GI ($p = 0.38$) systems, was identified. Moreover, at Mann–Whitney statistical test no significant correlations were recorded between the DVH parameters and the toxicities developed by the patients (see Table 3).

Furthermore, we evaluated the comparison between available individual parameters of patients and toxicity by applying an appropriate statistical test according to the variables under consideration (Mann–Whitney or Chi-square test) (see Table 4). Treatment outcome analysis with Kaplan–Meier (KM) and Cox regression univariate analysis (UVA) identified Gleason score = 7 ($p = 0.027$), Gleason score > 7 ($p = 0.01$) and the use of HT prior to RT (HT pre-RT) ($p = 0.024$) as predictive values of worse survival (OS) (Figs. 1 and 2). These factors were also predictive of DM-DFS ($p = 0.046$; $p = 0.02$; and $p = 0.037$, respectively) (Figs. 3 and 4).

HT pre-RT duration > 3 months correlated with worse LR-DFS ($p = 0.025$). On UVA only GS > 7 maintained a meaningful effect on OS ($p = 0.008$) and DM-DFS ($p = 0.01$), while GS = 7 became borderline ($p = 0.052$) and the deleterious effect of HT pre-RT lost its significance ($p = 0.13$). The following additional factors were examined but found to have no correlation to clinical outcomes on

Table 3 Correlations between DVH parameters and toxicity (*p* values from Mann–Whitney test)

	Tolerance	Acute cystitis	Acute proctitis	Late cystitis	Late proctitis
PTV volume	0.20	0.46	0.80	0.79	0.39
CTV volume	0.70	0.80	0.62	0.21	0.81
Rectum volume	0.27	0.44	0.18	0.87	0.50
Rectum V50	0.67	0.36	0.92	0.44	0.91
Rectum V60	0.096	0.33	0.71	0.35	0.97
Rectum V65	0.17	0.23	0.89	0.44	0.54
Rectum V70	0.39	0.45	0.64	0.87	0.28
Rectum V75	0.93	0.68	0.29	0.98	0.10
Bladder volume	0.11	0.46	0.41	0.75	0.75
Bladder V50	0.18	0.54	0.48	0.99	0.98
Bladder V60	0.19	0.35	0.38	0.55	0.96
Bladder V70	0.31	0.67	0.23	0.28	0.89

Table 4 Correlations between individual characteristics and toxicity (*p* values from Mann–Whitney test or Chi-square test, as appropriate)

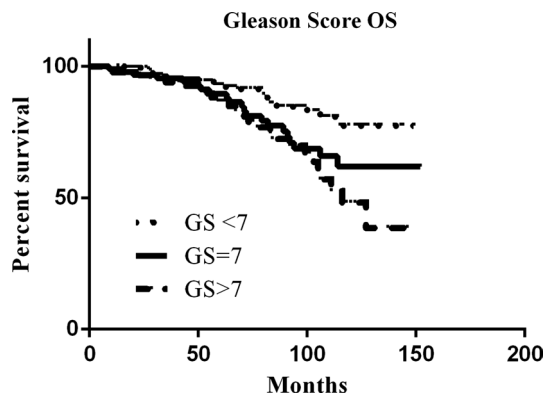|	Tolerance	Acute cystitis	Acute proctitis	Late cystitis	Late proctitis
Age	0.39	0.44	0.31	0.64	0.61
pT	0.56	0.45	0.99	0.44	0.81
Gleason	0.20	0.17	0.43	0.39	0.21
Initial PSA	0.94	0.83	0.078	0.71	0.74
PSA pre-RT	0.13	0.34	0.52	0.35	0.57
Volume	0.18	0.15	0.28	0.19	0.97
Prostate dose	**0.0001**	0.68	0.13	0.66	0.15

