Original article

Correlation between treatment plan parameters and particular prognostic factors in prostate cancer treated with high-dose-rate brachytherapy (HDR-BT) as a boost

Adam Chicheł, MD[1], Marek Kanikowski, MD[1], Janusz Skowronek, MD, PhD, Ass. Prof.[1], Magdalena Dymnicka, MSc[2], Tomasz Piotrowski, MSc, PhD[2]

[1]Brachytherapy Department, [2]Medical Physics Department, Greater Poland Cancer Centre, Poznan, Poland

Abstract

Purpose: Certain constraints for target coverage and dose limits in Organs at Risk (OARs) shows some evidence that doses values and homogeneity index in treated volume depends on prognostic factors such as prostate volume, location of urethra and the number of inserted applicators. Our study is to determine the relation between values of the doses in prostate, OARs and particular prognostic factors related to HDR-BT of prostate cancer.

Material and methods: The amount of 190 patients with localized prostate cancer were treated with interstitial HDR-BT between July 2006 and July 2007. The HDR-BT was administered as a boost for previously delivered 50 Gy dose from external beam radiotherapy. Dose volume parameters were determined such as: D_{min}, D_{max}, D_{mean}, D_{90}, V_{100}, V_{150} and V_{200} for prostate and D_{min}, D_{max}, D_{mean}, D_{10} and V_{100} for urethra and rectum (OARs), respectively. These parameters were correlated with prognostic factors such as: age, staging (TNM), Gleason score, initial PSA level (i-PSA), number of needles and volume of the prostate.

Results: The mean value of D_{90} was 91.3%, range 65.9-102.8%. Mean urethral D_{10} was 121, 8%, range 78.8-152.9%. Mean rectal D_{10} was 81.3%, range 37.4-101.0%. Statistically significant relationship was found between staging (TNM), prostate volume, and the number of needles used for implant and increased prostate D_{90} and decreased V_{200}. The prognostic factor was only the age which was related to increased urethral D_{10} and D_{max}. No correlation was found between any prognostic factor and rectal wall DVH parameters.

Conclusions: Increased prostate volume with improved D_{90} and greater number of implanted needles results in better target coverage (higher V_{100}), better dose distribution (lower V_{200}) and decreased dose delivered to the urethra (lower urethral D_{10}, D_{max}), with no evident influence on rectal wall. Further investigation with closed follow-up should give an answer whether the above corresponds with morbidity and outcome.

J Contemp Brachyther 2009; 1, 1: 11-17

Key words: prostate cancer, HDR brachytherapy, doses values, prognostic factors.

Purpose

Modern high-dose-rate brachytherapy (HDR-BT) of prostate cancer enables the delivery of a very high single or multiple dose of radiation to the target volume (e.g. prostate capsule) and, at the same time, preventing the organs at risk from unnecessary radiation (e.g. urethra and rectal wall) [1-3]. The 3D reconstruction of ultrasound image series is used for prospective treatment planning which is based on dose volume parameters. There are certain dose volume constraints for target coverage and dose limits in OARs [4, 5]. Furthermore, there is some evidence that dose values in treated volume are dependent on different factors such as prostate volume, location of urethra and number of inserted applicators [6-9]. Amongst the large number of prostate cancer patients there is a group that is suitable for combined treatment of external beam radiotherapy (EBRT) and preceded or followed by HDR-BT. The feasibility and efficacy of such approach in localized prostate cancer has been already proven [4, 10, 11]. Combination of EBRT with HDR-BT boost is found to be effective and related to comparatively low incidence of side effects [4, 11-13]. It was noticed

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, fax +48 61 885 08 34, ✉ e-mail: achichel@go2.pl

Received: 30.12.08
Accepted: 13.02.09
Published: 19.03.09

Table 1. Patients characteristics (n = 190)

