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

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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_{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.

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
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.

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 (T1-3 N0 M0) has been treated with interstitial Iridium-192 (¹⁹²I) 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: Dmin (minimal dose), Dmax (maximal dose), Dmean (mean dose), D90 (the percentage of reference dose [Dref] delivered to 90% of treated volume), V100, V150, V200 (the volume of the target receiving 100%, 150% and 200% of reference dose, respectively) for prostate; Dmin, Dmax, Dmean, D10 (the percentage of the reference dose delivered to 10% of OAR volume) and V100 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 (D90 > 90%). Dose volume limitation of OARs such as urethral D10 < 120% and rectal D10 < 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, prostate dose-volume parameters were correlated with dose-volume parameters for urethra and,

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 83 up to 87 cc

Abbreviations: i-PSA – initial level of prostate specific antigen, ns – not specified, GS – Gleason score

![Fig. 1. SWIFT system (Nucletron®) for HDR brachytherapy of prostate cancer](image)
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 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).
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 Dmin and V100.

As for Gleason score (GS), it was found to be directly proportional to urethral Dmax and Dmean 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 Dmin, D90 and V100 and lower values of prostatic Dmean and V200. Prostate volume also exerts its impact on urethral parameters. Urethral Dmin and V100 are directly proportional and Dmax 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 D90 and V100 are inversely proportional to urethral D10 and Dmax and directly proportional to urethral Dmin, Dmean and V100 (Table 4). In a real situation the better target coverage is achieved, the lower D10 and maximal dose to the urethra is delivered. In the study, prostatic D90 and V100 did not associate with rectal DVH parameters. For prostatic V200 it was found to be directly proportional to urethral Dmax and D10; rectal Dmin, Dmax, Dmean, D10 and V200. Moreover, higher values of prostatic V200 were related to lower urethral Dmean and V100.

Discussion

Demanes et al. [1] reported excellent target coverage with D90 between 105% and 113% of the prescribed dose, Kini et al. [14] reached mean D90 of 97% and our median D90 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 2. Investigated parameters and the way of correlation

| Prognostic factors | DVH parameters |
|-------------------|----------------|
| Age               | Prostatic      |
|                   | Urethral       |
|                   | Rectal (anterior wall) |
| T stage           | Dmin           |
|                   | Dmin           |
|                   | Dmin           |
| i-PSA             | Dmax           |
|                   | Dmax           |
|                   | Dmax           |
| Gleason score     | Dmean          |
| other             | Dmean          |
|                   | Dmean          |
| Volume of prostate gland | V100 |
|                   | V100           |
|                   | V100           |
| Number of needles | V150           |
|                   | V100           |
|                   | V200           |

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), Dmin – minimal dose in treated volume, Dmax – maximal dose in treated volume, Dmean – mean dose, D90 – the percentage of prescribed dose delivered to 90% of treated volume, D10 – the percentage of the organ at risk receiving 10% of prescribed dose; V100, V150, V200 – the percentage of treated volume receiving 100, 150 and 200% of prescribed dose, respectively

References:

1. Demanes et al. (2009)
2. Lee et al. (2017)
3. Merric et al. (2018)
| 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<sub>min</sub> | D<sub>max</sub> | D<sub>m</sub> | D<sub>90</sub> | V<sub>100</sub> | V<sub>150</sub> | V<sub>200</sub> | D<sub>min</sub> | D<sub>max</sub> | D<sub>m</sub> | D<sub>10</sub> | V<sub>100</sub> | D<sub>min</sub> | D<sub>max</sub> | D<sub>m</sub> | D<sub>10</sub> | V<sub>100</sub> |
| Age                | x   | -0.188 | 0.177 | 0.222 |
| T                  | -0.188 | x   | 0.223 | 0.155 | 0.167 | 0.165 |
| GS                 | x   | 0.311 | 0.679 | 0.311 | -0.144 | 0.391 | 0.378 | -0.263 | 0.281 | -0.199 | 0.393 | 0.396 |
| i-PSA              | 0.223 | 0.114 | x   | 0.055 | 0.469 | -0.223 | 0.194 | -0.264 | 0.238 | 0.236 |
| Vol                | 0.155 | -0.351 | 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 |
| D<sub>min</sub>    | 0.311 | 0.348 | x   | 0.739 | 0.658 | -0.212 | 0.165 | -0.194 | 0.192 | 0.223 |
| D<sub>max</sub>    | x   | 0.640 | 0.525 | 0.267 | 0.182 | 0.199 | 0.154 | 0.240 | 0.218 | 0.216 | 0.238 |
| D<sub>m</sub>      | -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<sub>90</sub>     | 0.017 | 0.391 | 0.455 | 0.739 | x   | 0.235 | -0.365 | 0.223 | -0.192 | 0.246 |
| V<sub>100</sub>    | 0.165 | 0.378 | 0.469 | 0.658 | x   | 0.193 | -0.353 | 0.166 | -0.218 | 0.187 |
| V<sub>150</sub>    | 0.664 | x   | 0.294 | -0.242 | 0.260 | -0.349 |
| V<sub>200</sub>    | -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<sub>min</sub> – minimal dose in treated volume, D<sub>max</sub> – maximal dose, D<sub>m</sub> – mean dose, D<sub>90</sub> – the percentage of prescribed dose delivered to 90% of treated volume (PTV), D<sub>10</sub> – the percentage of the organ at risk receiving 10% of prescribed dose, V<sub>100</sub>, V<sub>150</sub>, V<sub>200</sub> – the percentage of treated volume receiving 100, 150 and 200% of prescribed dose, respectively; blank spaces – lack of statistically significant correlation.
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 inhomogeneous dose distribution and hot spots as a result of small number of implanted needles. Charra-Brunaud et al. [9] reported that prostatic and urethral V150 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 Dmin, D90 and V100, higher prostatic Dmean and V200, as well as lower urethral Dmin, Dmean, V100 and higher Dmax. 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, Borghezio 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 V200 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.

| Parameter | Direct proportion | Inverse proportion |
|-----------|-------------------|--------------------|
| Age       | UD10, UDmax       | T                  |
| T         | i-PSA, Vol, PD90, PV100 |
| i-PSA     | T                 | T                  |
| GS        | T, GS             | T                  |
| Vol       | T, NN, PDmin, PD90, PV100, UDmin, UDmr, UV100 |
| NN        | Vol, PDmin, PD90, PV100, UDmin, UDmr, UV100 |
| PD90      | UDmin, UDmr, UD10, UDmax, Dmin, Dmax |
| PV100     | UDmin, UDmr, UD10, UDmax, RDmin, RDmax, RDmin, RDmax, RV100 |
| PV200     | UD10, UDmax, RDmin, RDmax, RDmin, RDmax, RV100 |

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, Dmin – minimal dose in treated volume, Dmax – maximal dose, Dm – mean dose, D90 – the percentage of prescribed dose delivered to 90% of treated volume, D10 – the percentage of organ at risk receiving 10% of prescribed dose, V100, V200 – the percentage of treated volume receiving 100 and 200% of prescribed dose, respectively

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 D90 and V100, decreased V200. Amongst prognostic factors only the age was related to increased urethral D10 and Dmax. No relationship was found between any prognostic factor and rectal wall DVH parameters. In other words, increased prostate volume with improved D90 and larger number of implanted needles results in better target coverage (higher value of V100), better dose distribution (less hot-spots with lower value of V200) and decreased dose delivered to the urethra (lower urethral D10 and Dmax). 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.

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