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Original Article

High-dose-rate brachytherapy combined with hypofractionated external beam radiotherapy for men with intermediate or high risk prostate cancer: analysis of short- and medium-term urinary toxicity and biochemical control

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Abstract: The best management of localized and locally advanced prostate cancer remains controversial, but there are clinical evidences that for patients considered of unfavorable outcome that dose escalation radiotherapy has a significantly better outcome. Methods: Between 2005-2009 a total of 39 unfavorable patients were treated in a phase I-II trial for dose escalation with high-dose rate (HDR)- 30 Gy given by 4 fractions BID, in two separated implants and hypofractionated conformal/tri-dimensional radiotherapy (hEBRT) – 45 Gy (3 Gy per fraction in 3 weeks), at Hospital AC Camargo, Sao Paulo, Brazil. Results: Median age of patients was 69 (range, 58-80) years old. With a median follow up of 42.5 months the highest RTOG acute severe genitourinary toxicity (GU-TX) was grade 3 in two (5.1%) patients. Late severe GU-TX was observed in one (2.6%) patient. On univariate analysis the prostate volume > 45cc (p=0.024), <11 needles per implant (p=0.038) and urethral dose >130% of prescribed dose (p<0,001) were statistical significant predictive factors. Multivariate analysis showed urethral dose >130% as the only predictive factor for late severe GU-TX, p=0.017 (95%CI–1.39-29.49), HR-6.4. The actuarial overall survival, biochemical control and disease specific survival rates for the entire group at 3.5-years were 92.0%, 87.6% and 96.9%, respectively. Conclusion: HDR combined to hEBRT is well tolerated in the short and medium term. Acute toxicity was minimal and improved outcomes in terms of reduced late toxicity can be achieved using at least 11 needles and prostate with no more than 45cc to be implanted. The maximum urethral dose should be kept bellow 130% of prescribed dose.

Keywords: Prostate cancer, radiotherapy, brachytherapy, toxicity, biochemical control

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer in the United States. In 2009, there were expected to be 192,000 new prostate cancer diagnoses and about 27,000 prostate cancer deaths [1]. Men with PCa have different clinical outcome based on their risk. The best management of both localized and locally advanced PCa remains controversial. Surgery, radiotherapy, hormonal therapy, and watchful waiting can be used isolated or in combination to treat patients classified in different risk groups for treatment failure. For the patients considered of unfavorable outcome significant clinical data are available demonstrating that dose escalation radiation therapy has a significantly better outcome as the dose to the prostate is increased [2-4]. The rationale for the use of tumor dose escalation is that it should hypothetically overcome radioresistance of tumor clonogens seen at conventional dose levels. Studies of the radiobiology of PCa also suggest that it may be more susceptible to large fraction sizes when compared to standard fractionation of external beam radiation (EBRT)

[5,6]. Furthermore, all major prospective phase III randomized trials completed suggest that long-term adjuvant androgen deprivation therapy (ADT) improves survival in very high risk patients managed with EBRT [7,8], but data regarding dose escalation and ADT is still missing.

Conformal high dose rate brachytherapy (HDR) is a successful method for delivering higher dose of radiation to the prostate when compared to EBRT alone, with some potential additional advantages over normal tissues sparing and on reducing miss dose to the prostate [9]. We hypothesized that the association of hypofractionated conformal tri-dimensional radiotherapy (hEBRT) and HDR for dose escalation in the treatment of PCa would led to better, or at least equal, biochemical control rates (bC) when compared to conventional dose fractionation, with less time spent for treatment.

The primary aim of this report is to summarize the mature acute and late toxicity data, and preliminary bC outcome of an ongoing Phase II protocol, developed to assess the feasibility of delivering HDR combined with hEBRT for unfavorable risk patients.

Materials and methods

Patients with initial or locally advanced, biopsy proven prostate adenocarcinoma, Gleason scored and considered of unfavorable outcome, with a life expectancy of at least 5 years, pretreatment PSA levels <50 ng/ml and prostate volume up to 60 cc, after signing an informed consent, were treated with HDR followed by hEBRT at the Department of Radiation Oncology, Hospital AC Camargo, Sao Paulo, Brazil, from February 2005 to March 2009.