Characteristics	All cases (n = 190)
Age, median (range)	68 (52-81)
T stage	
T1	22.6% (43)
T2	69.0% (131)
T3	8.4% (16)
i-PSA	
< 10 ng/ml	36.3% (69)
10-20 ng/ml	30.0% (57)
> 20 ng/ml	33.7% (63)
Gleason score	
2-6	52.1% (99)
7	28.4% (54)
8-10	16.3% (31)
ns	3.2% (6)
Risk groups	
low [T1-2a, GS ≤ 6, i-PSA ≤ 10]	17.9% (34)
intermediate [T2b-c, GS = 7, i-PSA 10-20]	37.4% (74)
high [T3, GS ≥ 8, i-PSA ≥ 20]	44.7% (85)
Prostate volume, cc, median (range)	25 (9-87)*
Hormonal therapy	
yes	66.8% (127)
no	33.2% (63)

** in 3 cases treated volume exceeded recommended 60 cc and achieved 81 up to 87 cc*
Abbreviations: i-PSA – initial level of prostate specific antigen, ns – not specified, GS – Gleason score

during clinical practice in the department that the final outcome of consecutive HDR-BT treatment plans optimization was connected, to some extent, to e.g. prostate volume or number of needles used for the implant. A question has been posed about the nature of this observation and whether it could be related to other prostate cancer prognostic factors.

The aim of this study was to determine the relation between dose-volume parameters (in the prostate and OARs) obtained from HDR-BT treatment plans and particular prostate cancer prognostic factors along with prostate volume and the number of implanted needles. In the study, morbidity was not taken into consideration.

Fig. 1. SWIFT system (Nucletron®) for HDR brachytherapy of prostate cancer

Material and methods

High-dose-rate brachytherapy for prostate cancer was introduced to the Brachytherapy Department in Greater Poland Cancer Centre in July 2006. Since that time till July 2007, the number of 190 patients (age 52-81, median 68 years) with localized prostate cancer ($T_{1\text{-}30}N_0M_0$) has been treated with interstitial Iridium-192 (^{192}I) HDR-BT (Table 1). All patients were treated with combination of external beam radiotherapy. According to the institutional protocol, dose of 50 Gy (dose fraction of 2 Gy) was initially administered to the prostate and pelvis (in case of high risk of nodal involvement). Intensity modulated radiotherapy (IMRT) or 3-dimentional conformal radiotherapy (3DCRT) techniques were used. After 2-4 weeks patients were admitted for 48 hour in-ward stay to be boosted with HDR-BT. To all men, dose of 15 Gy boost to CTV1 (encompassed by prostate capsule) was administered in a single fraction. Examples of treatment procedure are presented in Figs. 1-2.

Prognostic factors such as age, staging, Gleason score, initial PSA level, and prostate volume (based on transrectal ultrasound examination) were assessed before the procedure.

Real-time intraoperative treatment planning software (Nucletron B. V., SWIFT®) was used in order to incorporate blind inverse planning optimization and is complementary to microSelectron® HDR remote afterloader (Nucletron B. V., Veenendaal, The Netherlands) (Fig. 2). This system enables the operator to acquire series of ultrasound images, offers real-time visualization of the needle placement, display 2D and 3D volumes for 3D planning as well as gives the opportunity to optimize a conformal treatment plan and to generate the dose volume parameters with dose volume histogram (DVH). Dose volume parameters were determined as follows: D_{min} (minimal dose), D_{max} (maximal dose), D_{mean} (mean dose), D_{90} (the percentage of reference dose [D_{ref}] delivered to 90% of treated volume), V_{100}, V_{150}, V_{200} (the volume of the target receiving 100%, 150% and 200% of reference dose, respectively) for prostate; D_{min}, D_{max}, D_{mean}, D_{10} (the percentage of the reference dose delivered to 10% of OAR volume) and V_{100} for urethra and rectum (OARs), respectively (Fig. 3).

As it is accepted in our department, the aim of each good quality implant is to deliver more than 90% of prescribed dose to at least 90% of target volume (D_{90} > 90%). Dose volume limitation of OARs such as urethral D_{10} < 120% and rectal D_{10} < 75% were taken into account during treatment plan optimization. Once the data was collected, the dose volume parameters were correlated with prognostic factors, prostate volume and number of needles used for particular implant.

