Original Article

Conventional External Beam Radiation Therapy and High Dose Rate Afterloading Brachytherapy as a Boost for Patients Older than 70 years

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Abstract

The treatment options for patients with non metastatic prostate cancer range from observation, radical prostatectomy, radiation therapy, hormonal therapy to various combination of some to all of them. **Objective:** We evaluated the impact on biochemical control of disease (bNED), acute and late intestinal (GI) and urological (GU) morbidity for a group of patients older than 70 years presenting initial or locally advanced prostate cancer treated with fractionated high dose rate brachytherapy (HDRB) as a boost to conventional external beam radiation therapy (RT) at the Department of Radiation Oncology from Hospital do Câncer A. C. Camargo, São Paulo, Brazil. **Methods:** A total of 56 patients older than 70 were treated from March, 1997 to June, 2002. All patients had prior to HDRB a course of RT to a median dose of 45 Gy. HDRB doses ranged from 16 Gy to 20 Gy, given in 4 fractions. **Results:** The median age of the patients was 74.4 years (range 70-83) and the median follow-up 33 months (range 24 to 60). The 5-year actuarial bNED rate was 77%. Acute GU and GI morbidity G1-2 were seen in 17.8% and 7.1% of patients, respectively. Late G1 or G2 GU morbidity was seen in 10.7% of the patients, while late G3 morbidity was observed in 7.1% of the patients, represented by urethral strictures. **Conclusion:** this group of patients had similar bNED rates when compared to literature, with acceptable morbidity rates.

Key words: Prostatic Neoplasms. Brachytherapy. Morbidity. Treatment outcome.

Introduction

With the emergence of prostatic specific antigen (PSA) screening, the proportion of cases of prostate cancer (PC) diagnosed at an early stage has been increasing. For male population of western countries, the probability of dyeing of PC is about 3%.[1] Currently, Brazilians' men life expectancy stands at 70.4 years.[2]

In 2005 it is expected 46,300 new diagnoses of PC in Brazil, with estimated risk of 51.12 new diagnosis per 100,000 men.[3]

The treatment options for patients with non metastatic PC range from observation, radical prostatectomy, radiation therapy, hormonal therapy, different combinations of some or of all.[4] Watchful waiting is an alternative to active treatment and generally offered to men considered low risk for biochemical failure (bF) PC, but it is not clear how these options impact on health related quality of life.[5]

Data suggests that local control of PC is directly related to dose, however the proximity of critical normal structures, as rectum and bladder, limits the

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dose that can be safely delivered, without producing acute and late morbidity.[6] With the improved technology of transrectal-ultrasound guided brachytherapy, the temporary high dose rate transperineal implantation (HDR-B) is now increasingly been used to boost external beam radiation therapy (RT) at some centers.[7,8]

The symptoms related to treatment of PC vary according to different modalities. The psychosocial variables have shown to be important to quality of life and have rarely been examined.[9] The most common related morbidity associated to prostate HDRB is rectal and urethral. It ranges from frequency increase of evacuation to rectal bleeding and, from nocturia to urinary bleeding or obstruction, symptoms that may occur in up to 70% of the patients, in different grades.[10]

Regarding patients older age and complications chances related to treatment, it has not been established yet whether these patients should be treated or submitted to a watchful waiting police, starting active treatment only when symptoms became a problem, since the chance of dyeing of PC is relatively low.[11]

We have evaluated the biochemical control (bNED), acute and late urological (GU) and gastro-intestinal (GI) morbidity in a group of patients above 70 years old and that have been treated with prostate HDRB used as a boost to conventional RT.

Material and Methods

From March 1997 through June 2002, a total of 384 patients with proven biopsy prostate adenocarcinoma were treated at the Department of Radiation Oncology, Cancer Hospital, Sao Paulo, Brazil. To the patients with initial or locally advanced disease, that were evaluated and approved by the anesthesiology department, it was offered the treatment option of pelvic localized RT in combination with HDR-B as boost, due the lack of conformal facilities at that time. A total of 154 patients have had this treatment. Those who have not been candidate or have refused this treatment option have had EBRT alone.