Study design

The treatment protocol was approved by the institutional review board (Hospital AC Camargo, São Paulo, Brazil) and the overall treatment course was limited to < 10 weeks. The study primary endpoints were to test whether the acute and late (>3-months) genitourinary and gastrointestinal adverse mild and severe events were acceptable (less than 30% and 10%, respectively). Toxicities were assessed according to the Radiation Therapy Oncology Group/ European Organisation for Research and Treatment of Cancer (RTOG/EORTC) scoring system. The urinary function was assessed using the *International prostate symptom score* (IPSS). The secondary endpoints of the study included biochemical control (bC), freedom from PSA (PSAF) or clinical failure, disease specific (DSS) and overall survival (OS).

Definition of risk group for biochemical failure

Patients were grouped into two different subgroups of risk for PSAF, according to the Fox Chase definition [10]. Patients with either stage T2b, Gleason score 7 or initial PSA value ranging from 10–20 ng/ml were considered intermediate risk (IR) for PSAF. Patients who presented two or more of the characteristics of the IR or iPSA > 20 ng/ml, Gleason score > 7 or clinical satge > T2b were grouped into the high risk (HR) for PSAF. At the discretion of the referral urologists, patients into any of both groups received a course of central or peripheral neoadjuvant androgen deprivation (NAAD), with goserelin and/or flutamide or ciproteron acetate, 3 to 6 months prior to hEBRT, but no short or long term concomitant / adjuvant androgen deprivation was allowed for study entry.

Brachytherapy

All patients were treated with 3D image guided ultrasound based planning HDR. Technical details of HDR have been already published elsewhere [11]. In brief, implants were performed in the operating room, under spinal or local anesthesia, with the patient in lithotomic position. At the beginning of the implant, a Foley catheter was inserted to help visualize the urethra. With the patient in lithotomic position, a TRUS probe from Siemens Sonoline Prima Ultrasound System (Siemens Medical Solutions–Ultrasound Division, Mountain View, CA) linked to a Winston -Barzell track-stepper unit (Barzell-Whitmore Maroon Bells, Sarasota, FL) with integrated needle guide were used for the implant procedure. All the implants were performed with steel needles, uniformly placed into all the prostate volume, but avoiding the urethra.

The images from TRUS were transferred to the BrachyVision Planning System (Varian Medical Systems, Palo Alto, CA), where the prostate and critical organs including bladder, rectum, and urethra were contoured. The Planning Target Volume- PTV was created by an expansion of

Table 1. Clinical characteristics of patients

Variable		n	%	median	range
Age (years)				68	58-80
PSAi (ng/ml)				12.0	1.9-48.7
Clinical Stage	T1C	26	66.7		
	≥ T2a	13	33.3		
Gleason Score	≤ 6	3	7.7		
	7	28	71.8		
	≥ 8	8	20.5		
Risk Group	IR	16	41.0		
	HR	23	59.0		
Comorbidities*	No	25	64.1		
	HTN	6	15.3		
	CAD	5	12.8		
	DM	7	17.9		
	Two or +	4	10.3		
Total		39	100.0		

PSAi: initial PSA value; IR: intermediate risk for biochemical failure; HR: high risk for biochemical failure; HTN: systemic arterial hypertension; CAD: coronary arterial disease; DM: diabetes mellitus. * Sum adds more than 100% in this column because some patients presented with more than one associated comorbidity.

the prostate (3-5 mm in all planes but with no expansion made for the posterior region). The urethra was defined by the outer surface of the Foley catheter.

The HDR dose optimization was based on inverse planning, with at least 95% of the PTV volume receiving 100% of prescribed dose (V100 > 95% of prescribed dose). Doses to the rectal anterior wall and urethra were also evaluated. Dose prescription was 7.5 Gy per fraction, b.i.d., up to 30 Gy, given by two separated implants with a one week interval. Treatment was delivered via the Varian-Gammamed Ir-192 remote afterloading system, source strength ranging from 1.84 to 4.61 cGy h-1 m-2 (4.5–10 Ci).