The correlation was done in six ways (Table 2). Firstly, prognostic factors were correlated with actual prognostic factors, followed by dose-volume parameters for the prostate, urethra and anterior rectal wall, respectively. Secondly, prostatic dose-volume parameters were correlated with dose-volume parameters for urethra and,

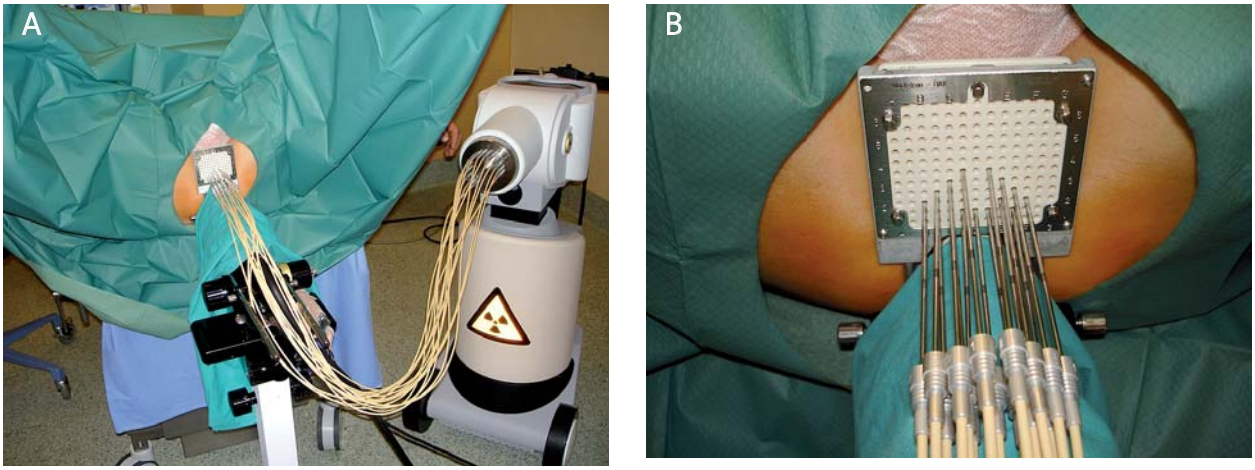

Fig. 2. Example of HDR brachytherapy of prostate cancer (SWIFT®); templates, steel needles and connection cables visible