Patients with the following characteristics were eligible for study entry: age above 70, adenocarcinoma proven biopsy, Gleason scored (GS), clinical stage (CS) according to International Union Against Cancer classification system (1997) T3a or lesser and, prostate volume up to 60cc and no previous trans urethral resection within the prior 36 months.

All the patients have had a history and physical evaluation, including a digital rectal exam, chest X ray, and routine serum laboratory studies (complete blood count, biochemistry panel). Pre-treatment PSA levels were also recorded.

They have been divided into two major groups for local recurrence risk and for dose-escalation for HDR-B treatment. Patients of the low risk group (LR) have presented GS $\leq$ 6, T2a or lesser and or initial PSA $\leq$ 10ng/ml. The remaining patients have been enrolled in the high risk group (HR). At the discretion of the referral urologists, patients into both groups received a course of neoadjuvant total androgen deprivation (AD), with association of goserelin and flutamide or ciproteron acetate, three to six months prior to RT.

In the RT planning the prostate and seminal vesicles have been the target. They have been irradiated through a 4 or 6MV Varian Linear Accelerator, Varian Palo Alto, US, with four field-box technique. A two dimensional planning system has been used for treatment planning, following the ICRU report for dose prescription.[12] All patients have had a pretreatment diagnostic CT scan to assist in defining prostate, seminal vesicles and normal tissue volumes at risk. Urethrogram and rectal contrast have also been used. The prostate and seminal vesicles plus a margin of 1cm in all directions have been drawn based on the diagnostic CT for individual protection block confection. The urethral and anterior rectal wall have received 100% of prescribed EBRT dose. A total dose of 44 to 50.4Gy (1.8 or 2.0Gy per fraction) was given in five to seven weeks, including delays not programmed.

The implant procedures have been performed after 10 to 15 days after RT, under spinal anesthesia with the patient in lithotomic position. HDR-B treatments have been delivered via the micro-Selectron-HDR Ir-192, Nucletron B.V., Netherlands and Gamammed-Varian, Palo Alto, US, remote after

loading systems. The technique of HDR-B has been previously described elsewhere.[13] In summary, the apex and base of the gland have been identified and in a first moment two metallic markers have been inserted into the gland, one in the apex and the other in the base to ascertain any needle displacement quality control during the treatment and to allow any necessary correction. Data regarding the impact of the needles displacement and biochemical control rates have allso been previous published.[14]

All the implants were performed with steel needles, with a median number of 12 needles (range 7-16). A perineal template with 6cm diameter has been used for the implants. The needles were uniformly placed into all the prostatic volume, but avoiding the urethra, as no cystoscopy has been routinely performed.

After placement of needles, a CT scan has been performed to ensure that the entire gland has been implanted, and to help on defining the prostate volume and planning.

Semi-orthogonal X rays have been used for planning and dosimetric calculations. The dose prescription has been in the isodose line that involves the gland with 2 to 3mm margin. The treatment has been optimized using the standard geometric optimization. Dose prescription has been of 4Gy or 5Gy per fraction, BID, to a total dose of 16Gy for LR and 20Gy for HR patients. Doses to the anterior wall of the rectum, considered as a point at the anterior edge of the probe of US have been kept in the maximum of 82% of the prescribed dose. The maximum length of anterior rectal acceptable to receive this dosehas been of 20mm. The urethral marked region should not exceed 125% from dose prescription.

After completion of treatment patients have been seen in follow-up one month later and after that every 2 months for the first 12 months, thereafter patients have being seen in follow-up every 6 months.

The biochemical failure has been defined according to the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus panel statement.[15]

Gastro-intestinal and GU morbidity have been based upon the RTOG grading system,[16] summarized in table 1.

Table 1 - EORTC/RTOG acute radiation morbidity scoring criteria

Grade	RTOG definitions
0	No treatment related symptoms
1	Minor symptoms requiring no treatment
2	Symptoms responding to simple outpatient management, KPS is not affected
3	Distressing symptoms altering KPS, hospitalization for diagnosis or minor surgical intervention may be required
4	Major surgical intervention or prolonged hospitlization required
5	Fatal complication

Statistical analysis

Date of failure was the midpoint between the post-irradiation nadir PSA and the first of the three consecutive rises.

