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Optimization and it's influence on value of doses in HDR and PDR brachytherapy

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The aim of this work is to examine the influence of the dose optimization procedure on the value of radiation doses in organs of risk and to compare value of doses measured in healthy tissues according to chosen different PDR brachytherapy (PDRBT) and HDR brachytherapy (HDRBT) fractionation schedule. Fifty one patients treated with PDRBT were qualified for calculations. This group included patients with head and neck cancer, brain tumor, breast cancer, sarcoma, penile cancer and rectal cancer. The doses were calculated in chosen critical points in surrounded healthy tissues. For all treatment plans the doses were compared with the use of the BED (Biologically Equivalent Dose) formula and PDR along with HDR values were calculated. Differences among total doses in PDRBT and different schemas of HDRBT in critical points before and after dose point and volume optimization, were analyzed. The same dependences were examined also for BEDs. One ascertained that in biologic equivalent (to PDR) HDRBT the increase of fraction dose from 4 Gy to 10 Gy caused the necessity of decrease of total dose in treatment area ($p<0,001$). The use of HDR instead of PDR essentially lowered physical and biological doses in examined organs of risk. In many examined critical points in organs of risk where biological equivalence dose in the treatment area was the same, one ascertained the decrease of total physical HDR dose according to the growth of the fraction dose. Similar dependences appeared also for biologically equivalent doses. The optimization process in PDRBT improved the dose homogeneity in the treatment area, but simultaneously induced unprofitable (essential statistically) increase of dose in some healthy organs of risk, what makes an increase risk for radiation-induced complications. The use of biologically equivalent HDRBT instead of PDRBT makes for the decrease of physical doses in the treatment area and the decrease of physical and biologically equivalent doses in healthy organs of risk.

Key words: BED, PDR brachytherapy, HDR brachytherapy, healthy tissues, optimization

Pulsed Dose Rate (PDR) treatment is a new brachytherapy modality that combines physical advantages of HDRBT technology (isodose optimization, planning flexibility and radiation safety) with the radiobiological advantages of LDRBT brachytherapy (repair advantages) [1–6]. The resulting isodoses can be optimized by modulating the dwell time of the source as a function of its trajectory within the implanted volume [2, 7–9]. Computer planning allows a much better match between achieved and desired dose levels at specified points or volumes of clinical interest than manual methods do [10]. In general such a match is attained by optimizing the source configuration. Adjustment of the source configuration may be performed intuitively by the planner or automatically by computer. The computer uses algorithms that incorporate a set of decision criteria that will resemble the criteria used by the physician [10]. Various methods of optimization in treatment planning are described in the literature [11–16]. However, it is quite often not clear what is meant by an optimal plan. Usually one wants to optimize the physical dose distribution and sometimes radiobiological factors are included [10, 17].

In PDR brachytherapy each pulse delivers a small dose, is followed by an interval that allows some repairing and small increase of radiobiological effect. However, the main question is whether or not the increased effect is greater on late-responding normal tissues than on tumor cell kill. The interval between the pulses permits greater comfort of the patient and increases safety of the nursing staff. In principle, every move away from continuous exposure towards treatment with intervals, carries a radiobiological disadvantage. This is the equivalent to fractionation with larger dose per fraction and theoretical and experimental evidence that it will lead to a relative increase in late normal-tissue reactions. The magni-

tude of this effect has been considered acceptable by Brenner and Hall who concluded that for intervals between pulses up to 60 minutes the radiobiological deficit may be acceptable [18]. To reproduce the biological effects of LDRBT using PDR remote afterloading Brenner and Hall [18] along with Fowler and Mount [19] have given the following four recommendations: 1. same total dose, 2. same dose rate: generally about 0,5 Gy/hour, 3. pulse length of 10 minutes or more (or dose rate not exceeding 3 Gy/hour during the pulse), 4. pulse repetition every hour; typically 0,4 - 1,0 Gy/ hour. If these conditions are met, the biological effects of PDR radiation therapy should be equivalent to those of LDR radiation therapy for all tissues.