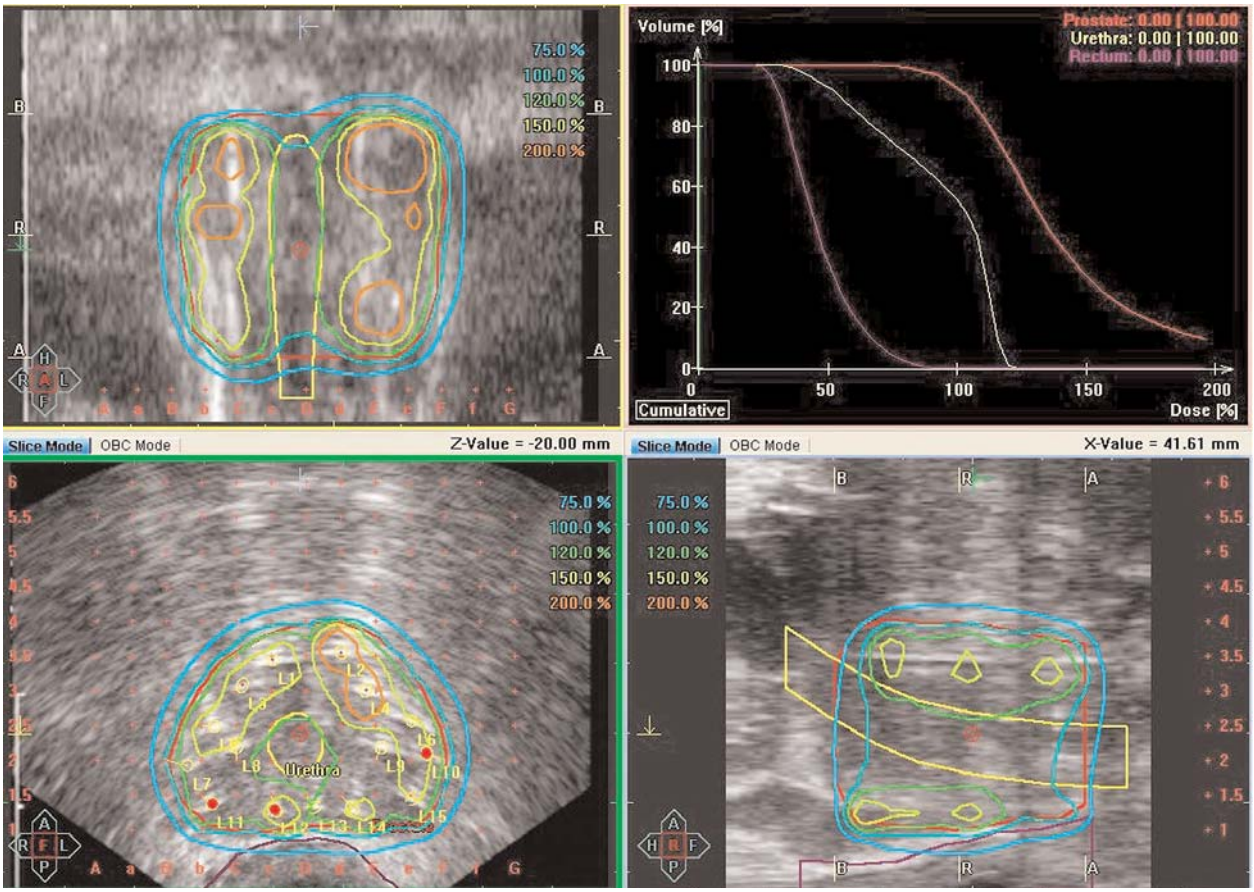

Fig. 3. Treatment plan, dose volume parameters and dose volume histogram (DVH) from SWIFT® planning system

separately, for the anterior rectal wall. Statistical analysis was prepared with the Spearman Correlation Index. All findings obtained from the calculation were taken into consideration only in case of attaining significant level of p-value < 0.05 (Table 3).

Results

The mean value of D_{90} was calculated to be 13.69 Gy which stands for 91.3% of D_{ref} (range 65.9-102.8%, median 91.8%). The mean urethral and rectal D_{10} was 18.27 Gy = 121.8% D_{ref} (range 78.8-152.9%, median 122.4%) and 9.96 Gy = 66.4% D_{ref} (range 37.4-98.1%, median 66.7%), respectively. The mean treated volume was 25 cc (range 9-87 cc).

Statistical analysis of prostate cancer prognostic factors correlated with dose-volume parameters, revealed as a set of results and pointed below.

Patient's age was found to be related to increase urethral D_{max} and D_{10}. This finding can be explained with another statistically significant relation between age and decreased

Table 2. Investigated parameters and the way of correlation

Prognostic factors	DVH parameters		
Age	Prostatic	Urethral	Rectal (anterior wall)
T stage	D_{min}	D_{min}	D_{min}
i-PSA	D_{max}	D_{max}	D_{max}
Gleason score	D_{mean}	D_{mean}	D_{mean}
other	D_{90}	D_{10}	D_{10}
Volume of prostate gland	V_{100}	V_{100}	V_{100}
Number of needles	V_{150} V_{200}		
The way of correlation [Spearman rank correlation coefficient; significance level: p-value < 0.05]			
1. Prognostic factors vs. prognostic factors			
2. Prognostic factors vs. prostatic DVH parameters			
3. Prognostic factors vs. urethral DVH parameters			
4. Prognostic factors vs. rectal DVH parameters			
5. Prostatic DVH parameters vs. urethral DVH parameters			
6. Prostatic DVH parameters vs. rectal DVH parameters			

Abbreviations: DVH – dose volume histogram, T – tumor stage according to TNM classification, i-PSA – initial level of prostate specific antigen (before treatment), D_{min} – minimal dose in treated volume, D_{max} – maximal dose in treated volume, D_m – mean dose, 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_{100}, V_{150}, V_{200} – the percentage of treated volume receiving 100, 150 and 200% of prescribed dose, respectively

T stage – the older the patient, the lower T stage is likely to be assessed. On the other hand, higher T stage (in relatively younger patients) is related to higher level of i-PSA and larger volume of prostate. The T stage is also proportional to final values of prostatic D_{90} and V_{100}.

