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Original Article

Late toxicity after single dose HDR prostate brachytherapy and EBRT for localized prostate cancer: Clinical and dosimetric predictors in a prospective cohort study

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ABSTRACT

Purpose: To describe the genitourinary (GU) and gastrointestinal (GI) late toxicity profile and to analyse the clinical and dosimetry outcomes predictors of the combination of EBRT and high-dose-rate (HDR) prostate brachytherapy (BT) for localized prostate cancer.

Materials and methods: Between January 2012 and May 2017, 210 patients were included in a prospective protocol. Treatment consisted in HDR-BT (15 Gy single fraction) plus 3DCRT (37.5 Gy/15 fractions). Univariate and multivariate logistic regressions were used to analyse the impact of variables on late toxicity.

Results: Median age was 71 (56–82), 12.4% of patients had low, 44.3% intermediate and 41% high-risk prostate cancer. Median prostate volume was 28.4 cc. Median V100, V150, V200 were 98.2%, 27% and 7.4% respectively. Median urethra Dmax, rectum D1cc and D2cc, were 113.5%, 62.2%% and 54.2% respectively.

After a median follow-up of 41 months (5–75) late G2 GU and GI late toxicity was observed in 14.8% and 5.2% of patients respectively. Late G3 GU and GI toxicity occurred in 0% and 1% of patients respectively.

There were no outcome correlations with late $G \geq 2$ GU toxicity on univariate analysis. Previous cardiovascular comorbidity ($p = 0.042$), and dose to the rectum D2cc ($p = 0.016$) and D1cc ($p = 0.017$) were associated with $G \geq 2$ GI toxicity.

Multivariate analysis showed that rectum D1cc (HR11.56; 95%CI 1.4–92.1; $p = 0.021$) and prior history of cardiovascular disease (HR3.6; 95%CI 1–12.9; $p = 0.045$) remained independent predictors of $G \geq 2$ GI toxicity.

Conclusions: There is a low incidence of late GU and GI morbidity using single fraction HDR-BT and hypofractionated EBRT. Previous cardiovascular disease and dose to the rectum were observed to correlate with GI toxicity.

Definitive radiotherapy is an effective and well-established treatment for localized prostate cancer. There is level 1 evidence proving that better biochemical control is achieved when dose escalation is applied to the prostate [1,2]. Besides, it is believed that due to the radiobiology characteristics of prostate cells (low alpha/beta ratio), the delivery of higher radiation doses per fraction could theoretically improve the efficacy of the treatment. In this regard, prostate brachytherapy (BT) allows the delivery of much larger doses per fraction and greater total doses than those achieved with external beam radiotherapy (EBRT) alone. Randomized trials and observational studies have confirmed this advantage by demonstrating improvements in biochemical control, metastasis free survival and cancer-specific mortality [3–5]. However, there is a rising concern over the potential morbidity of combined treatments based upon the report of toxicity rates in the ASCENDE-RT trial, a British phase III trial, and other observational series [4,6–8].

The improvement in BT techniques through more precise and reliable procedures could improve dramatically the morbidity

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associated with these approaches. It was our belief that HDR offers dosimetry and radiobiological advantages over permanent seeds. We hypothesized that the implementation of multi-parametric magnetic resonance (mpMRI) and transrectal ultrasound (TRUS) fusion protocol in real-time planning, could further reduce morbidity.

This is a late toxicity analysis of a prospective cohort of patients diagnosed with localized prostate adenocarcinoma who received a combination of 1 fraction of 15 Gy real-time HDR-BT and supplementary EBRT.

Materials and methods

A prospective treatment protocol was started at Cruces University Hospital in 2010 assessing the combination of prostate brachytherapy and EBRT in the management of localized prostate cancer. This study is a GU and GI late toxicity prospective analysis of 210 consecutive patients included in this protocol from January 2012 to May 2017. Eligibility criteria for this single institution protocol included: histological confirmation of prostate adenocarcinoma, clinical stage cT1-cT3 and N0-N1. Patients with clinical stage cT3a-b patients were only included if the extension of extra-prostatic and seminal vesicle disease coverage was deemed feasible by the treating physician. Performance status score ≤ 2 was required (Eastern Cooperative Oncology Group ECOG).

