Applied Cancer Research 2010;30(3)306-312

Original

Neoadjuvant Androgen Deprivation and Long-Term Results for Patients with Intermediate- and High-Risk Prostate Cancer Treated with High-Dose Rate Brachytherapy and External Beam Radiotherapy

Antonio Cassio Assis Pellizzon, MD, MsC, PhD;[1,2,3] Ricardo Cesar Fogaroli, MD; [1,2] Maria Letícia Gobo Silva, MD;[1] Douglas Guedes Castro, MD;[1] Maria Conte Maia MD;[1]

1-Radiation Oncology Department, Hospital A.C. Camargo, São Paulo, Brazil

2-Radiation Oncology Service, Instituto Arnaldo Viera de Carvalho, São Paulo, Brazil

3-Prostate Institute, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil

Abstract

Purpose: To evaluate the influence of neoadjuvant androgen deprivation (NAAD) and report the long term biochemical control rates according to the Phoenix Consensus Conference, and prognostic factors of intermediate- (IR) and high-risk (HR) prostate cancer treated with external beam radiotherapy and high-dose-rate brachytherapy (HDR-BT). **Methods and Materials**: Between March, 1997 and June, 2005, 184 patients considered IR or HR were treated with localized radiotherapy and HDR-BT at the Department of Radiation Oncology, Hospital A.C. Camargo, Sao Paulo, Brazil. Patient´s age, Gleason score, clinical stage, initial PSA value, risk group for biochemical failure, presence of NAAD, doses of radiotherapy and HDR-BT were evaluated. **Results:** Median age and follow-up were 70 years old (range, 47-83) and 74.5 months (range, 24–123 months), respectively. Patients considered IR were 91 (49.4%) and HR 93 (50.6%). Ninety-nine (53.8%) patients had no NAAD. The overall survival at 5 years was 93.6%. The 5-year actuarial biochemical control rates for all patients, IR and HR were 83.4%, 86.2% and 78.8%, respectively, p= 0.076. On univariate analysis the prognostic factors related to better biochemical control were Gleason score < 6 ng/ml (p= 0.037), radiotherapy dose > 45 Gy (p= 0.011) and HDR-BT dose > 20 Gy (p< 0.001). On multivariate analysis no statistical significant predictive factor related to biochemical control was found. **Conclusions**: The role of NAAD for IR and HR prostate cancer is still to be defined. HDR-BT combined to external radiotherapy is a successful form of treatment for these patients, with our results comparable to published data.

Keywords: Prostate cancer; Radiotherapy; Brachytherapy; Biochemical control; Neoadjuvant hormonal therapy

Introduction

Prostate cancer (PCa) is one of the most prevalent malignancies affecting men in the developed world. For the male population of western countries, the probability of dying of PCa is about 3%.[1]

When evaluating outcomes from external beam radiotherapy, brachytherapy or a combination of both, patients with PCa are classified as being at a low- (LR), intermediate-(IR) or high-risk (HR) for biochemical failure, as this dramatically affects outcomes. Although, 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 the different risk groups.[2]

The determination of risk groups for biochemical

Correspondence
Antonio Cassio Assis Pellizzon
Hospital ACCamargo,
Rua Prof. Antonio Prudente 211 - Liberdade
01509-020 São Paulo, Brazil
Phone: +55 11 21895101
E-mail: acapellizzon@hcancer.org.br

failure has been changed as more mature data from several centers have led to a comprehension of which patients were really at a higher risk for biochemical failure. A study performed with more than 1,500 patients treated with three-dimensional conformal radiotherapy at the Fox Chase Cancer Center, has included patients presenting with two of the parameters of intermediate risk into the high risk group for biochemical failure, with a significant reflection on biochemical control rates.[3]

For these patients, at IR or HR, significant clinical data are available demonstrating that dose escalation radiation therapy has a significantly better outcome as the dose to the prostate is increased.[4-6] The combination of radiotherapy plus long-term suppression of androgens also improved outcomes, but there is a lack of data regarding its combination with dose escalation or use of neadjuvant androgen deprivation (NAAD).[7]

Conformal high-dose rate brachytherapy (HDR-BT) is a successful method for delivering higher dose of radiation to the prostate when compared to radiotherapy alone.[8,9] HDR-BT also has some potential additional advantages over normal tissue sparing and on reducing miss dose to the prostate, due to imprecise target localization, treatment setup uncertainties, organ motion and/or deformation during the treatments, with a relative low incidence of severe acute and late side effects.[10]

This is a retrospective study to evaluate the biochemical control rates, according to the RTOG-ASTRO Phoenix Consensus Conference,[11] of patients considered IR or HR, who were not submitted to adjuvant androgen deprivation.

