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RESEARCH ARTICLE

Influence of the technique and comorbidities in hypofractionated radiotherapy for prostate cancer

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Abstract

Purpose To analyze the differences in toxicity and biochemical relapse-free survival with hypofractionated radiotherapy with three-dimensional radiotherapy (3D-CRT) or volumetric arc therapy (VMAT) for prostate cancer taking into account comorbidity measured using the Charlson Comorbidity Index (CCI).

Methods From January 2011 to June 2016, 451 patients with prostate cancer were treated with 60 Gy (20 daily fractions). VMAT or 3D-CRT was used. Distribution by stage: 17% low-risk, 27.2% intermediate-risk; 39.2% high-risk, 16.6% very high-risk. Mean CCI was 3.4.

Results With a median follow up of 51 months, most patients did not experience any degree of acute GI toxicity (80.9%) compared to 19.1%, who experienced some degree, mainly G-I /II. In the multivariate analysis, only technique was associated with acute GI toxicity $\geq$ G2. Patients treated with VMAT had greater acute GI toxicity compared with those who received 3D-CRT (23.9% vs. 13.5%, $p = 0.005$). With respect to acute GU toxicity, 72.7% of patients experienced some degree, fundamentally G-I/II. Neither age, CCI, nor androgen deprivation therapy (ADT) were associated with greater toxicity. Overall survival at 2, 5 and 7 years was 97%, 88% and 83% respectively. The only factor with statistical significance was CCI, with a greater number of events in individuals with a CCI ≥ 4 ($p < 0.03$).

Conclusions Hypofractionated radiotherapy for prostate cancer is an effective, well-tolerated treatment even for elderly patients with no associated comorbidity. Longer follow up is needed in order to report data on late toxicity.

Keywords Prostate cancer · Hipofractionation · Image guided radiotherapy · VMAT · Charlson index

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Introduction

Prostate cancer is one of the most prevalent tumours in Spain. According to the latest data published by the Spanish cancer registries network (REDECAN), it is estimated that in 2017, prostate cancer was the second most diagnosed tumour for both sexes, and the most common tumour among men in Spain, with an incidence of approximately 30,000 cases [1].

Radiotherapy is one of the treatment options for patients with localized prostate cancer. Since the escalation of doses has proved to be superior to standard doses in controlling the disease, it has become the gold standard for treatment [2, 3]. Dose escalation was initially accompanied by an increase in toxicity, but the appearance of the technological advances represented by intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have resulted in the possibility of increasing dose without increasing side effects [4].

On the other hand, theoretical studies based on radiobiology have determined the alpha/beta ratio for prostate cancer and shown that unlike most tumours, which have an elevated alpha / beta ratio (10 Gy on average), prostate cancer could have a low alpha / beta ratio of 1.5 Gy making this cancer particularly sensitive to high doses per fraction, which in turn would improve local control because the effective biological dose (BED) is increased [5–7].

Based on this premise, several randomised phase III clinical trials (RCT) have been published that attempt to establish the role of hypofractionation in prostate cancer, using different schedules and technologies [8–19].

From the results of a recent metaanalysis of nine RCT, concluded that hypofractionation is an optimal radiation treatment. These clinical trials are heterogeneous among them, with different dose, techniques and verification systems, so toxicity results are not as good as would be expected, although non-inferiority was shown in the majority. Probably more follow-up would allow us to establish better conclusions [20–22].

On the other hand, due to advanced age some patients are not considered for curative treatment, either surgery or radiotherapy (despite the fact that there may be elderly patients without comorbidity whose life expectancy is greater than that of other younger patients), thus denying older patients a curative treatment option [23].

The aim of this study is to analyse the series of 451 patients with prostate cancer treated in our institution with hypofractionated radiotherapy with three-dimensional radiotherapy (3D-CRT) or volumetric arc therapy (VMAT); to analyse the differences in toxicity and biochemical relapse-free survival (BRFS) with both techniques, and provide information about how comorbidity measured by Charlson Comorbidity Index (CCI) influenced each group.

Patients, material and methods

From May 2011 to June 2016, 451 patients with localised prostate cancer were treated with hypofractionated radiotherapy with or without androgen deprivation therapy (ADT).

All patients were assessed by a multidisciplinary committee and staging with digital rectal examination, a magnetic resonance imaging (MRI) of the pelvis, complete blood tests, a prostate-specific antigen test (PSA), a transrectal ultrasound and a bone scintigraphy before treatment was performed. Patients with low risk prostate cancer were treated without a work-up for metastases.