As for Gleason score (GS), it was found to be directly proportional only to i-PSA and inversely proportional to prostate volume, with no relation to any of dose volume parameters. As it can be derived from the above, i-PSA is proved to be related to T stage and Gleason score. No relation to any of dose-volume parameters was identified for i-PSA.

Furthermore, the larger the prostate volume and the higher T stage to be assessed, the lower GS can be determined and larger number of needles is required for implantation. Moreover, large prostate volume results in higher values of prostatic D_{min}, D_{90} and V_{100} and lower values of prostatic Dmean and V_{200}. Prostate volume also exerts its impact on urethral parameters. Urethral D_{min}, D_{mean} and V_{100} are directly proportional and D_{max} is inversely proportional to prostatic volume. It is quite clear that the number of needles used for an implant is directly related to the prostate volume. For a particular implant, the number of 14 needles was used in average (range 7-18). Correlation of the number of needles with prostatic and urethral dose-volume parameters resulted in the same findings such as the prostate volume. One could notice that no relationship was found between prognostic factors and dose volume parameters for rectal wall. All the collected data were secondarily analyzed paying particular attention to correlation between DVH parameters for prostate gland and OARs. As it turned out, the prostatic D_{90} and V_{100} are inversely proportional to urethral D_{10} and D_{max} and directly proportional to urethral D_{min}, D_{mean} and V_{100} (Table 4). In a real situation the better target coverage is achieved, the lower D_{10} and maximal dose to the urethra is delivered. In the study, prostatic D_{90} and V_{100} did not associate with rectal DVH parameters. For prostatic V_{200}, it was found to be directly proportional to urethral D_{max} and D_{10}, rectal D_{min}, D_{max}, D_{mean}, D_{10} and V_{200}. Moreover, higher values of prostatic V_{200} were related to lower urethral D_{mean} and V_{100}.

Discussion

Demanes *et al*. [1] reported excellent target coverage with D_{90} between 105% and 113% of the prescribed dose, Kini *et al*. [14] reached mean D_{90} of 97% and our median D_{90} was 91.8%. Some of our treatment plans were suboptimal, although the high single dose of 15 Gy was prescribed to CTV1 (prostate capsule) in contrast to CTV2 (peripheral zone) [4, 15] or CTV3 (tumor volume) [16]. It appears that differences came from various descriptions of the target and the method of 100% prescribed isodose normalization. Furthermore, the data is derived from the first set of implants used in the department which is also the cause of worse results. In the first year after introducing the procedure, the implantation technique has improved, in concordance with Lee *et al*. [17] and Merric *et al*. [18] who have reported their data about learning curve. The study results indicate that in the group of older patients one can expect relatively more difficulties in achieving good quality implants. It is due to the fact that older patients are more likely to be diagnosed with lower T stage, which results in smaller volume of the prostate. The small volume determines small amount of needles to

Table 3. Statistical analysis results (Spearman rank correlation coefficient; significance level: p-value < 0.05).

		Prognostic factors						DVH parameters for prostate gland (PTV)							DVH parameters for urethra (OAR)					DVH parameters for rectum (OAR)				
		Age	T	GS	i-PSA	Vol	NN	D_{min}	D_{max}	D_m	D_{90}	V_{100}	V_{150}	V_{200}	D_{min}	D_{max}	D_m	D_{10}	V_{100}	D_{min}	D_{max}	D_m	D_{10}	V_{100}
Prognostic factors	Age	x	**–0.188**													0.177		0.222						
	T	**–0.188**	x		0.223	0.155					0.167	0.165												
	GS			x	0.114	**–0.151**																		
	i-PSA		0.223	0.114	x																			
	Vol		0.155	**–0.151**		x	0.679	0.311		**–0.144**	0.391	0.378		**–0.263**	0.281	**–0.199**	0.393		0.396					
	NN					0.679	x	0.348			0.455	0.469		**–0.223**	0.194	**–0.264**	0.238		0.236					
DVH parameters for prostate gland	D_{min}					0.311	0.348	x			0.739	0.658		**–0.212**	0.165	**–0.194**	0.192		0.223					
	D_{max}								x	0.640				0.525	0.267		0.182	0.199	0.154	0.240		0.218	0.216	0.238
	D_m					**–0.144**			0.640	x			0.664	0.925		0.241		0.256	**–0.203**	0.220	0.177	0.214	0.220	0.250
	D_{90}		0.167			0.391	0.455	0.739			x				0.235	**–0.365**	0.223	**–0.192**	0.246					
	V_{100}		0.165			0.378	0.469	0.658				x			0.193	**–0.353**	0.166	**–0.218**	0.187					
	V_{150}									0.664			x			0.294	**–0.242**	0.260	**–0.349**					
	V_{200}					**–0.263**	**–0.223**	**–0.212**	0.525	0.925				x		0.313	**–0.221**	0.260	**–0.303**	0.179	0.165	0.175	0.188	0.238