Material and Methods

Patients

Patients with initial or locally advanced biopsy proven prostate adenocarcinoma, considered IR or HR, treated with pelvic localized conventional or tridimensional radiotherapy in combination with HDR-BT at the Department of Radiation Oncology, Hospital A.C. Camargo, Sao Paulo, Brazil had their charts retrospectively reviewed. Details as Gleason score, initial PSA value and clinical stage using the 1992 AJCC clinical stage were collected to define the risk group for biochemical failure, according to the Fox Chase definition.

External Beam Radiotherapy

In the first three years of the period of analysis, conventional two dimensional external radiotherapy planning was used, but all patients had a pretreatment diagnostic computed tomography scan (CT), urethrogram and rectal contrast to assist in defining the prostate, seminal vesicles and normal tissue volumes at risk. The defined targets for radiotherapy were the prostate and seminal vesicles, plus a 10 mm margin in all directions. After 1999, all patients were treated with localized conformal radiotherapy, when the margins used to the target were in the range of 7 to 10 mm.

Brachytherapy

Technical details of HDR-BT have been already published elsewhere.8,10 In brief, HDR-BT was performed 10 to 15 days after the completion of external radiotherapy. Implants were performed in the operating room, under spinal anesthesia and with the patient in lithotomic position. Two metallic markers were inserted into the gland, one in the apex and the other in the base of the prostate, to ascertain quality control of any needle displacement during the treatment and to allow corrections whenever it was necessary. All the implants were performed with steel needles, under perineal template guidance. The needles were uniformly placed into all the prostatic volume, but avoiding the urethra.

Definition of Risk Group for Biochemical Failure

Patients were grouped into two different subgroups of risk for biochemical failure. Patients with either stage T2b, Gleason score 7 or initial PSA value ranging from 10–20 ng/ml were considered IR. 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 HR. At the discretion of the referral urologists, patients into any of the groups received a course of central or peripheral NAAD, with goserelin and/or flutamide or ciproteron acetate, 3 to 6 months prior to external radiotherapy, but no short- or long-term adjuvant androgen deprivation was allowed for study entry.

Follow-up

After completion of treatment, patients were seen in follow-up with PSA testing one month later, every 3 months for 2 years and every 6 months after that. The primary definition of biochemical failure for this study was a 2 ng/mL rise above the PSA nadir (the "Phoenix" definition).

Statistical Analysis

All endpoints were calculated as the interval from pathologic diagnosis of PCa to biochemical failure. The biochemical failure was defined according to the RTOG-ASTRO Phoenix Consensus Conference. 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. Statistical tests were performed using SPSS 13.0 (SPSS, Chicago, IL).

Results

Between March, 1997 and June, 2005, a total of 239 patients with PCa were treated with a combination of radiotherapy and HDR-BT at the Department of Radiation Oncology, Hospital A.C. Camargo, São Paulo, Brazil. Of those, 184 patients were considered IR or HR and eligible for study entry. Median age of patients was 70 years old (range, 47-83) and median follow-up was 74.5 months (range, 24 –123 months). Clinical characteristics of patients are shown in Table 1.

Ninety-one patients were considered IR (49.4%) and 93 (50.6%) were considered HR. Ninety-nine (53.8%) patients did not use androgen deprivation prior to external radiotherapy.

The two groups were well balanced in terms of presence or absence of androgen deprivation, with no statistical significant difference between the groups (p= 0.437), as shown in Table 2.

The total dose of external radiotherapy ranged from 40 to 54 Gy (median 47 Gy) given in 20 to 30 daily fractions, with weekend rest. The total external radiotherapy treatment time ranged from 4 to 7 weeks (median, 5 weeks).