p values less than 0.05 are shown in bold

Fig. 1 OS by Gleason score

Fig. 2 OS according to administration of hormonal therapy (HT) before radiotherapy (RT)
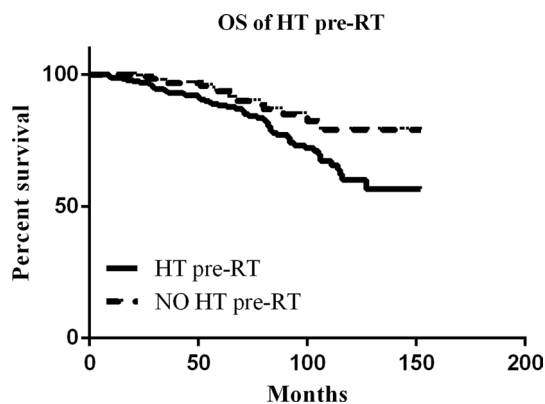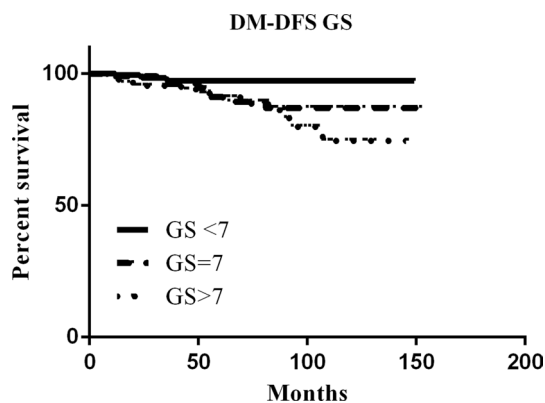

Fig. 3 DM-DFS by Gleason score

Fig. 4 DM-DFS according to administration of hormonal therapy (HT) before radiotherapy (RT)

Discussion

Comparison between radiotherapy and radical prostatectomy (RP) for localized prostate cancer is still a controversial issue. Many studies have been published, but no one showed a significant benefit of a treatment on the other. For example, Shrader-Bogen et al. [22] demonstrated that patients treated with prostatectomy fared worse, in regard to sexual and urinary functions, compared to those treated with external beam RT. Tyson et al. [23] recently demonstrated that low-risk prostate cancer patients reported a worst sexual evaluation, when treated by RT compared to RP. No differences in sexual functions were reported for high-risk patients. No clinically significant differences were reported for incontinence, bowel, irritative voiding and hormone domain, between the two treatments for all risk groups. They conclude that for high-risk patients, RP and RT can be considered equal treatments, as no other differences are shown in terms of toxicity.

Wallis et al. [24] recently published a review comparing efficacy and toxicity of the different treatment modes for prostate cancer patients. They showed that randomized trials are underpowered and demonstrated no differences in overall survival (OS). Observational studies are limited by selection bias and demonstrated a benefit in OS for men who underwent RP compared with RT. On the other hand, RT and surgery are comparable in terms of health-related quality of life in three randomized trials. They conclude that comparison between RT and RP for prostate cancer patients is still insufficient, both in terms of OS and in terms of treatment-related toxicity. Randomized clinical studies are necessary to better understand the benefits and risks of each therapeutic approach.

We know that higher doses administered are associated with more probability of local control in prostate cancer. Dose escalation of RT has been clearly linked with improved

UVA: cT < 3 versus > 3, RT dose < 76 Gy versus > 76 Gy and HT (see Tables 5 and 6).

Of note, OS and DM-DFS were significantly worse in the high-risk subgroup ($p = 0.048$) (Figs. 5 and 6).

Table 5 K–M analysis

Variable	Pts at start	Deaths	OS %	p value	LR	LR-DFS %	p value	DM	DM-DFS %	p value
cT										
1	31	2	–		4	–		0	–	
2	185	33		0.12	23		0.51	9		0.06
≥ 3	176	35			29			17		
Gleason score										
< 7	208	23	78.4		22	–		6	96.4	
7	97	22	58.7	**0.003**	18		0.09	8	83.7	**0.004**
> 7	89	25	38.7		16			12	75.5	
Initial PSA										
< 10	223	29	–		28	–		15	–	
10–20	113	27		0.15	17		0.71	5		0.46
> 20	58	14			11			6		
HT pre-RT										
No	151	15	78.8		19	–		4	96.9	
Yes	243	55	56.5	**0.022**	37		0.67	22	83.4	**0.028**
Time HT pre-RT										
≤ 3 months	29	5	–		7	58.5		4	–	
> 3 months	195	44		0.77	29	78.4	**0.025**	17		0.17
HT post-RT										
No	246	39	–	0.13	36	–	0.93	12	–	0.06
Yes	148	31			20			14		
Time HT post-RT										
≤ 6 months	42	11	–		6			2		
> 6 months	95	20		0.95	14	–	0.74	11	–	0.14
Doses RT										
≤ 76 Gy	24	1	–	0.80	1	–	0.90	1	–	0.40
> 76 Gy	370	69			55			25		
Total	394	70	63.1		56	75.3		26	87.9	

p values less than 0.05 are shown in bold

Pts patients, *OS* overall survival, *LR* local relapse, *LR-DFS* local relapse disease-free survival, *DM* distant metastasis, *DM-DFS* distant metastasis disease-free survival

biochemical control. Indeed, doses > 75 Gy have been associated with improved outcomes for patients with favorable, intermediate and unfavorable prognostic risk features [25–30]. However, despite the better local control rates and outcomes that can be achieved with higher doses, we know that it can be translated into a big cost in terms of toxicities, especially to the rectum and bladder. The rates of acute and late toxicities after definitive RT vary according to the published studies; generally grade 2/3 side effects can reach 40% of cases [31–33]. Literature helps us to estimate them; in fact, urinary incontinence and chronic proctitis are common and well-described side effects of radiotherapy, and sometimes they can develop into complications that can compromise the quality of life, some of which may even necessitate hospital admission or surgical intervention, namely post-treatment urinary or rectal bleeding, infections in the urinary tract or lower gastrointestinal tract and recto-urethral fistulae