Abbreviations: DVH – dose volume histogram, PTV – planning target volume, OAR – organ at risk, T – tumor stage according to TNM classification, GS – Gleason score, i-PSA – initial level of prostate specific antigen (before treatment), Vol – volume of prostate gland assessed before treatment, NN – number of needles used for implant, D_{min} – minimal dose in treated volume, D_{max} – maximal dose, D_m – mean dose, D_{90} – the percentage of prescribed dose delivered to 90% of treated volume (PTV), D_{10} – the percentage of the organ at risk receiving 10% of prescribed dose; V_{100}, V_{150}, V_{200} – the percentage of treated volume receiving 100, 150 and 200% of prescribed dose, respectively; blank spaces – lack of statistically significant correlation

Table 4. Correlation results divided into two groups of directly or inversely proportional relationships between investigated parameters

Parameter	Direct proportion	Inverse proportion
Age	UD_{10}, UD_{max}	T
T	i-PSA, Vol, PD_{90}, PV_{100}	Age
i-PSA	i-PSA	Vol
GS	T, GS	
Vol	T, NN, PD_{min}, PD_{90}, PV_{100}, UD_{min}, UD_m, UV_{100}	GS, PV_{200}, UD_{max}
NN	Vol, PD_{min}, PD_{90}, PV_{100}, UD_{min}, UD_m, UV_{100}	
PD_{90}	UD_{min}, UD_m, UV_{100}	UD_{10}, UD_{max}
PV_{100}	UD_{min}, UD_m, UV_{100}	UD_{10}, UD_{max}
PV_{200}	UD_{10}, UD_{max}, RD_{min}, RD_{max}, RD_m, RD_{10}, RV_{100}	UD_m, UV_{100}

Abbreviations: T – tumor stage according to TNM classification, i-PSA – initial level of prostate specific antigen (before treatment), GS – Gleason score, Vol – prostate volume, NN – number of implanted needles, P – prostatic, U – urethral, R – Rectal, D_{min} – minimal dose in treated volume, D_{max} – maximal dose, D_m – mean dose, 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_{100}, V_{200} – the percentage of treated volume receiving 100 and 200% of prescribed dose, respectively

be used for implantation. Akimoto *et al*. [7, 8] did not find significant correlation between the prostate volume and the number of needles implanted, but patients with 11 needles or less tended to develop higher grade genitourinary (GU) toxicity as compared with those with 12 needles or more. The GU toxicity was increased due to more inhomogenic dose distribution and hot spots as a result of small number of implanted needles. Charra-Brunaud *et al*. [9] reported that prostatic and urethral V_{150} increases whenever smaller number of needles is applied. This finding corresponds with our study, which show statistically significant relationship between small numbers of implanted needles and lower prostatic D_{min}, D_{90} and V_{100}, higher prostatic D_{mean} and V_{200} as well as lower urethral D_{min}, D_{mean}, V_{100} and higher D_{max}. Nevertheless, toxicity was not an issue in this study. On the contrary, the usage of small number of needles was intentional approach of Kovács *et al*. [4]. He prescribed reference dose of 15 Gy to peripheral zone of the prostate (CTV2) with critical structures covered by low-dose areas and neglecting, to some extent, the total dose covering of the prostate. Furthermore, Borghede *et al*. [16] focused on the tumor volume (CTV3) that was defined within the prostate gland. As per Duchesne *et al*. [19], it is essential to limit the level of V_{200} to 15% of the target, in order to decrease the risk of late GU morbidity. This can be achieved in relatively large prostate glands, implanted with greater number of needles; based on our study and published data [1, 2, 14].