The interval between external radiotherapy and HDR-BT varied from 7 to 15 days in all patients. One hundred seventy-nine (97.3%) patients started their treatment with external radiotherapy. The total treatment time, including external radiotherapy, break and HDR-BT ranged from 5 to 9 weeks (median, 7 weeks).

Table 1 - Patient characteristics

Variable		N	%	Range	Median
Age-years				47-83	70.0
iPSA (ng/ml)				4.1-175	15.1
Gleason score				3-10	7
Follow up (Months)				24-120	74.5
Ethnicity	Asiatic	12	10.9		
	Caucasian	132	71.7		
	Black	26	14.1		
	Other	6	3.3		
Clinical Stage	T1	65	35.3		
	T2a	59	32.1		
	T2b	31	16.8		
	T3a	29	15.8		
NAAD-	No	99	53.8		
	Central	64	34.8		
	Peripheral	21	11.4		
Risk Group	Intermediate	91	49.5		
	High	93	50.5		
Total		184	100		

iPSA, initial PSA value; IR, intermediate risk for biochemical failure; HR, high risk for biochemical failure; NAAD, neoadjuvant androgen deprivation; EBRT, external beam radiotherapy; HDR-BT, high dose rate brachytherapy

The dose of HDR-BT ranged from 16 to 30 Gy given in 4 fractions, twice a day, administered in two days. Median HDR-BT dose was 20 Gy.

The overall survival (OS) at 5 years was 93.6% (Figure 1). Actuarial 5-year disease-free survival was 87.4% (Figure 2). Ten patients had died at the time of this analysis. Seven (3.8%) patients died due to PCa disease progression. Three (1.6%) patients died due to cardiac disease, two (1.1%) patients of second primary tumor (pancreas origin) and one from complication of Bowen disease.

The 5-year actuarial biochemical control rates for all patients, IR and HR were 83.4%, 86.2% and 78.8%, respectively, p= 0.076 (Figure 3).

On univariate analysis, the prognostic factors related to better biochemical control rates were Gleason

Table 2 - Univariate analysis

Variable		Total	Bioch. Control	%	p
Age	< 60	25	17	66.7	0.823
	61-70	70	47	66.7	
	>_70	89	69	77.5	
Race	Asiatic	11	7	63.6	0.140
	Caucasian	148	105	70.9	
	Black	19	17	89.5	
	Other	6	4	66.7	
Ipsa	<10	47	33	70.2	0.577
	10-20	82	59	72.0	
	20	55	41	74,5	
Risk Group	Intermediate	91	72	79.1	0.076
	High	93	57	61.3	
GS	<6	113	87	77.0	0.037
	7	48	33	68.8	
NAAD	Yes	85	63	74.1	0.238
	No	99	70	70.7	
EBRT	45Gy	107	63	58,8	0.011
	45Gy	77	70	90.9	
HDR-BT	20Gy	79	39	49.4	0.001
	20Gy	105	94	89.5	
Total		184	133	72.3	

iPSA – initial PSA value, GS – Geason score IR- intermediate risk for biochemical failure, HR – high risk for biochemical failure, NAAD – neoadjuvant androgen deprivation, EBRT – external beam radiotherapy, HDR-BT – high dose rate brachytherapy

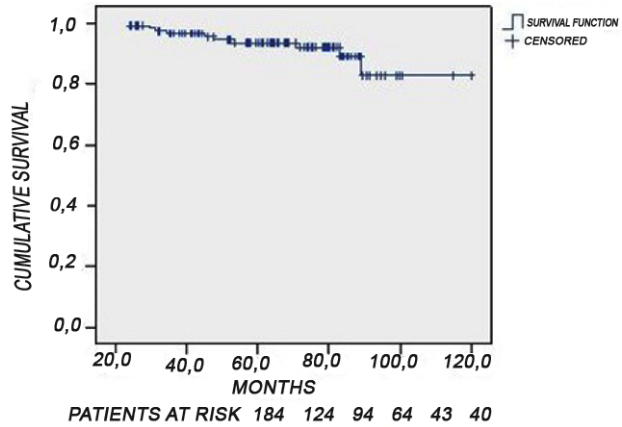


Figure1-Overall Survival Rate (OS). Numbers below each time point indicate the number of observations remaining

