Original article

Vital role of volume and number of needles in HDR brachytherapy (HDR-BT) of prostate cancer

Adam Chicheł, MD, Marek Kanikowski, MD, Janusz Skowronek, MD, PhD, Ass. Prof.

Brachytherapy Department, Greater Poland Cancer Centre, Poznań, Poland

Abstract

Purpose: The quality of HDR-BT of prostate cancer depends on operator skills, anatomy, prostate volume and relation to surrounding tissues as well as previous diseases and treatments of a patient. There is a rare data available concerning the minimum number of needles and its influence on dose distribution, side effects and long-term outcome. The study is to determine the minimal prostate volume and minimum number of needles suitable for HDR-BT in order to obtain an implant of good quality.

Material and methods: 181 patients with localized prostate cancer were treated with interstitial HDR-BT boost. 15 Gy from HDR-BT was administered after 50 Gy from EBRT. Clinical, volumetric and dosimetric data were collected. Treatment plans were divided into Group A, consisted of optimal treatment plans (P-D_{90} > 90%, P-V_{200} < 15%, U-D_{10} < 125%, U-D_{max} < 160%, R-D_{10} < 85%) and Group B, with suboptimal plans.

Results: The difference between two groups was statistically significant (p = 0.013) with regard to number of needles. There was no statistically significant difference concerning prostatic volume. Median number of inserted needles in the first and the second group resulted in 15 (range 9-18) and 13 (range 8-18), respectively. Differences were the most eminent in patients with prostate glands of small volume (< 20 cc). In the study, either the minimum number of needles nor minimal prostate gland volume were not clearly defined in terms of high probability of achieving a good quality implant.

Conclusions: Larger volume and higher number of needles are related to an advanced probability of treatment plan with all DVC fulfilled. The minimum number of needles suggested is > 9, optimally ≥ 13. Furthermore, the minimal prostate volume recommended is > 12 cc, optimally ≥ 18 cc. The volume of insufficient size and/or small number of needles results in suboptimal treatment plans.

J Contemp Brachyther 2009; 1, 3: 145-150

Key words: prostate cancer, HDR brachytherapy, volume, number of needles.

Purpose

One of the current approaches for the management of localized prostate cancer is a combination of external beam radiotherapy (EBRT) with interstitial high-dose-rate brachytherapy (HDR-BT) boost with or without additional hormonal therapy. Its safety and effectiveness has been proven elsewhere [1-3]. According to different authors, 5-year long biochemical control of the disease is achievable in 53 to 93% of cases [4-9].

As it is well known to the professionals accustomed to this method, the quality of prostate cancer interstitial brachytherapy depends on operator skills, anatomy of prostate, its volume and relation to surrounding tissues (pubic arc interference) as well as previous diseases and treatments of a patient (e.g. TURP, hormonal therapy). Clinical practice prove that the number of implanted needles is also very important. However till date, only an occasional data is available regarding the minimum number of needles and its influence on dose distribution, side effects and long-term outcome [1, 10-15].

In consecutive series of patients certain characteristic relation was noticed. The prostate glands of small volumes were obviously implanted with low number of needles, which, in turn, caused increased occurrence of suboptimal treatment plans. Suboptimal plans were described as a set of treatment plan parameters exceeding any of dose-volume constraints (DVC) established in the department (Table 1). Such situations were much less common during treatment of large prostate glands.

There is a few data available that indicate the dose values and homogeneity index (HI) in treated volume to be dependent on such prognostic factors as prostate gland volume, location of intraprostatic portion of urethra and the number of interstitially inserted applicators

Address for correspondence: Adam Chicheł, MD, Brachytherapy Department, Greater Poland Cancer Centre, 15 Garbary Street, 61-866 Poznań, Poland, phone +48 61 885 09 18, +48 0600 687 369 (mobile), fax +48 61 885 08 34, ✉ e-mail: achichel@go2.pl

Received: 29.08.09
Accepted: 24.09.09
Published: 05.10.09

[10-12, 16, 17]. Moreover, what is predominant in the literature, authors prefer focusing on relations between particular treatment plan parameters and long-term outcome, along with acute and late toxicity.