Hypofractionated Conformal Tri-dimensional Radiotherapy (hEBRT)

All patients were treated with localized hEBRT (6 or 10 MV photons, using 8-coplanar field technique) up to 45 Gy given in 15 fractions over 3 weeks, to cover the prostate plus the seminal vesicles, with a safety in the range of 5 to 10 mm.

Follow up

Follow up with PSA testing occurred every 3 months for the first two years and every 6 months subsequently. The primary definition of PSAF was a 2 ng/ml rise above the PSA nadir (the ''Phoenix'' definition).

Statistical analysis

All endpoints were calculated as the interval from the start of treatment to clinical or PSAF. Pearson chi-square and t tests were used to compare differences in categorical and continuous patient characteristics, respectively. Survival data were generated using the Kaplan-Meier method, with log-rank test used to compare equality of survivor functions. For the statistical tests the SPSS 13.0 software (SPSS, Chicago, IL) was used.

Results

Between February, 2005 and March, 2009 a total of 41 patients with unfavorable PCa were treated with combination of HDR and hEBRT and no further treatment at the Department of Radiation Oncology, Hospital AC Camargo, Sao Paulo. Two patients were excluded from the analysis: one due to the use of ADT prescribed by the referral urologist, and the other one because an extensive scrotal hematoma at the time of second HDR procedure that was aborted. Median age of remaining 39 patients was 69 years old (range, 58-80). Ten patients presented controlled co-morbidities, 6 (14.4%) systemic arterial hypertension, 5 (12.8%) coronary arterial disease, 7(17.9%) diabetes mellitus and 4 (10.3%) two or more associated co-morbidity. Clinical characteristics of patients and co-morbidities associated are shown in **Table 1**.

Table 2. Classification of patients by risk group and presence of NAAD

Risk Group	NAAD		Total	p
	No	Yes		
IR	9 (56.2%)	7 (43.7%)	16 (41.0%)	0.407
HR	15 (65.2%)	8 (34.8%)	23 (59.0%)	0.740
Total	24 (61.5%)	15 (38.5)	39 (100.0%)	

NAAD: neoadjuvant androgen deprivation; IR: intermediate risk for biochemical failure; HR: high risk for biochemical failure.

Table 3. Classification and incidence of acute and late urinary toxicity after the end of combined treatment (HDR and hEBRT)

	Acute Toxicity (by 3 months), Grade						Late (by 12 months) Grade					
Toxicity (%)	1		2		3		1		2		3	
Cystitis	4	10.2%	2	5.1%	0		2	5.1%	0		0	
Urinary frequency	2	5.1%	3	7.7%	0		4	10.2%	2	5.1%	0	
Hematuria	0		0		1	2.6%	0		0		0	
Pain	0		0		1	2.6%	0		0		0	
Slow stream	0		2	5.1%	0		0		0		1	2.6%
Total	6	15.4%	7	17.5%	2	5.1%	6	15.4%	2	5.1%	1	2.6%

HDR: high dose rate brachytherapy; hEBRT: hypofractionate external beam radiotherapy

Sixteen (41.0%) patients were considered IR and 23 (59.0%) were considered HR. Fifteen (38.5%) patients had NAAD prior to hEBRT, 7 (18.0%) considered IR and 8 (20.5%) HR. There was no statistically significant difference between both groups, as shown in **Table 2**.

All the patients received the hEBRT and HDR doses as specified per protocol in a median time of 55 days (range, 45-69). In one patient the second HDR treatment was aborted because of displacement of the implant before starting the treatment. This patient was rescheduled for a new HDR procedure to complete the HDR dose.

The median interval between HDR and hEBRT was 12 days (range 7-21). At the time of this analysis, all patients have completed at least 22 months of follow up. The median follow up 42.5 months (range, 22-69).

Toxicity and urinary function

Acute and late toxicities were assessed according to the Radiation Therapy Oncology Group/ European Organisation for Research and Treatment of Cancer (RTOG/EORTC) scoring system and urinary function was assessed using the IPSS.