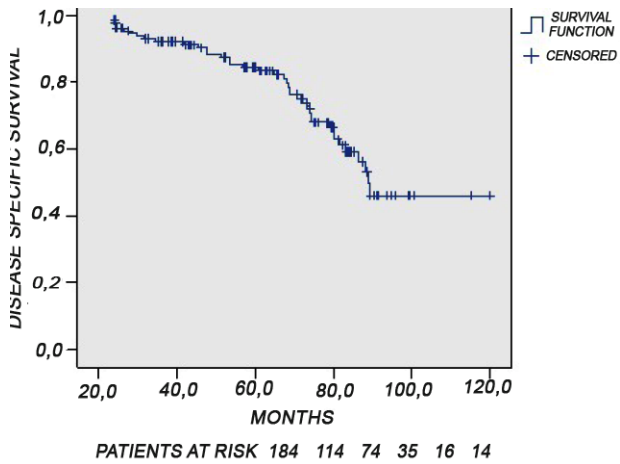


Figure 2 – Freedom from failure for all patients treated. Numbers bellow each time point indicate the number of observations remaining.

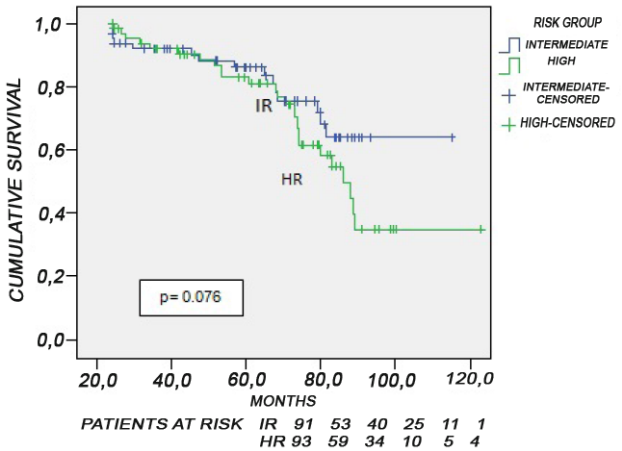
Table 3 – Distribution of patients according to Risk group and use of neoadjuvant androgen deprivation and dose escalation HDR-BT

	Risk Group						
	IR			HR			
	Total	Bioch Control	%	Total	Bioch control	%	p
NAAD	52	39	75,6	47	19	40,4	
Central	23	20	86,9	34	23	67,6	0.297
Peripheral	16	13	81,2	12	7	52.6	

IR- intermediate risk for biochemical failure, HR – high risk for biochemical failure, NAAD – neoadjuvant androgen deprivation

score < 6 ng/ml (p= 0.037), external radiotherapy T >45 Gy (p= 0.011) and HDR-BT > 20 Gy (p< 0.001) (Table 2). The association of NAAD and risk groups for biochemical failure was also explored with no statistical significance (p= 0.121) (Table 3).

On multivariate analysis, no statistically significant predictive factor related to biochemical control was found.



Risk Groups for biochemical failure – IR – intermediate risk, HR - high risk

Figure 3 – Biochemical control by risk group for biochemical failure

Discussion

The use of PSA as an effective marker of clinical success in the absence of measurable disease has been a boon to the evaluation of prostate cancer therapies. When comparing treatment outcomes of PCa from different studies, it is important to know the distribution of risk groups for biochemical failure as this dramatically affects results. Although there may be some differences between institutions in classification systems, there is a consensus that standard definitions must involve clinical stage, Gleason score and initial PSA value.

We defined as IR patients with either stage T2b, Gleason score 7 or initial PSA value ranging from 10–20 ng/ml. Patients who presented two or more of the characteristics of IR or initial PSA > 20 ng/ml, Gleason score > 7 or clinical stage > T2b were grouped into the HR group, based on a research from Fox Chase Center of over 1,575 patients.[3]

Several retrospective studies have previously described the outcome of patients treated with combination of external radiotherapy and HDR-BT[8,9,12,13] but data from prospective randomized trials comparing results of this combination with dose escalation protocols are still missing.