The study is to determine the minimal prostate volume suitable for treatment and minimum number of needles which should be used for HDR-BT to obtain an implant of good quality. Once the answer is obtained, it could influence the recommendations for HDR-BT of prostate cancer treatment. Side effects and long-term outcome were not an issue in the study.

Material and methods

From April 2007 till December 2008 a number of 181 patients (median age 64, ranged 51-70) with localized prostate cancer ($T_{1-3}N_0M_0$) were treated with interstitial HDR-BT in the Brachytherapy Department in Greater Poland Cancer Centre (Table 2). In all cases, the treatment was a combination of external beam radiotherapy (EBRT) and HDR-BT. Boost of 15 Gy was administered as a single dose after 50 Gy delivered from EBRT.

Table 1. Dose-volume constraints (DVC) for HDR-BT, accordingly to the institutional recommendations

Target (CTV1)	Urethra	Rectal wall
D_{90} > 90%	D_{10} < 125%	D_{10} < 85%
V_{200} < 15%	D_{max} < 160%	
D_{max} possibly lowest		

CTV1 – clinical target volume (encompassed by prostate capsule), D_{90} – the percentage of prescribed dose delivered to 90% of treated volume, D_{10} – the percentage of the organ at risk receiving 10% of prescribed dose, V_{200} – the percentage of treated volume receiving 200% of prescribed dose, D_{max} – maximal dose in treated volume

Table 2. Patients characteristics (n = 181)

Characteristics	All cases (n = 181)
Age, y, median (range)	64 (51-70)
T stage	
T1	39.8% (72)
T2	51.4% (93)
T3	8.8% (16)
i-PSA	
< 10 ng/ml	35.9% (65)
10-20 ng/ml	29.8% (54)
> 20 ng/ml	34.3% (62)
Gleason score	
2-6	53.0% (96)
7	28.7% (52)
8-10	18.3% (33)
Risk groups	
low [T1-2a, GS ≤ 6, i-PSA ≤ 10]	21.5% (39)
intermediate [T2b-c, GS = 7, i-PSA 10-20]	32.6% (59)
high [T3, GS ≥ 8, i-PSA ≥ 20]	45.9% (83)
Prostate volume, cc, median (range)	24 (8-81)
Hormonal therapy	
yes	66.8% (121)
no	33.2% (60)

** in 1 case treated volume exceeded recommended 60 cc and achieved 81 cc*
i-PSA – initial level of prostate specific antigen, GS – Gleason score

Study inclusion criteria were such as: men aged 50 to 70 years with prostate cancer confined to the gland ($T_{1-3}N_0M_0$), no regional and/or distant metastases, optional neoadjuvant hormonal therapy (3 to 6 months) and a written consent. The exclusion criteria were as follow: ≤ 6 months after transurethral resection of prostate (TUR-P), concomitant diseases disqualifying the patient from general anesthesia, expected survival < 5 years, the presence of metastases, anatomical obstacles – pubic arch interference, adenomectomy in anamnesis and large defect after TUR-P. Detailed clinical, volumetric and dosimetric data were collected. All 181 treatment plans were analyzed, paying special attention to meeting the requirements of dose values for target coverage and dose limits for organs at risk (dose-volume constraints, DVC) (Table 1). Subsequently, all plans were split into two groups. Group A consisted of treatment plans which met every requirement of a good implant, whereas Group B consisted of suboptimal treatment plans, in which not all DVC met their recommended values. The aim of each good quality (optimal) implant was to deliver more than 90% of prescribed dose to at least 90% of the target volume (D_{90} > 90%). The most important dose volume limitations in urethra and rectal wall were D_{10} < 125% and < 85%, respectively. For delivery of radiation the operators used microSelectron® HDR remote afterloader (Nucletron B.V., Veenendaal, The Netherlands) working on a software for real-time intraoperative treatment planning (Nucletron B.V., SWIFT®) with blind inverse planning optimization.