[30]. The availability of three-dimensional conformal radiation therapy (3D-CRT) in addition to intensity-modulated radiation therapy (IMRT) has prompted several investigators in the last 20 years to explore the use of these technologies to escalate the radiation dose in prostate cancer avoiding worsening of the possible side effects. 3D-CRT, not long ago, had allowed a better sparing of the adjacent OARS and a resultant decrease in rectal and bladder toxicity when compared to earlier techniques [25, 28, 29]. In recent years, this advantage has even become greater with the development of IMRT that allows a sharper dose falloff gradient, concave dose distributions and narrower margins with a more conformal delivery of isodose lines to PTV. Most of the trials involving IMRT use for prostate cancer therapy have demonstrated both safety and efficacy of dose escalation supported by the results shown in the literature [34, 35]. So, image guidance has allowed for further PTV margin reduction

Table 6 Cox regression analysis (univariate and multivariate)

Variable	Univariate		Multivariate	
	p value	HR (95% CI)	*p* value	HR (95% CI)
OS				
Gleason score				
< 7		1 (ref.)		1 (ref.)
7	**0.027**	1.94 (1.08–3.48)	0.052	1.80 (1.00–3.26)
> 7	**0.001**	2.52 (1.43–4.44)	**0.008**	2.22 (1.24–3.99)
HT pre-RT				
No		1(ref.)		1(ref.)
Yes	**0.024**	1.93 (1.09–3.42)	0.13	1.58 (0.87–2.85)
LR-DFS				
Time HT pre-RT				
≤ 3 months		1 (ref)		
> 3 months	**0.025**	0.40 (0.17–0.91)		
DM-DFS				
Gleason score				
< 7		1 (ref.)		1 (ref.)
7	**0.046**	2.94 (1.02–8.48)	0.09	2.57 (0.88–7.49)
> 7	**0.02**	4.71 (1.88–12.54)	**0.01**	3.80 (1.38–10.44)
HT pre-RT				
No		1 (ref.)		1 (ref.)
Yes	**0.037**	3.12 (1.07–9.01)	0.17	2.16 (0.72–6.49)

p values less than 0.05 are shown in bold

p value, hazard ratio and 95% confidence interval; *OS* overall survival, *LR* local relapse, *LR-DFS* local relapse disease-free survival, *DM* distant metastasis, *DM-DFS* distant metastasis disease-free survival
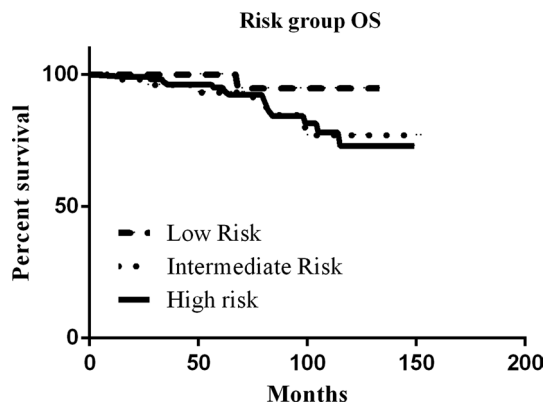
Fig. 5 OS by risk group

Fig. 6 DM-DFS by risk group

and consequently less toxicity profile. Based on the growing body of literature in this regard, IMRT has become the standard of care and most commonly employed technique.