Some studies have already evaluated results in terms of biochemical control rate when combining external beam radiotherapy and HDR-BT. Tang et al. evaluated results of 88 patients treated with 46 Gy given by external radiotherapy plus 16 or 20 Gy boost given by HDR-BT. No NAAD was allowed in their cohort. The 5-year actuarial biochemical control rates were 58.8% and 77.3% favoring the 20 Gy group (p= 0.07).[14] Galalae et al. published results of 611 patients treated with combination of external radiotherapy and HDR-BT. For the different risk groups, the actuarial 5-year biochemical control rates were 96% for LR, 88% for IR and 69% for HR. They noted that Gleason score, initial PSA value, clinical stage and classification into different risk groups were statistically significant predictive factors of biochemical failure.15 Deger et al. also reported the results of 422 patients. The 5-year biochemical control rates rates were 81% for LR, 65% for IR and 59% for HR.[16]

All studies mentioned above have shown statistical significant correlation between biochemical control outcomes and initial PSA value, risk group classification and Gleason score. In our analysis, the biochemical control rate at 5 years also had a statistical significant difference when higher total HDR-BT doses were administered ($p < 0.001$).

The use of long-term adjuvant androgen deprivation and external radiotherapy for patients grouped into IR and HR has been extensively explored. Pilepich et al. reported the results of 945 patients enrolled in the trial RTOG 85-31, observing that the actuarial 5-year biochemical control rate was superior for patients who had androgen blockage (84% x 71%, $p < 0.0001$).17 The updated results of this trial with a median follow-up for all patients of 7.6 years showed an increased 10-year biochemical control rate favoring the use of androgen deprivation (38% versus 23%, $p < 0.0001$).18

Bolla et al. published the results of another prospective randomized trial comparing 70 Gy given by external radiotherapy with or without adjuvant long-term use of goserelin in 415 patients. With a median follow-up of 45 months, the actuarial 5-year overall survival were 79% for the combined treatment group and 62% in the radiotherapy group alone ($p=0.001$).[19] The EORTC trial 22861 has shown that androgen suppression with LHRH analogue given during and for 3 years after external radiotherapy improved overall survival, whatever the Gleason score.[20] One might observe that patients at IR or HR should have adjuvant androgen deprivation based on the published data, but many patients in our cohort, especially the youngest ones, still refuse its use due to intent of potency preservation.

The potential benefit for the use of NAAD deprivation is still controversial for patients into IR or HR group for biochemical failure. Martinez et al. in a study of 1,260 patients treated with pelvic radiotherapy and HDR-BT observed similar overall and disease-free survival and also biochemical control for patients who were treated with or without the addition of NAAD up to 6 months prior to radiation. They also observed that

it added side effects and cost, and furthermore, for the most unfavorable group, there was a higher rate of distant metastasis and more prostate cancer-related deaths.21 We observed in our study that the use of NAAD was not associated with an improvement in biochemical control rates (p= 0.238).

Although the number of studies published reporting the combination of HDR-BT and external radiotherapy is increasing, what is still not answered is whether adding pelvic radiation, instead of prostate localized radiotherapy in combination to HDR-BT for PCa patients with a more than 15% risk of positive lymph nodes, will really improve outcome. Vargas et al. performed a matched-pair analysis of 1432 patients treated with radiotherapy and HDR-BT between 1993 and 2003. There were 755 cases identified as having more than 15% of risk of positive pelvic lymphonodes. Of those, 255 cases were treated without pelvic radiotherapy and randomly matched by Gleason score, clinical stage and initial PSA value to 500 cases treated with pelvic radiotherapy, resulting in 250 pairs. As results they observed that biochemical control rates and overall survival were not significantly different for patients treated with pelvic radiotherapy. At a median follow-up of 4 years, biochemical control and overall survival rates were 78%, 86%, 89% and 88%, respectively. [21]

In our analysis, the overall survival at 5 years was 93.6% and the 5-year actuarial biochemical control rates for IR and HR were 90.2% and 88.5% (p= 0.216), respectively.