Additionally, both implant quality groups were investigated in terms of differences in prostate gland volume, PTV and the number of implanted needles. Prostatic volume was assessed on the basis of the measurements derived from transrectal ultrasound (TRUS), which in every case was performed by a radiologist before the treatment. TRUS was also used to define the initial technical applicability of HDR-BT and was enabled to exclude patients with pubic arch interference. CT scans collected in purpose of EBRT, especially in patients with prostate volume ≥ 50 cc played the same role [18].

In analyzed series, out of 181 patients, 121 (66.8%) received a neoadjuvant hormonal therapy. The purpose of such management was to diminish the risk of a relapse in intermediate and high risk groups of patients, according to current recommendations. The investigated group was also divided into two subgroups of patients treated with hormonal therapy and no hormonal therapy administered. Both subgroups were compared on the subject of prostatic volume.

Statistical analysis of the above relations was prepared with the assistance of Mann-Whitney U test; assumed significance level $p < 0.05$.

Results

In radiological assessment of prostatic volume (P-Vol) the difference was not significant between two groups (Fig. 1.;

p = 0.170). In case of PTV one could notice only slight tendency towards suboptimal treatment plans in the group of small volumes (Fig. 2, p = 0.060). The lower limit of prostate gland volume, below which any implant would certainly be suboptimal was not identified on the basis of investigated material. Such threshold could be a contraindication for using HDR-BT.

Figure 3 illustrates statistically significant difference in the number of implanted needles between DVC groups (p = 0.013). The median number of needles in group A and B resulted in 15 (range 9-18) and 13 (range 8-18), respectively. It appears that in the group of optimal treatment plans (Group A), in comparison with the group of suboptimal treatment plans (Group B), considerably higher number of needles was used for implantation (p = 0.026). This difference was most eminent in patients with a small volume of prostate glands (< 20 cc).

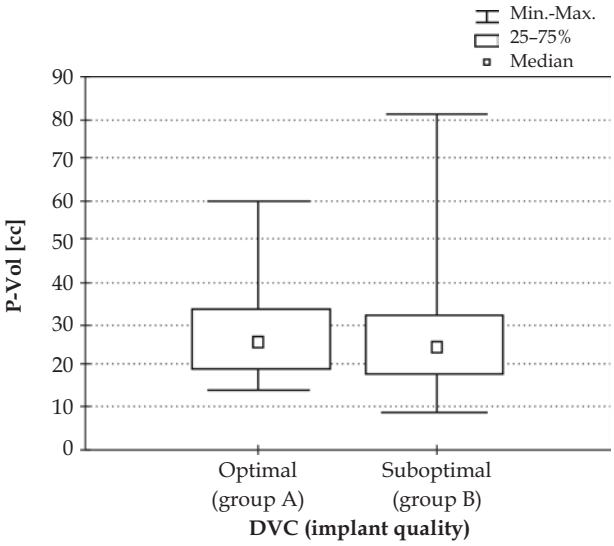
The lowest number of needles that is necessary to prepare an implant and achieve an optimal treatment plan was also not identified on the basis of investigated material. That demonstrate, that in both situations, there is no simple transformation to numbers, which could be clearly verified by statistics. However, under real clinical circumstances, there are many additional factors of possible great importance to have an influence on the final DVH, such as: anatomy of a patient (shape, mobility of prostate gland and its capsule flexibility, localization of the urethra, pubic arch interference, etc.). In the study, the median number of needles in Group A was 15, and in Group B – 13. Nevertheless, on the basis of collected data one can assume, that the minimum number of implanted needles should exceed 9, optimally ≥ 13. The minimal volume of the prostate gland suitable for HDR-BT should exceed 12 ml, optimally ≥ 18 ml (Figs. 1-3).

In subset of patients with intermediate and large prostate volumes obtaining satisfactory or excellent target coverage (high values of D90 and V100) along with proper dose distribution (less hot-spots with lowered V200), HDR-BT was possible thanks to implantation of a large number of needles (maximally 18) and ability to place the needles in a safe distance from the urethra (recommended > 5 mm). Under such conditions, DVC can easily meet their requirements. Nevertheless, in spite of a large volume, in some patients suboptimal treatment plans originated from sudden occurrence of pubic arch interference, excessively large defects after TUR-P, unusual anatomy, asymmetric benign hypertrophy or massive calcifications.