Short-term (6 months) and long-term (18–24 months) androgen deprivation therapy (ADT) was prescribed according to NCCN risk group stratification (i.e. short-term for high-tier intermediate risk and long term or high-risk patients) provided there were no contraindications.

Patients were not excluded from the study based upon large prostate size. If the prostate volume at presentation was greater than 60 cc a short-term course of ADT was prescribed to shrink the prostate target.

No IPSS restriction was used, however patients with severe obstructive symptomatology were not considered candidates for HDR brachytherapy and received EBRT exclusively.

Treatment protocol

Our HDR real time MRI-TRUS fusion protocol has been previously described [9,10]. Briefly, treatment consisted of a single real time HDR fraction of 15 Gy, followed in 2–4 weeks by EBRT (37.5 Gy in 15 fractions or 46 Gy in 23 fractions). The brachytherapy implant was performed under general or spinal anaesthesia as an outpatient procedure. An MRI-TRUS fusion protocol using axial T2-weighted volumetric sequence (VISTA) is performed in every patient. The MRI and TRUS-MRI fusion techniques have been described elsewhere [9]. If the patient underwent neo-adjuvant ADT, cognitive fusion by the treating physician was performed instead of the TRUS-MRI fusion protocol.

The organs at risk (OAR) defined in every implant were the rectum, the urethra and the Folley catheter balloon as a surrogate for the dose delivered to the bladder neck.

The homogeneity parameters used for implant dose optimization aimed for prostate V100 >95%, V150 of 25–33%, and V200 <8%, where Vn is the fractional volume of the organ that receives n% of the prescribed dose; maximum point dose inside the urethral volume (urethral Dmax) <115%; and the dose to 1 cc of rectal wall (RD1 cc) is limited to <70% of the prescribed dose.

EBRT was delivered using conformal 3D technique. The clinical target volume (CTV) included the whole prostate. The seminal vesicles were completely encompassed by the CTV in T3b tumours, in high risk or high-tier intermediate risk tumours the most proximal 2 cm were included in the CTV. The planning target volume (PTV) was created adding 5 mm posteriorly and 7 mm in any other direction to the CTV. Regional lymph nodes were irradiated only in case of nodal invasion.

Patient follow-up and toxicity assessment

Every event occurring 3 months after the end of EBRT was classified as late toxicity. Late GU and GI toxicity events were classified and graded according to the Common Terminology Criteria for Adverse Events (CTCAEs) V4.0 scoring system.

Baseline patient symptom and morbidity status was recorded before radiation therapy and at every follow-up visit by the treating physician. Patient follow-up was programmed 1 month after EBRT, every 6 months for the first three years and once a year thereafter.

Statistical analysis

A descriptive analysis was carried out for all relevant clinical and dosimetric variables using median and range for continuous variables and percentages for categorical variables.

The highest chronic GU and GI toxicity was recorded at each visit and graded from 0 to 5 according to CTCAE. Cumulative incidences were calculated using the Kaplan–Meier method. A comparison of dosimetry mean values between patients with and without $G \geq 2$ GU and GI toxicity was performed using the T-test for independent variables.

Univariate and multivariate logistic regression were used to analyse the impact of dosimetric and clinical variables into late toxicity.

Variables included in the univariate analysis were previous history of cardiovascular disease, hypertension, diabetes mellitus, the use of antiplatelet or anticoagulant drugs, prostate volume at diagnosis, IPSS, year of brachytherapy implant (2012–2014 vs 2015–2017), clinical T stage, use of androgen deprivation therapy, prostate V100, prostate V125, prostate V150 and prostate V200. In addition, for GI toxicity analysis we included the presence of haemorrhoids or diverticulosis, Rectum Dmax, Rectum D1cc and Rectum D2cc whereas for GU toxicity we included previous trans-urethral resection (TUR) and Urethra Dmax. The cut-off value employed to perform the analysis was the median of each variable in our series (Table 2).

All variables with a P value < 0.15 in the univariate analysis were selected and included in the stepwise selection procedure of the multivariate analysis. We eliminated the variable with the highest p-value and repeated the model until all variables are statistically significant ($p < 0.05$). The goodness of fit of the model was tested with the Hosmer–Lemeshow test and the predictive ability of the final multivariate model was assessed by the area under the receiver operating characteristic curve (AUC) analysis.