Patient's CCI was calculated on the first visit. The CCI is a system of evaluating life expectancy at ten years which depends on the subject's age at the time of evaluation and the comorbidities. In addition to age, it consists of 19 items which, if present, have been found to influence the life expectancy of a subject in a concrete way. Initially conceived to assess survival at one year, it was finally developed in its definitive form for survival at ten years. The age adjusted CCI was calculated for all patients to determine the probability of their being alive at 10 years. A 75-year-old patient with no comorbidity had a CCI score of 3, which gives a probability of being alive at 10 years of 77.48% [24, 25]. Patients < 80 year with only one comorbidity (except neoplasm) have a CCI of 4, so this point was considered to establish the different study groups.

For simulation and treatment, patients were immobilized in supine position using a personalised body-fix device with ankle support. A planning CT scan of the pelvis was obtained at 5-mm intervals from the mid-abdomen to 5 cm below the ischial tuberosities with an empty rectum and a full bladder. To prepare the rectum, a laxative was prescribed to be taken for a week prior to and during the treatment. Slides were taken every 3 mm.

Based on the literature available at that time, the chosen scheme was 60 Gy in 20 fractions of 3 Gy to the prostate or to the prostate and seminal vesicles if they were T3b stage. Based on the Gallina nomogram, which establishes the risk of involvement of seminal vesicles; if the probability of them being affected was greater than 15%, they were included with a dose of 44 Gy in 20 fractions of 2.4 Gy by integrated boost.

Patients were treated using an Elekta LINAC equipped with a (120 multi-leaf collimator) and XVI®. Initially, image-guided IMRT (IG-IMRT) with VMAT and 3D-CRT with daily cone beam CT (XVI®) verification were used. Dose-volume histograms (DVH) were analysed for each case and if they fitted well with 3D-CRT this technique was used. Subsequently, all patients underwent IG-IMRT with VMAT due to shorter treatment time and more favourable DVH.

The dose was calculated such that 95% of the clinical target volume and ≥ 90% of the planning target volume (PTV) would receive the corresponding dose prescription. The results of previous studies indicated that the dose–volume constraint was 87.5% and 62.5% of the prescribed dose to < 30% and < 50% of the rectal wall, and < 50% and < 70% of the bladder wall, respectively [26]. Constraints employed in our protocol were rectum and bladder V40 < 70%.

Acute and late toxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. Acute gastrointestinal (GI) and genitourinary (GU) toxicity were assessed weekly during radiotherapy (RT) and for 1 month after the end of treatment. Late toxicity was defined as rectal or urinary symptoms occurring or persisting for six months after the end of RT. Biochemical relapse-free survival (BRFS) was defined as the interval from the last day of RT to the date of biochemical relapse, defined according to the most recent Phoenix definition of the nadir prostate-specific antigen level plus 2 ng/mL [27].

Statistical analysis

Statistical analysis was performed using SPSS 15.0 software. The association between categorical variables was studied with the chi-square test and Fisher's exact test when appropriate. The end points of interest used in this study were overall survival (OS) and biochemical recurrence free survival (BRFS). OS was defined by the time that elapsed from first treatment until the event of death due to any cause. BRFS was defined by the time that elapsed from the beginning of RT to biochemical recurrence. Patients without biochemical recurrence were censored. The pattern of occurrence of the different end points was carried out by estimating Kaplan–Meier survival curves. The threshold for significance for two-side analysis was set to $p < 0.05$.

Results

Four hundred and fifty-one patients were analysed. Their median age was 68 years (45–81). The median PSA was 9.3 ng/dl (0.51–111 ng/dl).

According to The National Comprehensive Cancer Network (NCCN) [28], which takes into account PSA level, size of prostatic involvement, findings of needle biopsy and T-stage of cancer, we classified patients as low-risk, intermediate-risk, high or very high-risk, with a corresponding 17% (77), 27.2% (124), 39% (176) and 16.6% (75), respectively. Regarding comorbidities, 78% (352 patients) presented a CCI score ≤ 4; and 22% (99 patients) > 4.

Seminal vesicles were treated in 47% of the cases; 11.5% with radical doses (prostate cancer with T3b stage) or electively (35.5%).

Regarding technique, 208 patients (46.1%) were treated with 3D-CRT radiotherapy, and 243 (53.9%) with VMAT. Table 1 summarizes the characteristics of the cohort.