Amongst the investigated group, 7 out of 181 (3.8%) and 41 out of 181 (22.6%) patients were assessed to have prostate gland volume ≤ 12 cc and < 18 cc, respectively. There were also 6/181 (3.3%) and 49/181 (27.1%) patients which were implanted with ≤ 9 and < 13 needles, respectively.

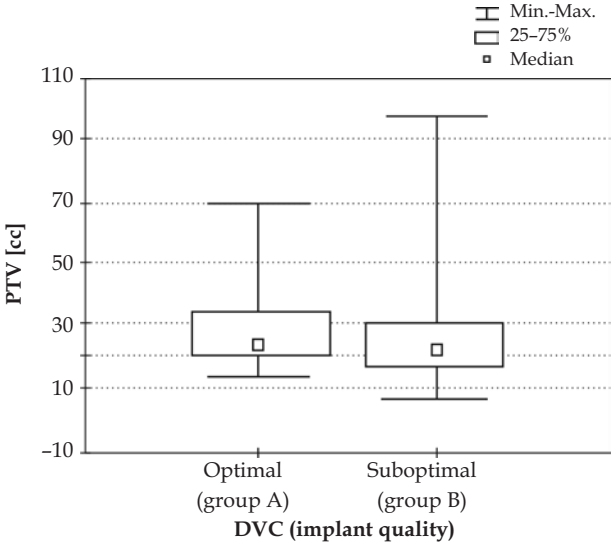
It was proven, that subgroup of patients with additional hormonal therapy differed significantly from the subgroup without additional treatment (p < 0.001) (Fig. 4). Hormonal therapy prescribed before HDR-BT decreased the prostate gland during the treatment. The mean prostate volume in hormonally treated patients was 23.3 cc and 33.5 cc in these without neoadjuvant treatment. Hormonally triggered shrinkage of prostate gland resulted in 30% reduction of volume.

Additional analysis of the hormonal therapy regimens (antiandrogens alone, LH-RH analogues alone or both) and



P-Vol – prostatic volume
DVC – dose-volume constraints

Fig. 1. Difference in prostate gland volumes between two groups of patients. In Group A all DVC met their requirements (optimal treatment plans), in Group B they did not meet their requirements (suboptimal treatment plans) (p = 0.17), Mann-Whitney U test



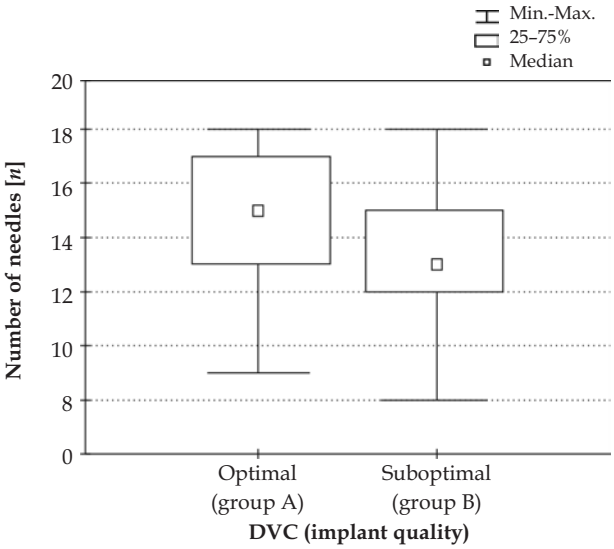
PTV – planning target volume
DVC – dose-volume constraints

Fig. 2. Difference in PTV between two groups of patients. In Group A all DVC met their requirements (optimal treatment plans), in Group B they did not meet their requirements (suboptimal treatment plans) (p = 0.06), Mann-Whitney U test

the duration of treatment did not reveal any statistically significant differences in regard to the degree of prostate gland shrinkage.