All statistical analyses were performed using the Statistical Package for Social Sciences, version 23.0 software.

Results

Two hundred and ten patients were included in the analysis. The median follow-up for this series was 41 months (5–75). Twenty-six (12.4%) patients had low, 93 (44.3%) intermediate and 86 (41%) high-risk prostate cancer. Median initial PSA was 11 ng/mL (range 2.9–156 ng/mL); 69.5% patients had T1c and 52.9% had Gleason score 7 tumours. Median baseline IPSS was 5 (range 0–28). Patient's demographics and brachytherapy dosimetry are summarized in Tables 1 and 2.

Table 1
Patients' characteristics. iPSA (initial PSA), ECOG (Easter Cooperative Oncology Group), EBRT (external-beam radiotherapy).

	N	Percentage
Median Age (range)	71 (56–82)	
Gleason score		
6	45	21.4%
7	111	52.9%
8	27	12.9%
9	24	11.4%
10	2	1%
Median iPSA ng/mL (range)	11 (2.9–156)	
Conventional T stage		
1b	3	1.4%
1c	146	69.5%
2a	29	13.8%
2b	6	2.9%
2c	13	6.2%
3a	11	5.2%
3b	1	0.5%
MRI T stage		
<T2b	48	22.9%
T2c	60	28.6%
T3a	62	29.5%
T3b	22	10.5%
Not available	18	8.6%
Risk Group		
Low	26	12.4%
Intermediate	93	44.3%
High	86	41%
ECOG score		
0	45	21.4%
1	164	78.1%
2	1	0.5%
EBRT dose		
46 Gy in 23 fractions	13	6.1%
37.5 Gy in 15 fractions	197	93.8%

Table 2
Implants' dosimetric characteristics.

	Median	Range
Prostate vol. cc	40	5–153
Number of needles	16	9–18
Prostate		
V100	98.2	80.9–99.9
V125	61.7	44–71.8
V150	26.4	2.5–36.5
V200	7.1	0.1–29.4
D90	110.4	106.1–115
Urethra		
Dmax	113.5	103.4–118.9
D10	109.4	101.8–127.4
D1cc	84.1	5.9–190
Rectum		
Dmax	81.1	5.0–190
D1cc	62.2	4–97.8
D2cc	54.2	4.3–70.5

GU toxicity

The crude incidence of late grade 2 GU (G2) toxicity was 14.8% (31 patients). There were no grade 3, 4 or 5 events. The 5-year cumulative G2 GU morbidity incidence was 15.4%. Forty-five per cent of patients (14 patients) suffering G2 GU toxicity had increased urinary frequency and 26% (8 patients) had dysuria. The other grade 2 events were due to urethral strictures (3 patients), incontinence (3 patients), haematuria (2 patients) and retrograde ejaculation (1 patient).

G2 GU symptoms were resolved in 21/31 cases at the time the most recent analysis. Median time to the development of G2 GU toxicity was 13.5 month (3–63.6). The median duration of G2 events was 8.3 months (3.6–30.6).

None of the outcome variables were significantly associated with the development of late $G \geq 2$ GU toxicity on univariate analysis and therefore no multivariate analysis was performed (Table 3).

There was no significant difference in the comparison of dosimetry mean values between patients with and without $G \geq 2$ GU toxicity (Supplementary material 2).

GI toxicity

The incidence of late G2 and G3 GI toxicity was 5.2% (11 patients) and 1% (2 patients) respectively. No grade 4 or 5 events were observed. The 5-year $G \geq 2$ GI toxicity cumulative incidence was 10% and the 5-year G3 GI toxicity cumulative incidence was 1.2%. The 2 G3 events reported consisted in rectal bleedings. Regarding G2 toxicity, 5 patients had rectal bleeding and other 5 patients had proctitis. One case of G2 rectal fistula was recorded.

Of the 13 patients presenting with $G \geq 2$ GI toxicity, 10 were free of toxicity by the time of the current analysis. Median time to the development of $G \geq 2$ GI toxicity was 11 months (3–44.2). The median duration of the events was 6 months (0.2–9.5).