With respect to the distribution of risk groups by technique, 70.1% of low-risk patients were treated with 3D-CRT and 29.9% with VMAT; intermediate-risk 63.3% with 3D-CRT and 36.7% with VMAT; high-risk 28% with 3D-CRT and 72% with VMAT, and very high-risk 40.5% with 3D-CRT and 59.5% with VMAT.

In short, more high-risk and very high-risk patients were treated with VMAT than with 3D-CRT because seminal vesicles were included, and constraints on rectum and bladder, as well as doses to the PTV, complied better with VMAT.

Regarding the associated hormonal treatment, 32.2% of tumours were treated with ADT for 6 months (intermediate-risk tumours), and 27.3% received treatment for 18 or 36 months (high or very high-risk tumours). Due to comorbidity or rejection 77% patients with intermediate-risk prostate cancer did not receive androgen deprivation therapy.

Table 1 Characteristics of the cohort

	n	%	Undetermined
Age			
< 68	213	47.2	–
≥ 68	238	52.8	
CCI			
≤ 4	352	78	–
> 4	99	22	
GS			
< = 7	295	65.4	13
> 7	143	31.7	
T-stage			
T1–T2	367	81.4	1
T3–T4	83	18.4	
Risk group			
Low	77	17	–
Intermediate	124	27.2	
High–very high	251	55.8	
ADT			
No	183	40.6	–
< 6 months	145	32.2	
> 6 months	123	27.3	
RT-ssvv			
No	239	53.0	–
Yes (elective and radical)	212	47.0	
RT technique			
3DCRT	208	46.1	–
VMAT	243	53.9	

CCI Charlson Comorbidity Index, *GS* Gleason Score, *ADT* androgen deprivation therapy, *RT-ssvv* radiotherapy for seminal vesicles

With a median follow-up of 51 months (6–88), only 1.6% (7 patients) had died due to the disease and approximately 6% of the total study population patients died due to second malignancies not related to the primary tumour. The most frequent locations of the second tumours were the lung (1.8%), bladder (1.6%) and colon cancer (1.3%).

Genitourinary and gastrointestinal toxicity were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. Acute GU and GI toxicity ≥ G2 were 26.6% and 3.8% respectively, whereas late GU and GI toxicity ≥ G2 were 2.8% and 0.9% respectively.

Most patients did not experience any degree of acute GI (rectal) toxicity (80.9%) compared to 19.1%, who experienced some degree, mainly G-I/II. In the multivariate analysis, only technique was associated with acute GI toxicity ≥ G2. Patients treated with VMAT had greater ≥ G2 acute GI toxicity compared with those who received 3D-CRT (23.9% vs. 13.5%, $p = 0.005$). Table 2 and Table 3 summarizes acute and late toxicity.

With respect to acute GU toxicity, 72.7% of patients experienced some degree, which was fundamentally G-I/II (46.1%, 25.9%). Grade III toxicity was found in 0.7%.

Only 2.7% of patients experienced any late GI toxicity, with no differences found between the techniques (VMAT 1.7% vs 3D-CRT 3.9, p: 0.14).

Regarding late GU toxicity, we found that 20.2% of patients experienced some degree (≤ G-II), which was mainly nocturia, and prevalent among previously symptomatic patients. There were no differences between techniques (20.7% in VMAT vs 19.8% 3D-CRT, p: 0.82). Neither age, CCI, nor ADT were associated with greater toxicity.

OS and BRFS were analysed according to technique, age, CCI, ADT, treatment of seminal vesicles and risk classification. Table 4 summarizes OS and BRFS analysis.

OS at 2, 5 and 7 years was 97%, 88% and 83% respectively. CCI was the only factor with statistical significance ($p = 0.03$), with a greater number of events in individuals with a CCI ≥ 4. OS at 2, 5 and 7 years in CCI ≤ 4 group was 99%, 98% and 98% respectively, whereas in the CCI group > 4 it was 93%, 90% and 90% respectively. Figure 1 shows OS by CCI.

There were no differences in 5-year biochemical relapse-free survival (BRFS) between RT techniques. Low-risk patients treated with VMAT presented a 5-year BRFS of 91% compared with 85% in patients treated with 3D-CRT. Intermediate-risk patients treated with VMAT presented a 5-year BRFS of 89% compared with 84% in those treated with 3D-CRT. High-risk patients presented a 5-year BRFS of 83% compared with 82% in VMAT and 3D-CRT respectively. Finally, VMAT patients presented a 5-year BRFS of 85% compared with 74% in 3D-CRT patients ($p = 0.42$).

