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Influence of technique and comorbidities in hypofractionated radiotherapy for prostate cancer

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Abstract:	Purpose To analyze the differences in toxicity and results with hypofractionated radiotherapy with three-dimensional radiotherapy (3DCRT) or volumetric arc therapy (VMAT) taking into account comorbidity measured using the Charlson Comorbidity Index (CCI). Methods From January 2011 to June 2016, 452 patients 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. Median 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 ≥ G2. Patients treated with VMAT had greater acute GI toxicity compared with those who received 3DCRT (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 (46.1%, 25.9%). No grade III toxicity was found. Neither age, CCI, nor TAD 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 (p = 0.00) was CCI, with a greater number of events in individuals with a CCI ≥ 3.5. Conclusions Hypofractionated radiotherapy for prostate cancer is an effective, well-tolerated treatment even for elderly patients with associated comorbidity. Longer follow up is needed in order to report data on late toxicity.
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Influence of technique and comorbidities in hypofractionated radiotherapy for prostate cancer

Title Page

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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 modulated intensity radiotherapy (IGRT) have resulted in the possibility of increasing dose without increasing side effects[4].

On the other hand, studies conducted in recent decades 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 has a low alpha / beta ratio of 1.5 Gy making this cancer particularly sensitive to high doses per fraction, which in turn improves local control because the effective biological dose (EBD)[5],[6], [7] is increased.

Based on this premise, several randomised clinical trials (RCT) have been published that attempt to establish the role of hypofractionation in prostate cancer, using different schedules and technologies [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19].

From the results of a recent metaanalysis of nine RCT, the conclusion reached is that hypofraction seems safe, but further follow-up would be necessary to draw more consistent conclusions[20], [21], [22].

The clinical trials studied differ in dose, techniques and verification systems, so we believe that they are quite heterogeneous and the results are not as good as might be expected.

On the other hand, the advanced age of some patients means that they are not considered as candidates for radical treatment, whether surgery or radiotherapy, because chronological age carries more weight than comorbidity (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].

Objective:

The aim of this report is to analyse the series of 452 patients with prostate cancer treated in our institution with hypofractionated radiotherapy with three-dimensional radiotherapy (3DCRT) or volumetric arc therapy (VMAT); to analyse the differences in the profile of toxicity and results with both techniques, and provide information about how comorbidity measured using the Charlson Comorbidity Index (CCI) influenced each group.

Patients, material and methods

From May 2011 to June 2016, 452 patients with localised prostate cancer were treated with hypofractionated radiotherapy with or without hormone therapy.

All patients were assessed by a multidisciplinary committee and underwent an extension study consisting of a physical digital rectal examination, a computed tomography (CT) of the abdominopelvic area, complete blood tests, a prostate-specific antigen test (PSA), a transrectal ultrasound and a bone scintigraphy before treatment was performed. The patient's CCI was calculated on the day of 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 3.5, which gives a probability of being alive at 10 years of 67.02%[24], [25].

For simulation and treatment, patients were immobilised 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. The cuts were every 3 mm.

Based on the literature available at that time, the chosen scheme was 60 Gy to 3 Gy/ fraction in 20 fractions 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 in the treatment with a dose of between 44Gy and 2.4Gy that was administered by integrated boost.

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

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].

Acute toxicity was evaluated using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer system (RTOG/EORTC). Acute rectal gastrointestinal (GI) and genitourinary (GU) toxicity were assessed weekly during radiotherapy (RT) and for 1 month after the end of treatment. Late toxicity was evaluated using a modified (''clinical'') Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management, Analytic (SOMA) scale, from which the side effects that can only be assessed by laboratory or technical investigations were eliminated[27]. Late toxicity was defined as rectal or urinary symptoms occurring or persisting for six months after the end of RT. Freedom from biochemical failure (FFBF) 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[28]

Statistical analysis:

To determine the relationship of different variables to each other, the Chi-Square test was used for descriptive analysis of frequency. Actuarial analysis of survival and time to progression was performed using the Kapan-Meier, and the relationship between survival and different prognostic factors was calculated by means of the Log-Rank test. A value of $p < 0.05$ was considered statistically significant.

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 (0.51-111ng / dl). Table 1 shows the patient characteristics.

According to The National Comprehensive Cancer Network (NCCN)[29], 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 17.1% (77), 27.3% (123), 39% (176) and 16.6% (75), respectively.

With regard to comorbidities, 50.1% (226 patients) presented a CCI score <3.5; and 49.9% (225 patients) > 3.5.

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 3DCRT radiotherapy, and 243 (53.9%) with VMAT.