On univariate analysis, previous cardiovascular disease ($p = 0.042$), rectum D2cc ($p = 0.016$) and rectum D1cc ($p = 0.017$) were associated with grade ≥ 2 GI toxicity. On multivariate analysis rectum D1cc (HR 11.56; 95% CI 1.4–92.1; $p = 0.021$) and prior history of cardiovascular disease (HR 3.6; 95% CI 1–12.9; $p = 0.045$) remained significant predictors of grade ≥ 2 GI toxicity (Table 4, Supplementary material 1).

There was no significant difference in the comparison of dosimetry mean values between patients with and without $G \geq 2$ GI toxicity (Supplementary material 3).

Discussion

Our results show that the combination of HDR brachytherapy and hypo-fractionated EBRT is a safe approach to localized prostate cancer management with excellent toxicity results. In this prospective analysis no severe GU or GI toxicity (i.e. grade 4 or 5) was observed. Besides the proportion of grade 3 events was rather low. No grade 3 GU event was recorded and just 1% of our population suffered from grade 3 GI toxicity. Even the incidence of grade 2 events was fine, just 14.8% and 5.2% of our patients developed grade 2 GU and GI toxicity respectively. Moreover, increased urinary frequency and dysuria accounted for the vast majority of GU grade 2 events and these events can be successfully managed through medical support treatment. No severe urethral strictures or fistulae were observed. Also, most of the events were transient with a median duration of G2 toxicity around 8 months.

Dose escalation improves local control in prostate cancer and lowers the risk of biochemical failure and is considered nowadays the standard of care in EBRT protocols [1,2]. In addition to dose escalation, the use of hypofractionation is an important radiobiological advantage of HDR brachytherapy because prostate cancer cells have a low alpha/beta ratio in the linear quadratic model of radiation dose response [11–13]. In this scenario the combination of prostate brachytherapy and EBRT offers the advantage of highly conformal dose distribution, hypofractionation and dose escalation while sparing the adjacent organs at risk and potentially preventing from increased toxicity.

Two randomized clinical trials performed with modern permanent seeds and HDR brachytherapy techniques have demonstrated a significant improvement in biochemical control with brachytherapy in combination with EBRT compared to EBRT alone in intermediate and high-risk prostate cancer (10-year biochemical relapse free survival (b-RFS) 46% vs 39% (p 0.04) in the British trial and

Table 3
Univariate and multivariate model for late $G \geq 2$ GU toxicity.

	Univariate		Multivariate
	p-value	OR (IC 95%)	
CV disease	0.5	0.75 (0.3–1.7)	
Hypertension	0.64	1.19 (0.5–2.6)	
Diabetes mellitus	0.64	0.76 (0.2–2.3)	
Use of anticoagulants	0.24	2.3 (0.6–9.1)	
Use of antiaggregants	0.99	–	
Manipulation of urinary tract	0.79	0.81 (0.2–3.7)	
BPH	0.14	2.5 (0.7–8.5)	
Use of ADT	0.76	0.88 (0.4–2)	
IPSS $\geq$ 15	0.41	1.64 (0.5–5.3)	
Year of brachytherapy implant < 2015	0.45	1.35 (0.6–3)	
Clinical T stage < T3	0.82	1.1 (0.5–2.3)	
Prostate D90 > 110.43%	0.26	2.32 (0.5–10.2)	
Prostate V100 > 95%	0.31	0.42 (0.07–2.2)	
Prostate V125 > 61.7%	0.49	1.54 (0.4–5.3)	
Prostate V150 > 26.44%	0.41	1.38 (0.6–3)	
Prostate V200 > 7.1%	0.75	0.88 (0.4–1.9)	
Urethra Dmax > 113.58%	0.44	0.73 (0.3–1.6)	
Urethra D10 > 109.4%	0.41	1.38 (0.6–3)	
Urethra D1cc > 84.13%	1	1 (0.4–2.2)	

Numbers in bold indicate statistically significant *p*-values.

Table 4
Univariate and multivariate model for late $G \geq 2$ GI toxicity.