Due to the high number of intermediate-risk patients who were not treated with ADT, this subgroup of patients was analysed separately but we didn't find statistically significant differences in BRFS at 2, 5 and 7 years (89% vs. 88%, 82% vs. 70%, and 79% vs 70% respectively, $p = 0.57$).

Figure 2 shows BRFS by risk group.

Table 2 Acute toxicity

Acute toxicity	Gastrointestinal(recta)l		*p*	Genitourinary		*p*
Total	No toxicity	Some degree		No toxicity	Some degree	
	365 (80.9%)	86 (19.1%)		123 (27.3%)	328 (72.7%)	
RT technique						
VMAT	185 (76.1%)	58 (23.9%)	0.005	67 (27.6%)	176 (72.4%)	0.87
3DCRT	180 (86.5%)	28 (13.5%)		56 (26.9%)	152 (73.1%)	
Age						
< 68	170 (79.8%)	43 (20.2%)	0.56	62 (29.1%)	151 (70.9%)	0.4
≥ 68	195 (81.9%)	43 (18.1%)		61 (25.6%)	177 (74.4%)	
CCI						
≤ 4	189 (78.8%)	51 (21.3%)	0.21	58 (24.2%)	182 (75.8%)	0.57
> 4	183 (81.3%)	42 (18.7%)		65 (31%)	145 (69%)	
ADT						
No	146 (79.8%)	37 (20.2%)	0.32	47 (25.7%)	136 (74.3%)	0.43
Short	123 (84.4%)	22 (15.2%)		37 (25.5%)	108 (74.5%)	
Long	96 (78%)	27 (22%)		39 (31.7%)	84 (68.3%)	
RT-ssvv						
Yes	168 (79.2%)	44 (20.8%)	0.39	64 (30.2%)	140 (69.8%)	0.19
No	197 (82.4%)	42 (17.6%)		59 (24.7%)	180 (75.3%)	

CCI Charlson Comorbidity Index, *ADT* androgen deprivation therapy, *RT-ssvv* radiotherapy for seminal vesicles, *VMAT* volumetric arc therapy, *3D-CRT* three-dimensional radiotherapy

Table 3 Late toxicity

Late toxicity	Gastrointestinal(rectal)		*p*	Genitourinary		*p*
Total	No toxicity	Some degree		No toxicity	Some degree	
	437 (96–9%)	12 (2.7%)		358 (79.4%)	91 (20.2%)	
RT technique						
VMAT	238 (98.3%)	4 (1.7%)	0.14	192 (79.3%)	50 (20.7%)	0.82
3D-CRT	199 (96.1%)	8 (3.9%)		166 (80.2%)	41 (19.8%)	
Age						
< 68	208 (97.7%)	5 (2.3%)	0.68	172 (80.8%)	41 (19.2%)	0.61
≥ 68	229 (97%)	7 (3%)		186 (78.8%)	50 (21.2%)	
CCI						
≤ 4	234 (97.5%)	6 (2.5%)	0.8	181 (75.4%)	59(24.6%)	0.6
> 4	202 (97.1%)	6 (2.9%)		176 (84.6%)	32(15.4%)	
ADT						
No	174 (96.1%)	7 (3.9%)	0.42	148 (81.8%)	33 (18.2%)	0.52
6 months	142 (97.9%)	3 (2.1%)		116 (80%)	29 (20%)	
> 6 months	121 (98.4%)	2 (1.6%)		94 (76.4%)	29 (23.6%)	
RT-ssvv						
Yes	207 (98.1%)	4 (1.9%)	0.33	165 (78.2%)	46 (21.8%)	0.44
No	230 (96.6%)	8 (3.4%)		193 (81.1%)	45 (18.9%)	

CCI Charlson Comorbidity Index, *ADT* androgen deprivation therapy, *RT-ssvv* radiotherapy for seminal vesicles, *VMAT* volumetric arc therapy, *3D-CRT* three-dimensional radiotherapy

Discussion

Escalated hypofractionated radiotherapy is an effective and well tolerated treatment even for elderly patients. From our point of view image-guided radiotherapy techniques and daily verification maximize the benefit since they achieve high doses in the target volume and low doses in the organs at risk.