Actuarial results were calculated by the Kaplan-Meier method.[17] Chi-square tests were used to detect differences in proportions. Log-rank test was used to compare equality of survivor functions.[18]

Results

From 03/97 to 06/02 there were 154 patients enrolled in our trial. Of these, 56 have been considered for study entry due to the age above 70 . Median age was 74.4 years (range 70-83) and the median follow-up was 33 months (range 24 to 60). Characteristics of patients are shown in Table 2.

The crude bNED rate was 73.2%. Actuarial 5-year bNED rate was 77% (Figure 1). Four patients have died due other pathologies (mainly heart disease), but with bNED at time of death. No cancer-specific mortality has been recorded in the studied population.

There were 53.6% (30) of patients into the LR and 46.4% (26) into the HR group. Patients into both, LR and HR groups have had AD at the description of the referral urologist, then sub-grouped as follows: 37.5% (21) were grouped into LR, 16.1% (9) LR+AD, 35.7% (20) HR and 10.7% (6) HR+AD.

PSA failure have occurred in 26.7% (15) patients in a median interval of 22.6 months (range 17 to 34 months), standard deviation 6.

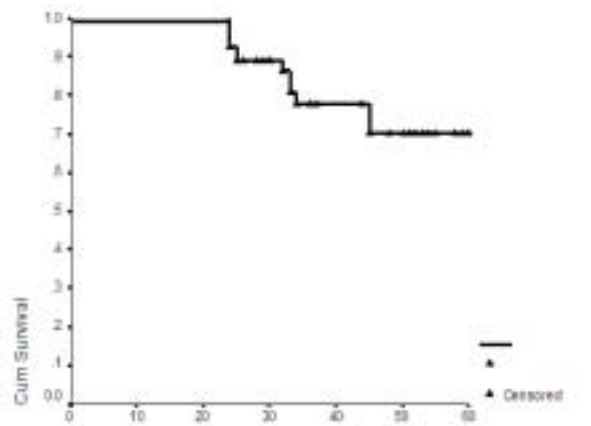
Table 2 - Characteristics of patients

Variable	n	%	mean
Age (years)			74.4
> 70	56	100.0	
PSAi (ng/ml)			15.4
≤ 10	28	50.0	
> 10	28	50.0	
Risk Group			
Low	30	53.6	
High	26	46.4	
Gleason Score			
≤ 6	40	71.4	
> 6	16	28.6	
Clinical Stage			
≤ T2a	46	82.1	
> T2a	10	17.9	
NAD			
Yes	15	26.8	
No	41	73.2	

Legend: PSAi= initial PSA value, Risk Group for biochemical failure, NAD Neoadjuvant androgen deprivation

The bNED rates for the LR and HR groups have not been not statically significant, p=0.9169 as shown in Figure 2. The bFs occurred in 4 patients into LR group, 3 into LR+AD, in 5 patients into HR- group and in 3 patients into HR+AD, p= 0.6241.

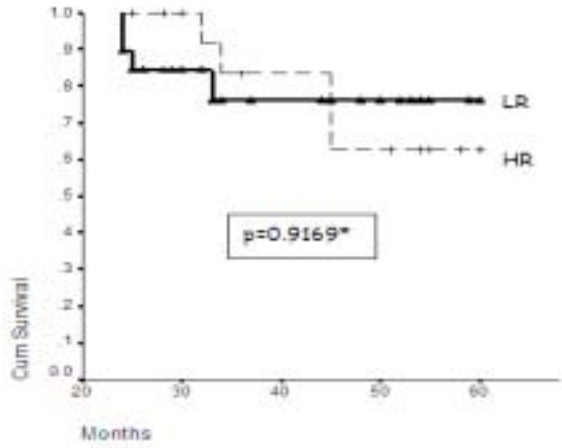
The univariate analysis has showed no statistical significant predictive factor for bNED (Table 3).



bNED 5 years =77%

Figure 1 - Actuarial 5-year bNED

Acute GU and GI morbidity G1-2 were seen in 17.8% (10/56) and 7.1% (4/56) of patients, lasting from fifteen to thirty days. Late GI has not occured in any patient. Late G1-2 GU morbidity was seen in 10.7% (6/56) of the patients, mainly dysuria or increase in urinary frequency, with no need of intervention. Grade 3 late GU morbidity has been observed in 7.1% (4/56) of the patients, represented by urethral strictures, lasting for a median period of 150 days (range 95-320) since their diagnosis, all have been treated by urethral dilatation and Foley catheters, with no patient using a catheter at the time of this analysis.