	Univariate		Multivariate	
	p-value	OR (IC 95%)	*p*-value	OR (IC 95%)
CV disease	**0.042**	3.32 (1–10.6)	**0.045**	3.64 (1.02–12.9)
Hypertension	0.54	0.7 (0.2–2.2)		
Diabetes mellitus	0.97	0.97 (0.2–4.6)		
Use of anticoagulants	0.68	1.56 (0.2–13.2)		
Use of antiaggregants	0.99	–		
Use of ADT	0.95	0.96 (0.3–3.2)		
IPSS $\geq$ 15	0.61	3.8 (0.9–15.7)		
Year of brachytherapy implant < 2015	0.08	6.32 (0.8–49.7)		
Clinical T stage < T3	0.65	0.76 (0.2–2.5)		
Prostate V100 > 98.15%	0.26	0.5 (0.1–1.7)		
Prostate V125 > 61.7%	0.99	–		
Prostate V150 > 26.44	0.24	2.11 (0.6–7.2)		
Prostate V200 > 7.1%	0.08	3.3 (0.8–12.6)		
Haemorrhoids/diverticulosis	0.37	2.05 (0.4–10)		
Rectum Dmax $\geq$ 81.15%	0.24	0.48 (0.1–1.6)		
Rectum D1cc > 62.24	**0.017**	12.5 (1.6–98.8)	**0.021**	11.56 (1.4–92.1)
Rectum D2cc > 54.2	**0.016**	12.62 (1.6–99.7)	NS	

9-year b-RFS 83% vs 62% ($p < 0.001$) in ASCENDE-RT) [3,4]. Also, a large data base analysis [14] has reported better metastasis free survival and cancer-specific mortality for the combination of prostate brachytherapy (using either permanent seeds or HDR brachytherapy) and EBRT compared to radical prostatectomy or EBRT alone in Gleason 9 or 10 prostate cancer. However, concerns have been raised about the morbidity of the combination of brachytherapy (either LDR or HDR) and EBRT, which has been considered one of the major drawbacks of this technique, especially the development of urethral strictures [15]. Grade 3 GU and GI toxicity range from 1.4% to 31% and 0% to 30% respectively among series [8,16–31]. Specifically, the incidence of urethral strictures ranges from 0% to 15.3% in HDR series [4,17,20,24,25,31,32]. This wide range of values reflects both the variation in morbidity reporting and differences in brachytherapy techniques between institutions.

There are two randomized trials of brachytherapy used as a boost to EBRT.

Hoskin et al. phase III randomized trial compared 55 Gy in 20 fractions of EBRT alone vs 35.75 Gy in 13 fractions plus an HDR-BT boost of 2 doses of 8.5 Gy in 24 hours. The cumulative incidence of severe GU events in the HDR-BT arm at 5- and 7-years were 26% and 31% [4,6]. Most events were transient; the maximum prevalence of severe urinary incidents was 14% at 5.5 years.

The ASCENDE-RT trial consisted of 46 Gy EBRT to the prostate and the pelvic lymph nodes followed either by a permanent seed boost of 115 Gy I125 (LDR-PB) or an EBRT boost to 78 Gy in 2 Gy fractions [7]. The incidence of both acute and late GU and acute GI toxicity shown in the experimental arm was significantly higher as compared to the EBRT group. The 2 and 5-year cumulative incidence of late G3 GU morbidity was 7.7% at 2 years and 18.4% at 5 years for LDR-PB versus 3.4% and 5.2% for EBRT boost. Urethral strictures accounted for nearly half of the grade 3 GU events. Nonetheless, many of the late GU events were transient so the prevalence of grade 3 toxicity at 5 years dropped to 8.6% in the LDR-PB arm and to 2.2% in the EBRT arm but the differences between treatment arms persisted ($p = 0.058$).

The toxicity results reported in our cohort are appreciably lower than those described in the aforementioned trials. In our opinion, this could be partly explained by our HDR-brachytherapy boost technique and the use of real-time MRI-TRUS fusion for treatment planning.

High dose rate brachytherapy has some theoretical advantages over low dose rate implants, such as used in the ASCENDE-RT trial.

HDR treatment can be delivered in whatever fractionation is most radiobiologically advantageous. The rapid dose fall-off inherent to brachytherapy can be applied to the best physical and radiobiological advantage with HDR brachytherapy.