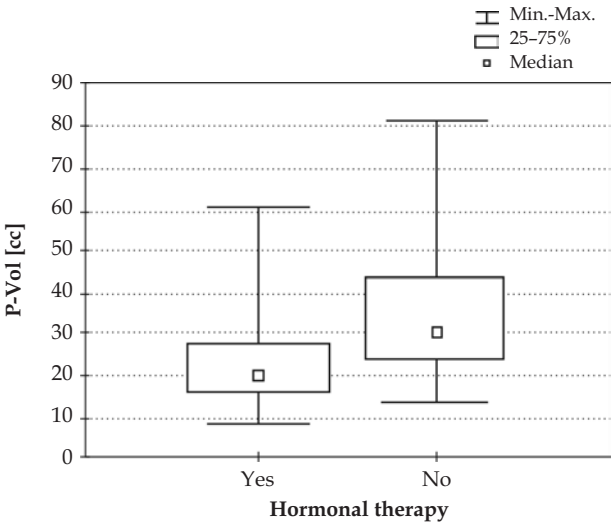
Discussion

Even though the difference in the prostate gland volume between Group A and B was found to be statistically insignificant, the volume seem to be strongly associated with the number of needles [13-15, 19]. The prostate volume and urethra are the major factors to influence the location and number of needles. Relatively large prostate gland volume enables the usage of higher number of needles in order to obtain a good quality implant. On the other hand, a large volume may result in pubic arch interference at the site and increased late toxicity [1]. As it was presented in a related study, the number of needles was found to be directly proportional to PTV, prostatic D_{90} and V_{100} and inversely proportional to V_{200} [19]. Similar conclusions are shown in paper of Charra-Brunaud *et al*. who stated, that the smaller the prostate volume, the stronger the influence of number of needles on higher values of treatment plan parameters, particularly V_{150} in CTV and urethra [12].



DVC – Dose Volume Constraints

Fig. 3. Difference in number of implanted needles between two groups of patients. In Group A all DVC met their requirements (optimal treatment plans), in Group B they did not meet their requirements (suboptimal treatment plans) (p = 0.013), Mann-Whitney U test



P-Vol – prostatic volume

Fig. 4. Difference in prostate gland volumes between two groups of patients, out of which one received hormonal therapy and the other did not obtain hormonal therapy (p < 0.001), Mann-Whitney U test

Most prostate cancer tumors are found in a peripheral zone. Clinicians intentionally follow this phenomenon by implanting the needles to the periphery in order to acquire an excellent target coverage and to minimize the urethral dose. Such approach is recommended by most of the authors [4, 8, 12-14]. However, in case of a very small prostate volume it is quite difficult to place the needles far from the urethra and the reference dose prescribed to CTV1 (prostate capsule) may cause difficulties. In such case certain compromise on particular DVC in target and/or organs at risk is necessary. One of the method to overcome this problem is to prescribe 100% isodose to CTV2 (peripheral zone) or even CTV3 (tumor volume) [1, 20, 21].

The study suggest to treat the organ which can be implanted with more than 13 needles. Mate *et al*. [22] recommended to use 18 to 22 needles in order to achieve an excellent target coverage with 100% isodose (V_{100} > 90%). Similar conclusions were published by Dinges *et al*. [23], who suggested implanting at least 20 needles to limit the dose delivered to 10 cc of target below 135% of reference dose. Furthermore, Borghede *et al.* [21] proved, that lesser dose heterogeneity inside the target can be easily achieved by placing higher number of needles. Focused rather on morbidity, Akimoto *et al*. [10, 11] suggested to implant more than 12 needles in order to minimize genitourinary (GU) toxicity. Furthermore, Duchesne *et al*., in order to decrease the risk of late GU morbidity, recommends to limit the level of V_{200} < 15% of PTV with higher number of needles in a large prostate glands [24]. Other published data share this presented view [12, 13, 15, 19]. On the contrary, Kovács *et al.* [1] intentionally uses small number of needles and prescribes reference dose to CTV2 (peripheral zone of the prostate) to cover the critical structures by relatively low dose areas.

According to the current recommendations, patients with intermediate and high risk of prostate cancer should be treated with neoadjuvant and/or adjuvant hormonal treatment [25, 26]. In the study they constituted a group of 141 out of 181 (78.4%) patients. The number of 121 (66.8%) patients were treated with hormonal drugs for up to 6 months before the actual HDR-BT. Statistical analysis revealed a significant influence of hormonal therapy on prostate volume in patients treated with HDR-BT.