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

In short, more high-risk and very high-risk patients were treated with VMAT than with 3DCRT because seminal vesicles were included, and the constraints on the rectum and bladder, as well as doses to the PTV, complied better with VMAT. Table 2

Regarding the associated hormonal treatment, 32.2% of tumours were treated with androgen blockade for 6 months (intermediate-risk tumours), and 27.3% received treatment for 18 or 36 months (high or very high-risk tumours).

With a median follow-up of 51 months (6-88), only 1.6% (7 patients) of the total study population had died due to the disease; 89.6% remained alive, 8.4% of whom suffered biochemical disease and 3.3% of whom had clinical disease (including adenophatic, bone and visceral involvement) (Figures 1 and 2). 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 (1.3%).

Genitourinary and rectal toxicity were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. Considering the excellent tolerance of the treatment, this variable was dichotomised into absence versus presence of toxicity. Tables 3 and 4 show the main toxicities.

Global acute GU and GI toxicity ≥ G2 were 26.6% and 3.8% respectively, whereas global chronic GU and GI toxicity ≥ G2 were 2.8% and 0.9% respectively.

Most patients did not experience any degree of acute 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 rectal toxicity ≥ G2. Patients treated with VMAT had greater acute rectal toxicity compared with those who received 3DCRT (23.9% vs. 13.5%, p = 0.005).

With respect to acute urinary toxicity, 72.7% of patients experienced some degree, which was fundamentally G-I/II (46.1%, 25.9%). No grade III toxicity was found.

Only 2.7% of patients experienced chronic rectal toxicity, with no differences found between the techniques (VMAT 1.7% vs 3DCRT 3.9, p: 0.14).

With regard to chronic urinary 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% 3DCRT, p: 0.82). Neither age, CCI, nor hormonal blockade were associated with greater toxicity.

Table 5

Survival was analysed by factor according to technique, age, CCI, androgen blockade, treatment of vesicles, Gleason score, T stage and risk classification. (Table 6).

Overall survival at 2, 5 and 7 years was 97%, 88% and 83% respectively. The only factor with statistical significance (p = 0.00) was CCI (Table 6), with a greater number of events in individuals with a CCI greater than or equal to 3.5. Survival at 2, 5 and 7 years in the CCI group <3.5 was 99%, 94% and 90% respectively, and in the CCI group ≥ 3.5 it was 95%, 82% and 76% respectively.

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

Global BRFS at 2, 5 and 7 years was 96%, 83.8% and 77.9% respectively. Biochemical recurrences were 27 (11.1%) with VMAT and 33 (15.9%) with 3DCRT but this did not reach statistical significance (p = 0.13)

Figures 1,2,3.

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 in the organs at risk.

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

In our group of patients, overall, acute and chronic toxicity were acceptable if compared with the figures reported in hypofractionation studies, and in some cases were even somewhat better. We believe that the differences found may be due to the 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.

In the series where radiotherapy was carried out with the 2D / 3D four field box technique, the toxicity reported was greater than for IMRT, placing our series at values similar to those reported in the series that employed IMRT with daily image verification techniques.

With the results obtained, we observed a greater impact of acute urinary toxicity (72.7%), compared to the different published series, which range between 10 and 49%, but most of which refer to $\leq$ G2 toxicity. However, in our case, when we dichotomised the sample, we reflected the total percentage of patients who had some degree of toxicity. On the other hand, we also see how this acute toxicity is resolved by greatly reducing the percentage of chronic toxicity to 20.2%, with results similar to other series, with the same treatment scheme.

Regarding acute gastrointestinal toxicity, we found statistical significance in the technique using VMAT vs 3DCRT (23.9% vs 13.5%, respectively ($p = 0.005$). As we analysed the data, we found that 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 bear more relation with the total volume than with the technique used. Rectum V40 was 43.73% with VMAT vs 25.10% with 3DCRT ($p <0.001$)

We have focused on the CHHiP trial, since it was taken as the reference for our treatment schadule. 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. With regard to 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.

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 3.5Gy 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.[30]

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[31].

As for CCI, a higher score on the comorbidity index was found to be related to a decrease in overall survival. 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 chronic 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 associated comorbidity. 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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Table 1

		n	%	Undetermined
Age	<68	213	47.2	-
	≥68	238	52.8	
CCI	<3.5	226	50.1	-
	≥3.5	225	49.9	
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	76	16.9	-
	INTERMEDIATE	124	27.5	
	HIGH-VERY HIGH	251	55.7	
ADT	NO	183	40.6	-
	< 6 Mo	145	32.2	
	> 6 Mo	123	27.3	
RT-ssvv	NO	239	53.0	-
	YES (ELECTIVE & RADICAL)	212	47.0	
RT technique	3DCRT	208	46.1	-
	VMAT	243	53.9	