On the other hand, the HDR prostate boost in the experimental arm described by Hoskin et al was delivered using a CT based planning technique that requires patient displacement after completing the implant in order to acquire CT images. The treatment technique implemented in our department consists on a real-time planning procedure that eliminates the uncertainties associated with patient movement.

To our knowledge, the present work is the first prospective report of late morbidity in a cohort of patients treated with a real-time mpMRI-TRUS fusion HDR-BT protocol.

Over the last years, several groups have reported late toxicity outcomes after HDR-BT using either CT (majority) or TRUS without MRI real-time planning are available [16–21,24–31]. Most of these studies are retrospective analyses. Grade 3 morbidity incidence ranges from 0 to 3.6% for GI and from 0.5 to 10.6% for GU events. Grade 2 toxicity is even more variable, $G \geq 2$ GI ranges from 0.3 to 19% and $G \geq 2$GU from 15 to 59%. Since brachytherapy dose, fractionation and toxicity reporting methods vary widely among series, it is difficult to make definitive conclusions regarding optimal planning methodology. The variability in outcomes could be partly explained by the heterogeneity of techniques, treatment schemes, volume definitions and OARs constraints among groups. Among these series, only two report exclusively results of a treatment scheme similar to our protocol (i.e. HDR-BRT 15 Gy single fraction plus EBRT) and have achieved enough follow-up to make comparisons, one of them used CT-based HDR [17] whereas the other reports results on a real-time protocol [26]. Incidence of severe adverse events correlate well with our data and remained fairly low in all series: G3 GU and GI toxicity ranged from 0 to 4% and 0 to 1% respectively. G2 toxicity on the other hand differed: G2GU was 59% and G2GI was 42% in the CT-based HDR cohort whereas G2 GI was just 6.7% in the real-time study (the latter did not analysed GU morbidity).

The identification of predictive factors for outcomes is an important finding. Few groups have reported such analysis and the results are rather inconsistent. In ASCENDE-RT several IPSS values were associated with GU toxicity, but dosimetry parameters were not. Also, V200 in the prostate apex, urethra D30 and D5 and IPSS and the appearance of urethral strictures after LDR-BT [33]. Other clinical factors that appear to have an impact on toxicity after HDR-BT are prostate volume and Urethra D10 [17].

In our cohort, higher radiation doses to lower rectum (i.e. D1 cc > 62%) predicted the appearance of grade ≥ 2 GI toxicity. This replicates results published in other HDR series [26,28]. Chicas-Sett et al. found a relationship between rectum D2cc, and Kragelj and cols reported an association between the rectum D1cc and a deterioration of rectal problems. Interestingly, prior history of cardiovascular disease was also related to the development of grade ≥ 2 GI toxicity, this relationship has already been described in EBRT series [34].

Thus, despite the promising results in disease control reported in the aforementioned trials and observational studies, the morbidity outcomes showed in the experimental arms of the ASCENDE-RT and Hoskin et al. trials could be holding back the implementation of protocols incorporating the combination of brachytherapy and EBRT for localized prostate cancer. The toxicity rates observed in our series with no severe toxicity events, very few G3 and encouraging low rate of G2 events confirm that, when modern technology and protocols are used, the combination of prostate BT and EBRT is a feasible and safe approach for patients presenting prostate adenocarcinoma.

The low toxicity profile in our study compares well to the control arm of the ASCENDE-RT trial and it is as good or better than other EBRT and as noted in recent review of toxicity (3% G3 GU in standard fractionation IMRT and 7% for hypofractionation [35]).

The authors acknowledge the inherent selection bias in such an observational study. Our prospective study design, however, improves the reliability of the findings. One might argue that the follow-up time might not be enough to fully comprehend the morbidity profile of the studied technique. Nonetheless, the median time to the development of the events and their median duration suggest that a median FU of 41 months is representative enough.

The combination of HDR-BT and EBRT in the treatment prostate adenocarcinoma is a safe procedure with a toxicity profile comparable to exclusive EBRT schemes when highly conformal BT modalities and accurate imaging techniques are used. Therefore, fear for late significant late complications should not hold back the implementation of these strategies in radiation oncology departments.

Conflict of interest statement

None of the authors have conflicts of interest or financial disclosure.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.02.018.

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