These conclusions were made on the base of calculations of cell repair capacity (estimated by α/β value) and the kinetics of repair (estimated by $T_{1/2}$), for both tumors and late-reacting normal tissues. The value of α/β for tumors and late reacted human tissues was estimated and are often consistent with laboratory results using experimental animals. In contrast, caused by lack of clinical data, $T_{1/2}$ has been estimated mainly from experimental data [20]. However, it is likely that early-responding tissues such as tumors are repairing sublethal damage more rapidly than late-responding tissues do [21–24]. In 1996, Brenner and Hall exploited this difference to design a new therapeutic regimen. Using a half time for repair of sublethal damage of $T_{1/2}$ = 0,5 hours in early-responding tissues and $T_{1/2}$ = 4 hours in late-responding, they estimated that PDR brachytherapy that delivers series of pulses separated by 3-4 hours should produce better results than LDR brachytherapy [24–26].

In clinical practice there is a possibility of choice between HDR and PDR techniques but treatment schemas are not easily comparable. The aim of this work is to examine the influence of the dose optimization procedure on the value of radiation doses in organs of risk and to compare value of doses measured in healthy tissues according to chosen different PDR brachytherapy (PDRBT) and HDR brachytherapy (HDRBT) fractionation schedules. We have chosen the BED formula for doses calculations [27]. Influence of doses optimization on BED values was analyzed.

Patients and methods

Patients. The first 51 patients treated with PDR brachytherapy in Greater Poland Cancer Center in years 1999-2002 were included in the study. There were 22 males (43.1%) and 29 females (56.9%). Age of patients ranged from 22 to 85 years, median - 53 years. Values of doses and remaining physical and biological data were analyzed in 15 patients with head and the neck cancer, 23 - with brain tumor, 8 - with breast cancer, 3 - with soft tissues sarcoma, 1 – with penis cancer and 1 – with rectal cancer, respectively. The radical PDRBT included 2 treatment courses, each giving 20 Gy, separated by 3 to 4 days intervals (every fraction delivered in pulses of 0.6 – 1 Gy hourly). In palliative PDRBT one fraction of 20 Gy was used (pulses of 0.6-0.8 Gy hourly). We applied applicators such as: interstitial, elastic („blind-end") in breast cancer, head and neck cancer, sarcomas, rectal cancer, and penis cancer, French 6 endoluminal applicators (2 patients with nasopharyngeal cancer) and steel needles in 2 patients with lip cancer. The clinical data of patients are presented in Table 1.

Table 1 Clinical data of patients

Clinical data	Number, rate
Age:	
Median	53 years
Range	22 - 85 years
Gender:	
Male	22 (43.1%)
Female	29 (56.9%)
Tumor Site:	
Head and neck cancer	15
Brain tumor	23
Breast cancer	8
Soft tissues sarcoma	3
Penis cancer	1
Rectal cancer	1
Methods of treatment:	
Head and the neck cancer	Radical - 2 Palliative - 13
Brain tumor	Palliative - 23
Breast cancer	Radical - 8
Soft tissues sarcoma	Radical – 2 Palliative – 1
Penis cancer	Palliative – 1
Rectal cancer	Palliative – 1
Doses	
1 x 10 Gy (breast cancer)	8
1x 20 Gy (palliative treatment)	39
2 x 20 Gy (radical treatment)	4

PDRBT and HDRBT were applied in compliance with European recommendations [10, 28], using the following therapeutic equipment (Nucletron®): IBU (Integrated Brachytherapy Unit), PLATO planning system and microselectrons PDR and HDR (Nucletron BV®, Veenendaal, Netherlands).

Methods. The doses were calculated using PLATO planning system in prescribed reference point (CTV) and in some critical points in surrounded health tissues. In each group of patients critical points were chosen for doses measurements in critical points of healthy tissues. They are characterized in Table 2.