* Fisher´s exact test with significance level of 95%

Figure 2 - Actuarial 5-year bNED stratified by risk group for biochemical

Discussion

The treatment of early and locally advanced PC is a controversial issue in urology, and even for elderly patients the option of waiting and watching is still controversial. Men who elect watchful waiting as initial management for PC are older with lower GS and PSAi. In these men, age at diagnosis, PSAi and CS are the most significant predictors of requiring or selecting secondary treatment.[19]

Publications on radiation therapy in elderly patients showed that it is effective and well tolerated in patients beyond the age of 60–75 years.[20-22]

For patients with nonmetastatic PC the treatment options for radiation therapy have changed in the last two decades now ranging from conformal to intensity modulated radiation therapy, with better results related to dose escalation[13,23-25] but these treatment modalities are time consuming. The dose

Table 3 - Univariate analysis

Variable	n	bNED	%	p
PSAi (ng/ml)				
≤ 10	28	21	75.0	0.9701
> 10	28	20	71.4	
Risk Group				
LR	30	23	76.7	0.9169
HR	26	19	70.3	
Gleason Score				
≤ 6	40	31	77.5	0.8435
> 6	16	10	62.5	
Clinical Stage				
≤ T2a	46	34	73.9	0.9689
> T2a	10	7	70.0	
AD				
yes	15	9	60.0	0.4557
No	41	32	78.4	
RG & AD				
LR	21	17	80.9	
LR+AD	9	6	77.7	0.6241
HR	20	15	75.0	
HR+AD	6	3	66.6	

Legend: PSAi= initial PSA value, Risk Group for biochemical failure, AD= neoadjuvant androgen deprivation

with conventional RT that can be safely delivered without increasing morbidity is about 69Gy, what seems to be insufficient for tumor control.[26]

The technological advances have made the use of HDR more precise and appealing. The advantages on patient care are considerably, as the source stays in the patient for just a moment twice a day, offering a better radiation protection and safety issues for the patient, treating personnel and family. For developing countries HDR-B seems to be a reasonable option, specially because of the high number of centers that have the HDR after loading facilities, due the high incidence of cervix cancer.[13]

Some technical advantages of HDRB shall be highlighted and include a very good control of dose distribution, reposition and adjustment of needles prior to each treatment, elimination of radioprotection and safety issues for the patient and for his immediate family and a minor operator dependence for the procedure. It is also very conformal, allowing the avoidance of most normal surrounding tissues.[26]

Unfortunately in this retrospective analysis we could not attempt to have dose volume histograms for normal surrounding tissues. The only data available were of dose ranges to the anterior wall of the rectum, considered as a point at the anterior edge of the probe of US which were kept in the maximum of 82% of the prescribed dose and doses to the urethral marked region, that not exceeding 125% from the prescription. We could not correlate a higher dose to urethra region or rectal wall with an increased incidence of acute or late morbidity, but it is well known that tolerance doses are a function of the number and radio-sensitivity of target and normal surrounding cells in determined tissue and tumor volume.