By one year after the treatment with HDR and hEBRT the median pre-treatment IPSS changed from 8 (range-3-14) to 6 (range-3-21), p= 0.040. The proportion of patients with no or minimal urinary symptoms (IPSS <7) was 87.2% (34/39 patients) at 1 year.

The highest RTOG acute severe genitourinary toxicity (GU-TX) was grade 3 in 2 patients (5.1%), represented by increased urinary frequency and slow stream, resolved spontaneously by 3 months. On univariate analysis no statistical significant dosimetric or clinical predictive factor for acute GU-TX was found.

Table 3 depicts the acute and late GU-TX. **Table 4** shows the IPSS profile, pre-treatment and by 12 months of the end of combined treatment for all the patients in this analysis.

Table 4. *International prostate symptom score*. IPSS score pre- treatment and by 12 months post-treatment with combined treatment (HDR and hEBRT)

IPSS score	Pre-treatment		Post-treatment	
	N	%	N	%
3	1	2.6	1	2.6
4	7	17.9	15	38.5
5	3	7.7	9	23.1
6	3	7.7	7	17.9
7	2	5.1	2	5.1
8	8	20.5	4	0.3
9	6	5.4	0	0
10	3	7.7	0	0
11	1	2.6	0	0
12	3	7.7	0	0
14	2	5.1	0	0
21	0	0	1	2.6
Total	39	100	39	100

HDR: high dose rate brachytherapy; hEBRT: hypofractionate external beam radiotherapy;
IPSS SCALE: 0-7 mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic

Table 5. Univariate analysis – clinical and dosimetric factors and late urinary toxicity

Variable		N Total	Toxicity Grade >=1	%	p	Toxicity Grade >=2	%	p
Prostate volume (cc)	< 45	27	3	11.1	0.024	2	7.4	0.539
	> 45	12	6	50.0		1	8.3	
Clinical Stage	< T1c	22	8	36.4	0.086	2	9.1	0.570
	> T1c	17	1	5.9		1	5.9	
Number of Needles	< 11	12	5	41.6	0.038	1	8.3	0.122
	> 11	27	4	14.8		2	7.4	
Prostate volume (cc)	< 45	27	3	11.1	0.024	2	7.4	0.539
	> 45	12	6	50.0		1	8.3	
Urethral dose (% prescribed dose)	< 130	27	1	3.7	<0.001	0	0.0	0.008
	> 130	12	8	66.7		3	25.0	

Toxicity scale runs from 1-3. NAAD: neoadjuvant androgen deprivation; HTN: systemic arterial hypertension; CAD: coronary arterial disease; DM: diabetes mellitus; IPSS: *International prostate symptom score*; IR: intermediate risk for biochemical failure; HR: high risk for biochemical failure.

One (2.6%) patient developed urethral stricture after 14 months of the end of the combined treatment with HDR and hEBRT. On univariate analysis predictive clinical and dosimetric factors related to late GU-TX grade one or higher were prostate volume > 45 cc (p= 0.024), less than 11 needles for the implant (p= 0.038) and the urethral dose > 130% of prescribed dose (p< 0,001). The urethral dose > 130% was also confirmed as statistical significant predictive factor to development of late GU-TX grade 2 or higher (p=0.008), as shown in **Table 5**.

In this analysis the 3.5-year actuarial urethral stricture free rate was 95.8%. On multivariate analysis the only statistical significant predictive factor for late GU-TX was the urethral dose > 130%, p= 0.017 (95% CI – 1.39-29.49), HR 6.4, as shown in **Figure 1**.

Survival and biochemical control

The crude survival rate observed in this group of patients was 87.2%. The actuarial 3.5-year bC rate was 87.6%. PSA bouncing occurred in 4

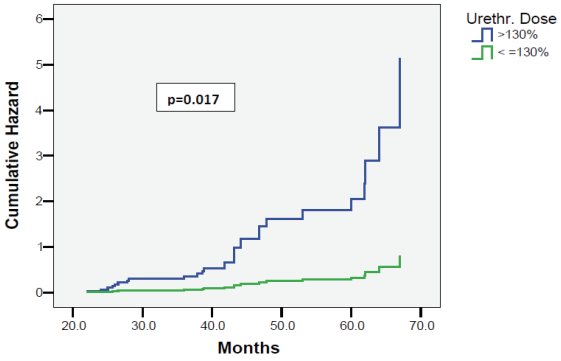

Figure 1. Hazard function for late GU-toxicity > grade 2 and urethral dose.