Chin et al. related the results of 65 consecutive patients treated between 1998 and 2004 with combination of radiotherapy and HDR-BT. Sixty patients (92.3%) were considered IR or HR. With a median follow-up of 3.5 years, the 3-year actuarial biochemical control rate was 90.8%.[23] Yamada et al. also reported the results of 105 patients consecutively treated between 1998 and 2004 with external radiotherapy and HDR-BT. With a median follow-up of 44 months, the 5-year actuarial biochemical control rates for patients grouped into IR and HR were 98%, and 92%, respectively.[24]

Patients considered HR have more chances of biochemical failure, so they are more likely to receive a higher dose of radiation or a "boost", as consequence of its lower biochemical control rates in various series. The tumor biology itself could explain the progression of the disease in the HR group despite the higher dose administered. Our results suggested that biochemical control is related not only to clinical characteristics of patients, as Gleason score, but it is also related to treatment parameters as total dose of HDR-BT and external radiation administered, despite no statically significant data found on multivariate analysis. In this view, risk-adapted therapy is very important in these cases.

The combination of radiotherapy and HDR-BT is an alternative strategy of dose escalation, as this combination can provide treatment to potential areas of microscopic spread outside the prostate for patients at HR.

Conclusion

HDR-BT combined to external radiotherapy is a successful form of treatment of PCa, with results comparable to published data, results that tend to be even better with the introduction of image guided brachytherapy. The challenge for the future is to determine which treatment option will have the best result for each patient and what the role of NAAD is when using radiotherapy combined to HDR-BT for IR and HR patients

References

1. Smith R.A., Cokkinides V., Eyre H.J.: American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin, 56:11,2006.
2. Ali A.S., Hamdy F.C.: The spectrum of prostate cancer care: from curative intent to palliation. Curr Urol Rep, 8:245, 2007.
3. Chism,D.B., Hanlon, A. L., Horwitz, E. M., Feigenberg A comparison of the single and double factor high-risk models for risk assignment of prostate cancer treated with 3D conformal radiotherapy. Int J Radiat Oncol Biol Phys, 58:1048,2004.
4. Morgan,P.B., Hanlon, A. L., Horwitz, E. M., Buyyounouski, M. K., Uzzo, R. G., Pollack, A.: Radiation dose and late failures in prostate cancer. Int J Radiat Oncol Biol Phys, 67:1074,2007.
5. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, Lee AK, Pollack A. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys.70:67–74,2008.
6. Martin JM, Bayley A, Bristow R, Chung P, Gospodarowicz M, Menard C, Milosevic M, Rosewall T, Warde PR, Catton CN. Image guided dose escalated prostate radiotherapy: still room to improve. Radiat Oncol. 2009 Nov 3;4:50.; Kwok Y, Yovino S. Update on radiation-based therapies for prostate cancer. Curr Opin Oncol. 2010 May;22(3):257-62],
7. Bolla,M; Reijke,TM; Geertjan Van Tienhoven, GV; Alphonsus C.M. Van den Bergh,ACM; Oddens,J; Poortmans,PMP; Gez,E; Kil, P; Akdas, A; Soete, G; Kariakine,O; van der Steen-Banasik, EM; Musat,E; Piérart, M.; Mauer, ME; Collette, L.. Duration of Androgen Suppression in the Treatment of Prostate Cancer. Volume 360:2516-2527, 2009.
8. Pellizzon AC, Salvajoli J, Novaes P, Maia M, Fogaroli R, Gides D, Horriot R. The relationship between the biochemical control outcomes and the quality of planning of high-dose rate brachytherapy as a boost to external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO Phoenix definition. Int J Med Sci. 4;5(3):113-20, 2008.