In addition, to improve treatment plan prepared for good implant it is advisable to use anatomy-based inverse optimization tools instead of e. g. geometrical ones [5, 20, 21]. Till date, no data was found regarding minimal prostate volume that should not be implanted and the smallest number of applicators to be used without compromising dose distribution, as well as acceptable incidence of side effects and satisfactory outcome.

Conclusions

In conclusion, statistical analysis revealed significant correlation between age, T stage, prostate volume and number of needles used for the implant and increased prostatic D_{90} and V_{100}, decreased V_{200}. Amongst prognostic factors only the age was related to increased urethral D_{10} and D_{max}. No relationship was found between any prognostic factor and rectal wall DVH parameters. In other words, increased prostate volume with improved D_{90} and larger number of implanted needles results in better target coverage (higher value of V_{100}), better dose distribution (less hot-spots with lower value of V_{200}) and decreased dose delivered to the urethra (lower urethral D_{10} and D_{max}). No evident influence on rectal wall was identified. Further investigation with close follow-up should give an answer whether the above arguments corresponds with morbidity and outcome.

References

1. Demanes D, Rodriguez R, Schour L et al. High-dose-rate intensity modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurie-therapy's 10-year results. *Int J Radiat Oncol Biol Phys* 2005; 61: 1306-1316.
2. Mate TP. Review of HDR prostate brachytherapy with 192-Irydium. In: Bruggmoser G, Mould RF, Tai THP, Mate TP (editors). Prostate cancer review. *Zuckschwerdt Verlag*, München 2003; Chapter 14: 85-90.
3. Holloway CL, Hsu I-CJ, Albert M et al. Prostate brachytherapy. In: Devlin PM (editor). Brachytherapy Applications and Techniques. *Lippincott Williams & Wilkins*, Philadelphia 2007; Chapter 8: 181-222.
4. 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.
5. Kirisits C, Siebert FA, Baltas D et al. Accuracy of volume and DVH parameters determined with different brachytherapy treatment planning systems. *Radiother Oncol* 2007; 84: 290-297.

6. 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.
7. 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.
8. 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.
9. 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.
10. Hansen EK, Roach III M. Prostate cancer. In: Hansen EK, Roach III M (editors). Handbook of evidence-based radiation oncology. *Springer Science+Business Media, LLC*, New York 2007; Chapter 25: 293-317.
11. Kanikowski M, Skowronek J, Milecki P et al. Brachyterapia HDR raka gruczołu krokowego. *Urologia Polska* 2007; 2: 5-11 [Polish].
12. Tetsuo A, Hiroyuki K, Shin-Ei N 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.
13. Galalae R, Kovács G. Conformal HDR brachytherapy & elective pelvic external irradiation. In: Bruggmoser G, Mould RF, Tai THP, Mate TP (editors). Prostate cancer review. *Zuckschwerdt Verlag*, München 2003; Chapter 12: 69-72.
14. Kini VR, Edmundson GK, Vicini FA et al. Use of three-dimentional 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.
15. 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.
16. 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.
17. Lee WR, deGuzman AF, Bare RL et al. Postimplant analysis of transperineal interstitial permanent prostate brachytherapy: evidence for a learning curve in the first year at a single institution. *Int J Radiat Oncol Biol Phys* 2000; 46: 83-88.
18. Merrick GS, Grimm PD, Sylvester J et al. Initial analysis of Pro-Qura: A multi-institutional database of prostate brachytherapy dosimetry. *Brachytherapy* 2007; 6: 9-15.
19. 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.
20. Akimoto T, Katoh H, Kitamoto Y et al. Anatomy based inverse optimization in high-dose-rate brachytherapy combined with hypofractionated external beam radiotherapy for localized prostate cancer: comparison of incidence of acute genitourinary between nanatomy-based inverse optimization and geometric optimization. *Int J Radiat Oncol Biol Phys* 2006; 64: 1360-1366.
21. Hsu I-CJ, Lessard E, Weinberg V et al. Comparison of inverse planning simulated annealing and geometrical optimization for prostate high-dose-rate brachytherapy. *Brachytherapy* 2004; 3: 147-152.