Up till now, the minimal prostate volume suitable for HDR-BT and minimum number of needles sufficient for interstitial treatment were not clearly determined. We suggest to remain the minimal number of needles used for each implant > 9, optimally ≥ 13. Prostates of volume less than 12 cc should not be qualified for HDR-BT, optimal threshold ≥ 18 cc. Patients with prostates of 12 to 18 cc constitute a specific "grey zone". Within this group of patients, HDR-BT treatment is still feasible, however under certain conditions such as small volume not accompanied by e.g. oblique urethra, asymmetric central lobe hypertrophy, post TUR-P defects and/or pubic arch interference.

Defining more strict indications for HDR-BT of prostate cancer could be advantageous. In our opinion, more precise selection of patients permits to avoid some cases which in the end are unintentionally treated with suboptimal treatment plans. Unsatisfactory target coverage, even in a small portion, may result in significant reduction in probability of cure [27]. On the other hand, properly administered HDR-BT has a double advantage: it increases the probability of local cure concomitantly with minimizing the incidence and severity of side effects.

Conclusions

In HDR-BT treatment of prostate cancer it is important, that relatively larger prostate volume and higher number of needles is related to a higher probability of achieving a treatment plan which meets the requirements of DVC. Suggested minimum number of needles that should be used for each implant is > 9, optimally ≥ 13. Recommended minimal prostate volume qualified for HDR brachytherapy should not be less than 12 cc, optimally ≥ 18 cc. Not sufficient volume of prostate and/or low number of implanted needles results in suboptimal treatment plans with disturbed target coverage, exceeded DVC and/or increased inhomogeneity.