In all cases basing on PDR brachytherapy treatment plan the influence of dose point and volume optimization on doses in organs of risk was examined. This data were used for the elaboration of hypothetical HDR brachytherapy treatment plans. In organs at risk the doses in chosen critical points were counted from the point of the risk of the late radiation complications. The model of the biological equivalent dose (BED) was used to calculate the dose and to compare the PDR doses. This data was then applied in the elaboration of hypothetical HDR brachytherapy treatment plans. One assumed constant

Table 2 Critical points in healthy tissues chosen for calculations

Tumor	Critical point	Description
Head and neck cancer	1. external jaw surface 2. internal jaw surface 3. external ear 4. spinal cord 5. orbit 6. brain	1 and 2 – points located on level of central plane of applicator 4. point located on level of the middle of applicator 5. point located in nearest distance from applicator 6. point located on base of the skull, lying in nearest distance from applicator
Brain tumor	1. orbit 2. sella 3. chiazma opticum 4. external ear 5. epipharynx 6. meninx 1-6	points located in nearest distance from applicator points on the surface of meninx, 2 cm one from another
Breast cancer	1. three points on external surface of pleura 2. three points on skin	1and 2 - points located every 2 cm, center point located on medial level of applicator
Soft tissues sarcoma	1. three points on bone surface 2. three points on skin	1and 2 - points located every 2 cm, center point located on medial level of applicator
Penis cancer	1. pubic symphysis 2. epidydimis 3. ischiadic tuber 4-6. three points on skin surface	points located in nearest distance from applicator
Rectal cancer	1. femoral bone head 2. sacra bone 3. pubic symphysis 4. obturator foramen 5. urinary bladder 6. mons pubis	points located in nearest distance from applicator

value of BED in reference point (in the treatment target) for hypothetical HDR plans and for real treatment PDR plans. On this base the physical and biological equivalent doses in reference point and in chosen critical points were calculated, for four treatment schemas with different HDR fractions size: 4 Gy, 6 Gy, 8 Gy and 10 Gy given once daily. The differences among total doses and BED (PDR brachytherapy and dissimilar schemas of HDR brachytherapy) at critical points before and after distance and volume optimization were analyzed. The same dependences were examined for biological equivalent doses. One advantage of using BED is its relative facility in use for different fractionation schedules [2, 14, 15, 17, 29, 30]. The values of α/β and $T_{1/2}$ were chosen from the literature [3, 31, 32].

The comparison of biological effect of total doses was fulfilled by using the linear-quadratic formula and mono-exponential repair models [31–33]. One assumed that radiation induced injuries could be incomplete during intervals between brachytherapy fractions, especially if $T_{1/2}$ is relatively high in relation to length of period. This incomplete repair decreases BED and requires adequate correction in calculations. The irradiation is delivered over a period of time comparable to low dose rate brachytherapy, however not continuously. The dose is delivered in pulses that are repeated in this study, at 1, 2 and 4 hours. Such interval between fractions is not sufficient enough to allow complete repair of sublethal damage. The estimation of equivalent dose takes into account incomplete repair factor ("H_m"), which depends on the number of fractions per day as well as the interval between fractions and $T_{1/2}$ [1]. This formula was presented earlier by Thames and Hendry [34], justified by Steel [27]:

$$BED = D[1 + d/(\alpha/\beta) + H_m \times d/(\alpha/\beta)],$$

where:

$$\Phi = \exp(-\mu\Delta T)$$
$$H_m = 2/m \times [\Phi/(1 - \Phi)] \times [m - ((1 - \Phi^m)/(1 - \Phi))]$$

D – total dose, d – fraction dose, m – number of fractions daily, ΔT – interval between fractions (pulses).

We choose following values of α/β: 1. for tumors, early reactions tissues α/β = 10 Gy, 2. for late reaction tissues α/β = 3 Gy, values of $T_{1/2}$: 0.5 h for tumors, early reactions tissues and $T_{1/2}$ = 1.5 h for late reaction tissues. Value μ is constant: $\log_e 2/T_{1/2} = 0.693/T_{1/2}$. Then for $T_{1/2}$ = 0.5 h μ carry out1.386, and for $T_{1/2}$ = 1.5 h – 0.462, respectively. Every treatment plan contained doses distribution in reference point and in critical points were calculated for following dwell – times. Doses distributions were calculated using real treatment plans of all 51 patients treated with PDRBT. The optimization on distance was done for applications where the catheters lied in a single

plane (slab volume) and where an isodose surface was required at a given distance from the catheters. All dwell positions in all catheters were taken into account.