9. Phan, T.P., Syed, A.M., Puthawala, A., Sharma, A., Khan, F.: High dose rate brachytherapy as a boost for the treatment of localized prostate cancer. J Urol,177:123, 2007; Galalae, R.M., Kovacs, G., Schultze, J., Loch, T., Rzehak, P., Wilhelm, R. Bertermann, H., Buschbeck, B., Kohr, P., Kimmig, B.: Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 52:81, 2002.
10. Pellizzon, A.C., Salvajoli, J.V., Maia, M. A., Ferrigno, R., Novaes, P. E., Fogarolli, R. C., Pellizzon, R. J.:, Late urinary morbidity with high dose prostate brachytherapy as a boost to conventional external beam radiation therapy for local and locally advanced prostate cancer. J.Urol, 171:1105, 2004.
11. Roach III, M., Hanks, G., Thames Jr, H., Schellhammer, P., Shipley, W. U., Sokol, G. H., Sandler, H.: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference: Int J Radiat Oncol Biol Phys, 65: 965,2006.
12. Pellizzon AC, Nadalin W, Salvajoli JV, Fogaroli RC, Novaes PE, Maia MA, Ferrigno R. Results of high dose rate afterloading brachytherapy boost to conventional external beam radiation therapy for initial and locally advanced prostate cancer. Radiother Oncol.66(2):167-72, 2003.
13. Hsu, I.C., Cabrera, A. R., Weinberg, V., Speight, J., Gottschalk, A. R., Roach III, M., Shinohara, K.: Combined modality treatment with high-dose-rate brachytherapy boost for locally advanced prostate cancer. Brachytherapy, 4: 202, 2005
14. Tang, J.I., Williams, S.G., Tai, K.H., Dean, J., Duchesne, G.M.: A prospective dose escalation trial of high-dose-rate brachytherapy boost for prostate cancer. evidence of hypofractionation efficacy? Brachytherapy, 5:256,2006.
15. [Galalae, R.M., Martinez, A., Mate, T., Mitchell, C., Edmundson, G., Nuernberg, N., Eulau, S., Gustafson, G., Gribble, M., Kovacs, G.: Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. Int J Radiat Oncol Biol Phys,58:1048,2004.
16. Deger, S., Boehmer, D., Roigas, J., Schink, T., Wernecke, K.D., Wiegel, T., Hinkelbein, W., Budach, V., Loening, S.A.: High dose rate (HDR) brachytherapy with conformal radiation therapy for localized prostate cancer. Eur Urol, 47:441,2005.
17. Pilepich, M.V., Caplan, R., Byhardt, R. W., Lawton, C. A., Gallagher, M. J., Mesic, J. B., Hanks, G. E., Coughlin, C. T., Porter, A., Shipley, W. U., Grignon, D.: Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. J Clin Oncol, 15: 1013, 1997.
18. Pilepich, M.V., Winter, K., Lawton, C.A., Krisch, R. E., Wolkov, H. B., Movsas, B., Hug, E. B., Asbell, S. O., Grignon, D.: Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys, 61:1285, 2005.
19. Bolla, M., Gonzalez, D., Warde, P., Dubois, J. B., Mirimanoff, R. O., Storme, G., Bernier, J., Kuten, A., Sternberg, C., Gil, T., Collette, L., Pierart, M.: Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med, 337: 295,1997.
20. Bolla, M., Maingon, P., Fourneret, P., Artignan, X., Descotes, J. L.: Indications of the association of radiotherapy and hormonal treatment in prostate cancer. Cancer Radiother, 9: 394, 2005.
21. Martinez, ,A., Galalae, R., Gonzalez, J., Mitchell, C., Gustafson, G., Kovacs, G.: No apparent benefit at 5 years from a course of neoadjuvant/concurrent androgen deprivation for patients with prostate cancer treated with a high total radiation dose. J Urol, 170: 2296,2003.
22. Vargas, C., Martinez, A., Galalae, R., Demanes, J., Harsolia, A., Schour, L., Nuernberg, N., Gonzalez, J.: High-dose radiation employing external beam radiotherapy and high-dose rate brachytherapy with and without neoadjuvant androgen deprivation for prostate cancer patients with intermediate- and high-risk features. Prostate Cancer Prostatic Dis, 9:245, 2006.
23. Chin YS, Bullard J, Bryant L, Bownes P, Ostler P, Hoskin PJ. High dose rate iridium-192 brachytherapy as a component of radical radiotherapy for the treatment of localised prostate cancer.Clin Oncol (R Coll Radiol). 18(6):474-9, 2006.
24. Yamada Y, Bhatia S, Zaider M, Cohen G, Donat M, Eastham J, Rabbani F, Schupak K, Lee J, Mueller B, Zelefsky MJ. Favorable clinical outcomes of three-dimensional computer-optimized high-dose-rate prostate brachytherapy in the management of localized prostate cancer. Brachytherapy. 2006 Jul-Sep;5(3):157-64.

Submitted: 05/03/2010
Aproved: 12/03/2010
Published: 23/11/2010