Several randomised trials have studied the role of hypofractionation in prostate cancer. The studies differ substantially in techniques, doses, fractionations and systems of reporting toxicities employed, which makes comparison difficult.

Acute and late toxicity in our series have been were comparable with those reported in hypofractionation studies, and in some cases were even somewhat better. We believe that the differences found may be due to technology used (2D, four field box technique, in some cases), PTV margins (up to 1.5 cm in some series) and the daily verification system.

We observed greater acute GU toxicity (72.7%), compared to the different published series, which range between 10 and 49%, but most of which refer to ≤ G2 toxicity. On the other hand, we also see how this acute toxicity is resolved by greatly reducing the percentage of late toxicity to 20.2%, with results similar to other series, with the same treatment schedule.

Regarding acute GI toxicity, we found that patients treated with VMAT had more toxicities compared with 3D-CRT (23.9% vs 13.5%, respectively, $p = 0.005$). As mentioned above, VMAT was the technique of choice for cases that require a greater volume of irradiation when including the seminal vesicles. This increase in toxicity could therefore be more related with the mean dose to rectum and bladder than with the technique used (rectum V40 was 43.73% with VMAT vs 25.10% with 3D-CRT, $p < 0.001$).

We have focused on the CHHiP trial, since it was taken as the reference for our treatment schedule. As far as radiotherapy technique is concerned, the CHHiP trial used IMRT with "portal imaging" whereas we employed VMAT with cone beam CT. In our case, the study population included patients with seminal vesicles and a Gleason Score of 8 (who were excluded from the CHHiP trial, but not from other trials).

Our results in acute and chronic toxicity are comparable to those described in the literature. Acute GU toxicity ≥ G2 in our case was 26.6% compared to the 49.9% of the CHHiP trial, and GI toxicity of ≥ G2 was 38% vs 3.8% respectively.

Regarding chronic toxicity CHHiP reports a GI toxicity ≥ G2 of 11.9% compared to the 0.9% in ours, and a GU toxicity ≥ G2 of 11.7% vs our 2.8%. Although an initial assumption could be to conclude that these results are better, we should bear in mind that our series is a retrospective study with the limitations that this entails. In any case, it can be inferred from the results of each trial that the most advanced techniques provide less toxicity.

Table 4 OS and BRFS

	Overall survival				BRFS			
	2 years (%)	5 years (%)	7 years (%)	*p*	2 years (%)	5 years (%)	7 years (%)	*p*
RT technique								
VMAT	97	88	82	0.8	97	85	78	0.47
3D	96	87	83		95	82	77	
Age								
< 68	96	89	83	0.86	95	83	76	0.79
≥ 68	97	86	83		96	84	79	
CCI								
≤ 4	99	98	98	0.03	99	98	98	0.03
> 4	93	90	90		94	90	90	
ADT								
No	96	85	83	0.5	96	83	76	0.56
< 6 months	99	91	84		96	86	79	
< 6 months	96	87	79		96	80	80	
RT-ssvv								
No	97	87	82	0.67	96	87	78	0.18
SI	97	89	84		96	79	79	
GS								
≤ 7	97	88	87	0.22	95	84	75	0.87
> 7	96	87	74		97	84	84	
T-stage								
T1–T2	97	87	83	0.83	96	85	78	0.18
T3–T4	96	92	79		97	78	78	
Risk group								
Low	98	94	90	0.25	100	90	87	0.06
Intermediate	96	83	83		94	83	66	
High	90	83	80		96	82	79	

CCI Charlson Comorbidity Index, *ADT* androgen deprivation therapy, *RT-ssvv* radiotherapy for seminal vesicles, *VMAT* volumetric arc therapy, *3D-CRT* three-dimensional radiotherapy

Another limitation of our study is the lack of patient self-assessment questionnaires to evaluate health-related quality of life, which might have resulted in an overall decreased or increased reporting of toxicity.

Given the results of studies and the variety of patient characteristics, doses and techniques used, in 2018 Arcangeli published a systematic review and meta-analysis to determine the optimal hypofractionation scheme, according to BPFS, chronic gastrointestinal and genitourinary toxicity at 5 years (34). This study confirms the equivalence in results between conventional fractionation and hypofractionation, with a wide safety window of dose, estimated up to 3.5 Gy per fraction. However, greater follow-up is necessary to determine the optimal hypofractionation scheme and its translation to an increase in overall survival.