References

1. Kovács G, Pötter R, Loch T et al. GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localized prostate cancer. *Radiother Oncol* 2005; 74: 137-148.
2. Hansen EK, Roach III M. Prostate cancer. In: Hansen EK, Roach III M (eds.). Handbook of Evidence-based Radiation Oncology. *Springer*, New York 2007; Chapter 25: 293-317.
3. Kanikowski M, Skowronek J, Milecki P et al. Brachyterapia HDR raka gruczołu krokowego. *Urologia Polska* 2007; 2: 5-11 [Polish].
4. Galalae RM, Kovacs G, Schultze J et al. Long term outcome after elective irradiation of the pelvic lymphatic and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys* 2002; 52: 81-90.
5. Prada PJ, Gonzalez H, Fernandez J et al. High-dose-rate intensity modulated brachytherapy with external-beam radiotherapy improves local and biochemical control in patients with high-risk prostate cancer. *Clin Transl Oncol* 2008; 10: 415-421.
6. Kestin LL, Martinez A, Stromberg JS et al. Matched-pair analysis of conformal high dose rate brachytherapy boost versus external-beam radiation therapy alone for locally advanced prostate cancer. *J Clin Oncol* 2000; 18: 2869-2880.
7. Martinez AA, Kestin LL, Stromberg JS et al. Interim report of image-guided conformal high dose rate brachytherapy for patients with unfavorable prostate cancer: The William Beaumont phase II dose escalating trial. *Int J Radiat Oncol Biol Phys* 2000; 47: 343-352.
8. Syed AMN, Puthawala A, Sharma A et al. High dose rate brachytherapy in the treatment of carcinoma of the prostate. *Cancer Control* 2001; 8: 511-521.
9. Hiratsuka J, Jo Y, Yoshida K et al. Clinical results of combined treatment conformal high-dose-rate iridium-192 brachytherapy and external beam radiotherapy using staging lymphadenectomy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004; 59: 684-690.
10. Akimoto T, Ito K, Saitoh J et al. Acute genitourinary toxicity after high dose rate (HDR) brachytherapy combined with hypofractionated external-beam radiation therapy for localized prostate cancer: correlation between the urethral dose in HDR brachytherapy and the severity of acute genitourinary toxicity. *Int J Radiat Oncol Biol Phys* 2005; 63: 463-471.
11. Akimoto T, Katoh H, Noda S et al. Acute genitourinary toxicity after high dose rate (HDR) brachytherapy combined with hypofractionated external-beam radiation therapy for localized prostate cancer: second analysis to determine the correlation between the urethral dose in HDR brachytherapy and the severity of acute genitourinary toxicity. *Int J Radiat Oncol Biol Phys* 2005; 63: 472-478.
12. Charra-Brunaud C, Hsu IC, Wienberg V et al. Analysis of interaction between number of implant catheters and dose volume histograms in prostate high-dose-rate brachytherapy using computer model. *Int J Radiat Oncol Biol Phys* 2003; 56: 586-591.
13. Demanes D, Rodriguez R, Schour L et al. High-dose-rate intensity modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocuriethерapy's 10-year results. *Int J Radiat Oncol Biol Phys* 2005; 61: 1306-1316.
14. Mate TP. Review of HDR prostate brachytherapy with 192-Irydium. In: Bruggmoser G, Mould RF, Tai TH, Mate TP (eds.). Prostate cancer review. *Zuckschwerdt Verlag*, München 2003; Chapter 14: 85-90.
15. Kini VR, Edmundson GK, Vicini FA et al. Use of three dimensional radiation therapy planning tools and intraoperative ultrasound to evaluate high dose rate prostate brachytherapy implants. *Int J Radiat Oncol Biol Phys* 1999; 43: 571-578.
16. Chen YC, Chuang CK, Hsieh ML et al. High-dose-rate brachytherapy plus external beam radiotherapy for T1 to T3 prostate cancer: an experience in Taiwan. *Urology* 2007; 70: 101-105.
17. Yen-Chao Chen, Cheng-Keng Chuang, Ming-Li Hsieh et al. High-dose-rate brachytherapy plus external beam radiotherapy for T1 to T3 prostate cancer: An experience in Taiwan. *Urology* 2007; 70: 101-105.
18. Wallner K, Ellis W, Russel K et al. Use of TRUS to predict pubic arch interference of prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999; 43: 583-585.
19. Chicheł A, Kanikowski M, Skowronek J. Correlation between treatment plan parameters and particular prognostic factors in prostate cancer treated with high-dose-rate brachytherapy (HDR-BT) as a boost. *J Contemp Brachyther* 2009; 1: 11-17.
20. Kovács G, Melchert C, Sommerauer M et al. Intensity modulated high-dose-rate brachytherapy boost complementary to external beam radiation for intermediate- and high-risk localized prostate cancer patients – How we do it in Lubeck/ /Germany. *Brachytherapy* 2007; 6: 142-148.

21. Borghede G, Hedelin H, Holmäng S et al. Combined treatment with temporary short-term high dose rate iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma. *Radiother Oncol* 1997; 44: 237-244.
22. Mate TP, Gottesman JE, Hatton J et al. High dose rate afterloading iridium-192 prostate brachytherapy: Feasibility report. *Int J Radiat Oncol Biol Phys* 1998; 41: 525-533.
23. Dinges S, Deger S, Koswig S et al. High dose rate interstitial with external beam irradiation for localized prostate cancer – results of a prospective trial. *Radiother Oncol* 1998; 48: 197-202.
24. Duchesne GM, Das R, Toye W et al. Dose distribution and morbidity after high dose rate brachytherapy for prostate cancer: Influence of V150 and V200 parameters. *Australasian Radiol* 2002; 46: 384-389.
25. Chung HT, Speight JL, Roach III M. Intermediate- and High-Risk Prostate Cancer. In: Halperin EC, Perez CA, Brady LW (eds.). Principles and Practice of Radiation Oncology. 5th ed. *Lippincott Williams & Wilkins*, Philadelphia 2008; Chapter 63: 1483-1504.
26. Hsu IC, Cabrera AR, Weinberg V et al. Combined modality treatment with high-dose-rate brachytherapy boost for locally advanced prostate cancer. *Brachytherapy* 2005; 4: 202-206.
27. Sanchez-Nieto B, Nahum AE. The delta-TCP concept: a clinically useful measure of tumor control probability. *Int J Radiat Oncol Biol Phys* 1999; 44: 369-380.