In our study, despite the use of higher radiation doses, the use of IG-IMRT resulted in a low incidence of severe toxicities. In fact, only two patients experienced acute G3 GU toxicity (0.5%) and no one developed > G3 late GU
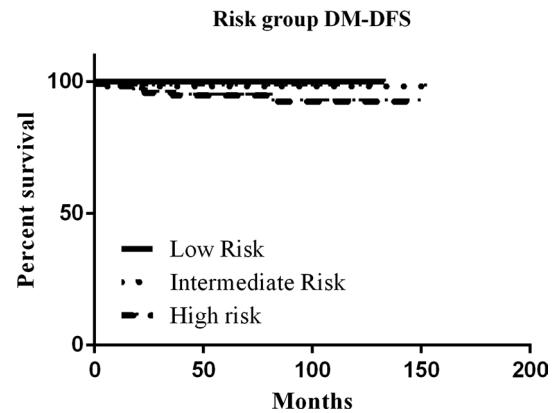
toxicity. Additionally, we recorded no G3 acute or late GI toxicity. Our results concerning the side effects with IMRT technique can confirm or even add something better to what has been reported in the literature. Recently, Michalski et al. [13] published their results from the Radiation Therapy Oncology Group 0126 Prostate Cancer Trial and demonstrated a significant reduction in acute GI/GU toxicity > G2 and a trend for a clinically meaningful reduction in late GI toxicity > G2 in patients treated with IMRT compared as 3D-CRT, while Vora et al. in an analysis of 302 patients receiving radical IMRT with a medium dose of 75.6 Gy for localized prostate cancer reported 2.6% and 2.3% rates of G3 acute and late GU toxicity as well as 0.7% and 1% rates of G3 acute and late GI toxicity, respectively [36–38].

Previous reports had noted a correlation between acute urinary symptoms and the long-term development of late urinary toxicity. Specifically, acute G2 toxicity was predictive of late severe toxicity (*p* = 0.005) [14, 29]. As a result, we investigated this relationship in our cohort but failed to re-demonstrate this effect. The presence of acute toxicity of any grade was not predictive of the development of late toxicity in either gastrointestinal or urinary systems. With regard to disease outcomes, our results are in line with other published experiences in demonstrating that definitive IG-IMRT in combination with ADT (as indicated) can achieve long-lasting disease control in low-/intermediate-risk patients.

We also showed favorable outcomes for patients with high-risk prostate cancer. Despite unfavorable prognostic factors, dose escalation offers excellent results while maintaining acceptable toxicity rates [39–41]. However, the high precision of this technique requires precise delivery methods in order to reduce to the maximum the possibility of geographical miss that may result in increased dose-volume effects on the OARs and in increased side effects, such as proctitis or cystitis [42]. In addition, missing the

target volume might result in higher rates of local failure. In our clinic, we used daily image guidance with kV and CBCT that enabled immediate pretreatment target correction. Such image guidance for dose-escalated IMRT should be the standard of care.

Several studies have analyzed both inter- and intrafractional displacements of the prostate, which ranged from 0.2 to 21 mm depending primarily on rectal and bladder filling. The magnitude and effect of organ motion of the prostate can be reduced significantly by standardized rectal and bladder filling and an accurate imaging [19] so their measures were used in our treatment.

In our study, HT pre-RT was associated with a worse survival and a higher risk of distant metastasis. Data from literature showed that HT pre-RT is associated with better outcomes in terms of survival and biochemical failure rate. Zapatero et al. [43] demonstrated that the use of long-course HT, from 3 months before high-dose RT to 2 years after, is associated with a better survival and a lower percentage of biochemical failure, without increasing radiotherapy toxicity. This was more evident for high-risk patients. Helgstrand et al. [44] published a review about the impact of HT on survival for patients affected by locally advanced prostate cancer. They showed that neoadjuvant HT, before radical prostatectomy, has no effect on survival, while neoadjuvant and adjuvant HT in combination with radiotherapy result in an increasing disease-specific and overall survival, although the duration of HT remains under debate. Gunner et al. [45], like Helgstrand, showed the same results. In their review, they show that there is no evidence to support the use of HT in low-risk patients. There appears to be an increased risk of cardiovascular morbidity and mortality associated with luteinizing hormone-releasing hormone agonists, particularly in men with preexisting cardiovascular disease, but the relevance of this in the adjuvant/neoadjuvant setting is currently unclear. A potential explanation for our results could be the heterogeneity of our population on the correlation of HT use with higher-risk disease based on D'Amico classification and consequently with a worse prognosis. Of note, this association did not persist on UVA.

Despite the retrospective nature of this study, we consider our conclusions to be informative and relevant. A particular strength of this analysis is that all of the patients included were treated at the same institution with the same positioning technique, identical delivery and immobilization devices, and a similar protocol for drinking and evacuation before treatment. This led to more standardization accounting for less inter- and intrafractional organ motion than in the previous reports.

Conclusions

Our data confirm the efficacy and limited toxicity of dose-escalated IG-IMRT for prostate cancer. Accurate image guidance should be mandatory and standard of care to guarantee the precision/safety of the treatment. Further improvements in treatment delivery and image guidance should be the focus of future investigation to further improve the therapeutic ratio.

Compliance with ethical standards

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