(10.2%) patients in a median time of 15 months (range, 12-19). One patient had a PSA failure after 17 months of the end of the treatment. He was diagnosed with iliac failure by PET-CT and underwent to salvage pelvic lymphonodes dissection and subsequent adjuvant androgen blockage. Four (10.2%) patients have died due to other causes and one (2.6%) patient due PCa at the time of this analysis. The actuarial 3.5-year overall survival (OS) and disease specific survival (DSS) rates were 92.0% and 96.9%, respectively, as shown in **Figure 2**.

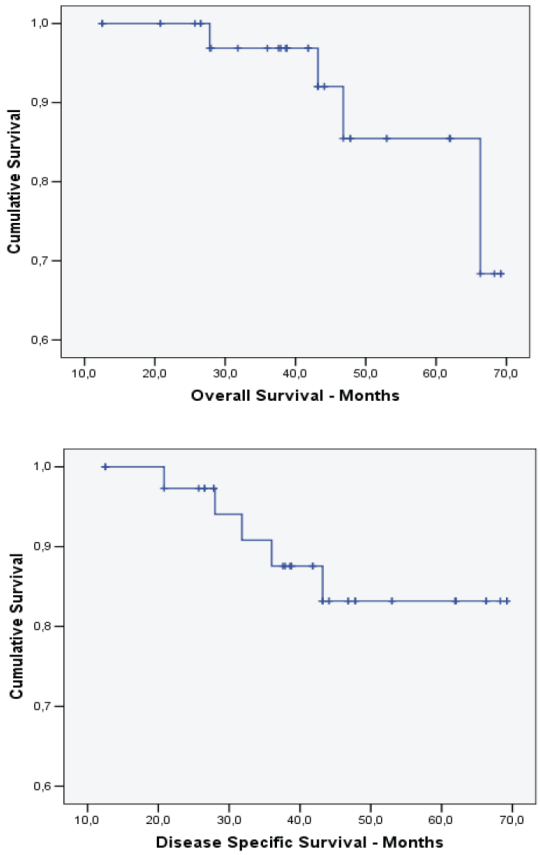

Figure 2. Kaplan-Meier curve - overall survival and disease specific survival for all patients in the analysis.

Discussion

Prostate cancer poses significant biologic, economic and personal burdens on healthcare systems and society in general. The optimal radiation schedule for the curative treatment of prostate cancer remains unknown. Standard treatment schedules with EBRT are relative long and most of the times impact the socio-economic behavior of the patients.

There are convincing evidences that bC is improved with higher cumulative doses of radiation given to the prostate. The rational for the use of tumor dose escalation is that it should hypothetically overcome radioresistance of tumor clonogens seen at conventional dose levelsl [12]. Studies of the radiobiology of PCa suggest that it may be more susceptible to large fraction sizes compared with standard fractionation of external beam radiation [5,6].

A recent meta-analysis has shown that higher than conventional dose radiotherapy (70 Gy) given to the prostate is superior in preventing PSA failures [13]. To further escalate dose given to the prostate, without adding toxicity, the combination of hEBRT and HDR is an alternative. Several retrospective studies have previously described the outcome of patients treated with the combination of EBRT and HDR, showing promise in bC with acceptable toxicity. The 5-year bC reported were 89-93% for IR and 69-83% for HR, respectively and the DSS rates were in the range of 96-98%, independent of risk group classification [14-16]. Unfortunately, data from prospective randomized trial comparing results of the combination of EBRT and HDR with other dose escalation protocols is still missing.