Table 2

		VMAT	3D	p
Rectum	**Volume**	54.13 cc	55.16 cc	
	Mean dose	35.65 Gy	28.60 Gy	0.001
	V40	43.73%	25.10%	0.001
	V50	15.28%	11.85%	0.001
	V60	0.88%	1.15%	0.27
Bladder	**Volume**	83.02	86.75	
	Mean dose	40.38 Gy	31.41Gy	0.01
	V40	53.86%	36.10%	0.01
	V50	40.26%	25.85%	0.01
	V60	17.27%	5.60%	0.01

Table 3

ACUTE TOXICITY		RECTAL		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	<3.5	182 (80.5%)	44 (19.5%)	0.82	59 (26.1%)	167 (73.9%)	0.57
	≥3.5	183 (81.3%)	42 (18.7%)		64 (28.4%)	161 (71.6%)	
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%)	

Table 4

CHRONIC TOXICITY		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
	3DCRT	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	<3.5	222 (98.2%)	4 (1.8%)	0.23	178 (78.8%)	48 (21.2%)	0.6
	≥3.5	215 (96.4%)	8 (3.6%)		180 (80.7%)	43 (19.3%)	
ADT	NO	174 (96.1%)	7 (3.9%)	0.42	148 (81.8%)	33 (18.2%)	0.52
	6 Mo	142 (97.9%)	3 (2.1%)		116 (80%)	29 (20%)	
	>6 Mo	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%)	

Table 5

Acute G-I toxicity		No	Some degree	p
Age	<68	170 (37.7%)	43 (9.5%)	0.56
	≥68	195 (43.2%)	43 (9.5%)	
CCI	<3.5	182 (40.4%)	44 (9.8%)	0.83
	≥3.5	183 (40.6%)	42 (9.3%)	
ADT	No	146 (32.4%)	37 (8.2%)	0.32
	6 mo	123 (27.3%)	22 (4.9%)	
	> 6 mo	96 (21.3%)	27 (6%)	
RT-ssvv	No	197 (43.7%)	42 (9.3%)	0.39
	Yes	168 (37.3%)	44 (9.8%)	
GS	≤7	239 (54.6%)	56 (12.8%)	0.74
	> 7	114 (26%)	29 (6.6%)	
T-stage	T1-T2	298 (66.2%)	69 (15.3%)	0.72
	T3-T4	66 (14.7%)	17 (3.8%)	
Risk group	Low	64 (14.2%)	12 (2.7%)	0.56
	Intermediate	97 (21.5%)	27 (6%)	
	High-very high	204 (45.2%)	47 (10.4%)	
Rt technique	VMAT	185 (41%)	58 (12.9%)	0.05
	3D	180 (39.9%)	28 (6.2%)	

Table 6

		OVERALL SURVIVAL				BPFS				CPFS			
		2 yr.	5 yr.	7 yr.	p	2 yr.	5 yr.	7 yr.	p	2 yr.	5 yr.	7 yr.	p
RT technique	VMAT	97%	88%	82%	0.8	97%	85%	78%	0.47	99%	96%	93%	0.43
	3D	96%	87%	83%		95%	82%	77%		99%	92%	91%	
Age	<68	96%	89%	83%	0.86	95%	83%	76%	0.79	98%	93%	89%	0.3
	>=68	97%	86%	83%		96%	84%	79%		100%	94%	94%	
CCI	<3.5	99%	94%	90%	0.0	96%	86%	80%	0.15	99%	97%	94%	0.11
	>=3.5	95%	82%	76%		95%	81%	75%		99%	90%	90%	
ADT	NO	96%	85%	83%	0.5	96%	83%	76%	0.56	98%	95%	95%	0.01
	< 6 Mo	99%	91%	84%		96%	86%	79%		100%	97%	95%	
	> 6 Mo	96%	87%	79%		96%	80%	80%		98%	86%	81%	
RT-ssvv	NO	97%	87%	82%	0.67	96%	87%	78%	0.18	99%	97%	96%	0.01
	SI	97%	89%	84%		96%	79%	79%		99%	89%	85%	
GS	<=7	97%	88%	87%	0.22	95%	84%	75%	0.87	99%	95%	95%	0.04
	>7	96%	87%	74%		97%	84%	84%		98%	90%	84%	
T-stage	T1-T2	97%	87%	83%	0.83	96%	85%	78%	0.18	99%	95%	94%	0.02
	T3-T4	96%	92%	79%		97%	78%	78%		97%	88%	80%	
Risk group	LOW	98%	94%	90%	0.25	100%	90%	87%	0.06	100%	100%	100%	0.03
	INTER-MEDIATE	96%	83%	83%		94%	83%	66%		99%	95%	95%	
	HIGH	90%	83%	80%		96%	82%	79%		98%	91%	87%	

Compliance with Ethical Standards

DECLARATIONS:

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

2. 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.