Taking into account the analysis of these publications, our work uses a fractionation of 60 Gy to 3 Gy per fraction in a total of 4 weeks, and includes patients of low, intermediate, high or very high-risk; without excluding patients due to age or associated comorbidity.

Delarney recently analysed a CHHiP trial subgroup of patients older than 75 years and concluded that hypofractionation is also safe for them. In the multivariate analysis performed on our series, age was not a risk factor either for toxicity or for survival free of biochemical or clinical recurrence; however, CCI was relevant for overall survival. In our opinion, CCI, which considers chronological age and other pathologies, should carry more weight than chronological age alone. We need to take into account the progressive aging of the population, and life expectancy should be assessed with reference to comorbidities, not just to age [29].

Regarding the progression of both biochemical and clinical disease, we observed high survival, with a BPFS and CPFS at 5 years of 83.8% and 94%. These figures are similar to other studies that, when compared to conventional fractionation, show a better control of local disease (Fig. 2).

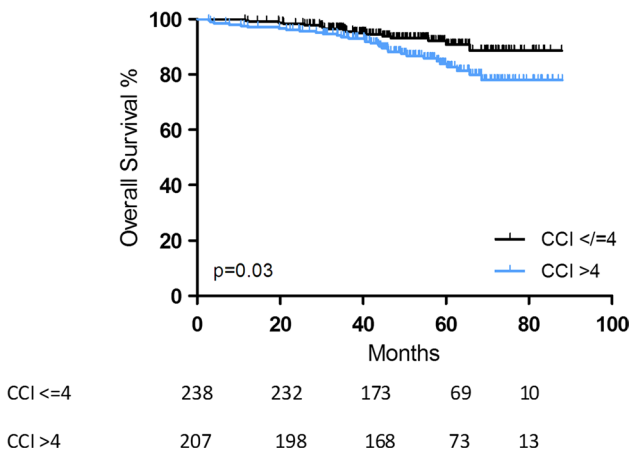

Fig. 1 Over all survival by CCI

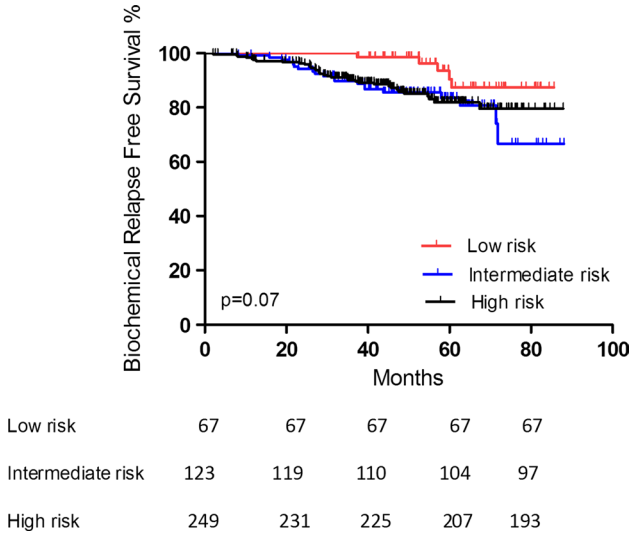

Fig. 2 Biochemical relapse free survival by risk group

As for CCI, a higher score on the comorbidity index was found to be related to a decrease in overall survival (Fig. 1). Analysing the cause of death, we find a very specific population: many are elderly men who sometimes have an associated pathology. Six per cent of our series died due to a second neoplasia. Among the second tumours are lung, bladder and colon cancer. The CHHiP trial reported 35% of second tumours in its series.

As limitations, we are faced with a retrospective study with different biases. For instance, a selection bias may condition the results of a higher toxicity with VMAT, as patients who had a lower volume of PTV were treated with 3D, which results in better statistics regarding toxicity for this group.

Conclusion

Hypofractionated radiotherapy for prostate cancer is an effective, well-tolerated treatment, with a low degree of late toxicity which reaches its highest benefit when performed with precise image-guided radiotherapy techniques and daily verification; so, it is a safe treatment, even for elderly patients with no associated comorbidities. This not only provides theoretical radiobiological advantages for tumour and healthy tissues, but also allows a reduction in the number of sessions, thus improving the quality of life and use of resources while decreasing the cost of treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate All procedures performed in the study were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent for the treatment proposed was obtained from all individual participants included in the study.

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