The use of hEBRT alone has already been used clinically for the treatment of favorable and unfavorable PCa patients for a number of years, particularly in Canada [17] and the United Kingdom [18]. Randomized hEBRT trials with slightly different eligibility criteria are also ongoing with

preliminary results published. The 5-year bC rates range from 39 to 83% with acute and late higher than grade 2 GU-TX incidence ranging from 3 to 9% [19-21], toxicity scores similar to the ones observed in the current analysis.

The combination of both, hEBRT and HDR, reducing overall treatment time associated to dose escalation is appealing. This would lead to significant savings in health care resources and increased patient convenience. The main advantage of HDR is the possibility of limiting the dose given to normal tissues and tightly conformed to the target, reducing the amount of tissue that has to be treated compared with EBRT. HDR has, to date, been reported as having low rates of acute and late GU-TX [9]. We observed only two (5.1%) occurrences of grade 3 acute GU-TX that required narcotics for pain, both resolved in 3 months. On univariate analysis we could not find any dosimetric or clinical statistical significant predictive factor for higher than grade 1 acute toxicity incidence.

Despite one (2.5%) patient presenting late grade 3 toxicity, a urethral stricture, we observed a statistical significant improvement on IPSS of most patients. The median pre- treatment IPSS changed from 8 to 6 (p= 0.040) by one year.

Urethral strictures are a potential complication following both radiation and surgical treatment for PCa. A review of over 25,000 men following radical retropubic prostatectomy found a crude stricture rate of 8.6% [22].

Crude rates of urethral strictures following HDR in the literature range from 0% to 14%. The majority of series report rates between 4% and 9% at 5 years [9,14]. The factors associated to an elevated risk of urethral stricture are prior history of TURP, hypertensive patients and those treated with increasingly high doses of radiation per fraction of HDR. Other factors related to an increased risk of urethral strictures are the age at the time of treatment, PSA value, Gleason score, stage, risk category, smoking history, vascular event history, diabetes presence, presence of androgen deprivation, the duration of urethral catheterizations also have been reported in the literature. We observed that 14 (35.9%) patients in our analysis presented associated co-morbidities as shown in **Table 1**, but no statistical significant correlation with the incidence of acute or late side effects was observed. Conversely to our own previous published data, we did not find age to be a statistical significant predictive factor for the incidence of severe late side effects [9].

Data regarding dose volume histograms for the urethra and its impact on toxicity incidence are missing in the literature. We kept the maximum urethral dose less than 150% of prescribed dose in all our implants and despite this, we could observe a statistical significant correlation between incidence higher than grade 1 and more severe, higher than grade 2, late toxicity incidence when maximum urethral dose was > 130% of prescribed dose, $p<0.001$ and $p=0.008$, respectively.

We also observed a statistical significant correlation between a smaller (<11) number of needles used to cover the target ($p=0.038$) and late GU-TX. We can speculate that a relative small number of needles led to areas of hot spots around them, and these hot spots could cause damage to specific points in the urethral mucosa. All our patients were treated using two separated implants and hence the purported impact of number of implants could not be examined in this analysis.

Fröhlich et al [23] evaluate the effect of the number of needles on the quality of dose distributions for HDR implants in 174 implants. They grouped the procedures according to the number of implanted needles: <15, 15-17 and >17. They also determined the maximum dose to some reference points as the urethra, observing that a higher dose given to the urethra was related to a higher number of needles. They also concluded, like us, that in most cases the use of 15-17 needles seems to provide a dosimetrically acceptable treatment plan.

TURP alone is associated with a urethral stricture rate ranging from 1.5% to 4% [24]. In our study, the excluding criteria of previous TURP may have added a protection factor to our patients. Sullivan et al [25] found a crude stricture formation rate of 8%, corresponding to an actuarial risk of stricture development of 12% at 6 years when using HDR as a boost or as monotherapy. They also observed a higher risk of incidence in monotherapy patients (15% at 3 years) when compared to HDR associated to EBRT (11% at 6 years).