Regarding toxicity, the most common related morbidity observed is rectal and genitourinary, ranging from increase in the evacuation frequency to rectal bleeding, and from nocturia to urinary bleeding or obstruction. In our series acute mild GU and GI morbidity were seen in 18.2% and 7.3% of patients, respectively. Urethral strictures occurred in 7.3% of patients, lasting for a median period of 150 days (range 95-320). All patients who presenting late GI morbidity have presented acute symptoms too. Akimoto et al.[27] reported on 67 patients with PC low, intermediate and high risk patients who have been treated by HDRB (18Gy in 2 fractions)combined with hypofractionated BBRT (51 Gy, 3Gy fractions, 3 times a week), observing the existence of a correlation between the acute GU toxicity severity and the urethral radiation dose in HDRB. Androgen ablation has been performed in all the patients. With a median follow-up duration of 11 months (range 3-24 months) they have observed G0-1 acute GU toxicity in 42 patients (63%)and G2-3 in 25 patients (37%). They have correlated a higher urethral dose to the incidence of G2-3 toxicity.[27]

Demanes et al.[28] have evaluated 491 patients treated between July 1991 and December 1998, using HDRB. Symptoms of urinary irritation occurred with variable intensity and abated rapidly 2 weeks after the procedures. There has not been observed high-grade chronic rectal morbidity and most patients reported no rectal symptoms or treatment-related chronic urinary incontinence.[28]

Geinitz et al.[22] in a recent publication have observed that conformal EBRT with doses of 70Gy have been well tolerated in 80 patients aged 75 or

older. The results in terms of bNED and toxicity have been compared with 221 patients younger than 75 years who have been treated during the same period of time, observing no significant differences in acute or late side effects between age groups. The frequency of G-3 symptoms have been ranged between 0 and 4% irrespective of age group. Older patients (76%) have had a better bNED at 4 years old than younger have (61%), p=0.042.[22]

A recent study of Merrick et al.,[29] with permanent implants has indicated that the implants that maintain the anterior rectal wall to about 85% of the prescribed dose and the length receiving 100% and 120% kept in approximately 10mm and 5 mm leading to an incidence of approximately 9% of mild self-limited proctites.[29] Vicini et al.[30] have observed 4% of grade-3 late toxicity consisting of urethral stricture or incontinence. Mate et al.,[31] have related 6.7% urethral strictures.

In a European report, Kovacs et al.[32] have described an incidence of proctitis or colitis of 15.5% in 174 patients evaluated. The incidence of dysuria and or cystitis in that same population has been of 11.5%.[32]

A recent study of Curran et al.[33] has shown that among 52 patients available for follow-up with average duration 11.8 months treated by HDRB, two patients have had grade-3 or 4 late effects.

The treatment results using combined therapy (RT plus HDR-B) have shown acceptable bNED rates, even in the presence of more locally advance disease. In our analysis there were 6 patients considered HR, using AD for a short period and no impact on bNED has appeared. Martinez et al.[34] and Pellizzon et al.[35] in recent publication have also observed that AD or a short course of adjuvant androgen deprivation, for less than 6 months may not impact on bNED, corroborating with a recent report of a subset analysis including data from RTOG 86-10, which have evaluated AD or concurrently with RT in patients with locally advanced PC, that have shown no advantage in overall eight years survival.[36]

Chiang et al.[37] in a recent publication have observed that the need for AD or short course hormonal therapy in LR patients might be less than the need for intermediate- or high-risk patients. There are no data regarding the use of NAAD and rectal morbidity increase rates, although such a short course of AD would not be expected to affect the morbidity results of this study.[37] There is a report of an increase in rectal morbidity rates for long-term hormonal therapy administered concurrently with RT.[38] Recent report of Lee et al., suggests that there is a subset of patients considered to be LR, to whom the addiction of hormonal therapy and or dose-escalation RT may improve outcome.[39]

The actuarial 5-year bNED in our analysis has been of 77%. For series published in this decade it has ranged from 67% to 84% in 5 years, [13, 31, 40] but none has evaluated just elderly patients. The option for treatment of elderly patients gave the same rates of bNED in younger population, with acceptable morbidity rates, with no impacted on quality of life.

The watchful waiting police may be adopted for a selected group of patients in wich life expectance is short due to associated co-morbidity. As we have observed in our analysis, the overall survival rate was lowered by deaths associated with other co-morbidities.

In conclusion, the option for treatment of elderly patients improved local control, with acceptable morbidity rates, that had no impact on quality of life. The watchful waiting police should be adopted for a selected group of patients in witch the life expectance is short due to associated co-morbidity or for those patients with LR who refuse an initial treatment.

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