Grills et al [26] reported the outcomes in terms

of GU-TX for patients treated with permanent seed implants and HDR as monotherapy. They noted a statistical significant decreased incidence of acute and late urinary toxicity favoring HDR treatments. The acute grade 3 GU-TX rates seen in patients receiving permanent seed implants was 25% and for those treated with HDR was 10%. They also observed no statistical significant difference in the rates of urethral stricture requiring dilation between both treatment modalities (p=0.177). Similarly to our results, they observed that the median time to development of urethral stricture was 16.5 months after the end of the treatment. Morton e al. [28] reported the results of patients treated with a single HDR fraction of 15 Gy followed by hEBRT two weeks later. The hEBRT schedule was 37.5 Gy in 15 daily fractions over 3 weeks. With a median follow up of 1.14 years (range, 0.1-2.6 years) and despite no data regarding bC published, the acute grade 2 and 3 GU-TX rates were 62% and 1.6%, respectively. In our analysis we observed correspondent rates of 17.9% and 5.1%, respectively. Conversely to our study, they observed no grade 3 late GU-TX, but their median follow up time is still to short to any comparison.

The use of ADT for unfavorable patients has also been tested in multiple prospective randomized trials, with two conclusions emerged from the comparison of EBRT in combination with ADT and EBRT alone: a- administration of ADT is superior to treatment with EBRT alone and b- long-term ADT (2 to 3 years) is superior to short-term ADT (4 to 6 months). These trials also showed an increased risk of fatal myocardial infarction and bone fractures associated to long long-term ADT. The 10-year results of European Organisation for Research and Treatment of Cancer (EORTC) 22863, a randomized trial of 415 patients treated between 1987 and 1995, reported, as previously, that the locoregional control was significantly improved in the combined treatment group when compared with the EBRT alone group (p<0.001) . At 10 years, the cumulative locoregional failure rates were 23.5% with radiation only, and 6.0% in the combined treatment group [7]. The major criticism to these studies is that none of them has escalated dose to more than 70 Gy. Furthermore, techniques employed at that time do not reflect those commonly implemented in contemporary radiation oncology practice. Martinez et al [28] evaluated 934 patients treated between 1986 and 2000 with pelvic EBRT (36-50 Gy) and HDR. From the total, 406 received up to 6 months of ADT. With a median follow up of 4 years they observed no difference in OS, DSS, or bC at 5- and 8-years. The corresponding 8-year bC rates with and without ADT were 85% and 81%, respectively. On multivariate analysis ADT did not predict for bC. The conclusion from all these data seems to be that ADT in addition to radiotherapy is superior in some reported trials, but other trials failed to confirm this.

The potential benefit for the use of NAAD is also controversial for patients into IR or HR. In our analysis, despite the small number of patients, we observed no difference on bC and severe complication rates for patients who had NAAD. Another study of Martinez et al [29] evaluating the benefits of NAAD in 507 unfavorable patients treated between 1986 and 2000 with the combination of HDR and EBRT has also failed to demonstrate a significant benefit for the addition of NAAD, and this finding was mirrored in our analysis, despite not a primary end point.

Our results suggest that dose escalation and association of NAAD can be reserved for selected patients, given the acute and potential chronic toxicity of hormonal manipulation, such as hot flashes, fatigue and impotence, as well as the financial burden of administration of the drugs. We observed no statistical significant influence in the presence of NAAD on the incidence of late GU-TX (p= 0.923), therefore, patients with prostate volumes above 45-50 cc could be candidates to use of NAAD for downsizing the prostate and, consequently, decreasing the potentiality of developing late GU-TX. We think there is still a great need for additional prospective randomized trials to define which patients treated with dose escalation should really receive NAAD and or ADT.

Conclusion

The clinical and biochemical endpoints evaluated in this study suggested that HDR combined to hEBRT is well tolerated in the short and medium term. Improved outcomes in terms of toxicity can be achieved when prostates with no more than 45 cc are implanted, using at least 11 needles and the maximum urethral dose is less than 130% of prescribed dose. More mature data is necessary, but this analysis also

suggests that there are, at least, subsets of patients considered IR and HR for whom NAAD or ADT could be safely withheld. The challenge for the future is to determine which treatment option will have the best result for each patient.

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