Optimization on volume (geometric optimization) was done for applications, where the catheters lied in multiple planes, aiming at a homogeneous dose distribution inside the PTV, i.e. and minimize the spread in the local doses. Only dwell positions that lied in the other catheters other than the catheter for which the dwell limes were calculated, were taken into account [10].

Statistical analysis. Wilcoxon test (non parametric test) for two dependent tests was used for analysis of correlation between value of doses in critical points in healthy tissues. It concerned physical and BED doses in critical points before and after optimization, correlation of doses in PDRBT and HDRBT according to different fraction size and treatment schedule (once or twice daily). Correlation between doses was also analyzed for every critical point. ANOVA Friedman and Kendall tau rank correlation for statistical analysis permitting analysis of dependent variables (several groups) was used. α = 0,05 significance level was accepted.

Results

Dose values analysis in PDRBT showed undesirable increase of dose (from 1.9 Gy to 13.4 Gy) at most of the points in organs at risk after optimization, depending on the length of interval between pulses and localization of the critical point in every analyzed patient**.** Values of doses were calculated basing on a real treatment plans. Our results showed the probability of undesirable increase of late complications in healthy organs after using the standard optimization available in the treatment planning systems used in Greater Poland Cancer Centre. One can ascertain that in biologically equivalent (to PDRBT) HDRBT, the increase of fractional dose from 4 Gy to 10 Gy should cause the necessity to decrease the prescribed total dose in the treatment target. These results suggest the use of HDR brachytherapy instead of PDR brachytherapy and indicate reducing the physical doses given to the treatment area that are greater in case of higher fraction doses. The median value of BED in chosen critical points in healthy tissues was statistically related to the length of intervals between PDR pulses and decreased exponentially with growing dimensions of intervals from 1 hour to 4 hours (Kendall tau rank correlation = from 0.48 to 1.0, p = from 0.002 to 0.00001). The optimization influenced the increase of doses in all measured points in healthy tissues. Similar dependences were observed in calculations for BED doses before optimization and after optimization on distance. Summarized BED values – different interval length, HDR fraction size and optimization status are presented in Tables 3 and 4.

BED values for different length of intervals between pulses were compared with 4 chosen HDR fractionation schemas. The comparison of BED [cGy] PDR and HDR (fractions of 4,6,8,10 Gy) for chosen critical point („internal jaw surface") before and after optimization is presented in Fig. 1-4. It seems, that BED boundary values (the highest and the smallest) for PDRBT were smaller than BEDs for different HDRBT fractionation schedules.

Table 3 Summarized BED values – different interval length between PDR pulses and optimization status

Options of PDR treatment		BED	
Optimalization method	Time between pulse [h]	Mean [Gy]	SD [Gy]
No	1	24,4	29,9
	2	18,3	20,8
	4	15,6	16,8
Point	1	25,4	29,2
	2	19,1	20,4
	4	16,2	16,5
Volume	1	10,6	7,4
	2	9,0	5,8
	4	8,3	5,1

Table 4 Summarized BED values in critical points – different HDRBT dose values and optimization status

Options of HDR treatment		BED	
Optimalization metod	Dose per fraction [Gy]	Mean [Gy]	SD [Gy]
No	4	32,1	53,1
	6	29,4	51,1
	8	27,3	49,3
	10	25,8	47,8
Point	4	32,8	50,4
	6	28,6	44,0
	8	25,9	40,4
	10	23,9	38,2
Volume	4	6,8	6,0
	6	5,9	5,4
	8	5,3	5,0
	10	4,8	4,7

Discussion

The optimization algorithm itself is a mathematical process independent of the type and geometry of sources. The 3D dose distribution and the anatomical structures (volumes of interest, points), together with the constraints make up the input to the optimization algorithm [35,36]. Examples of criteria

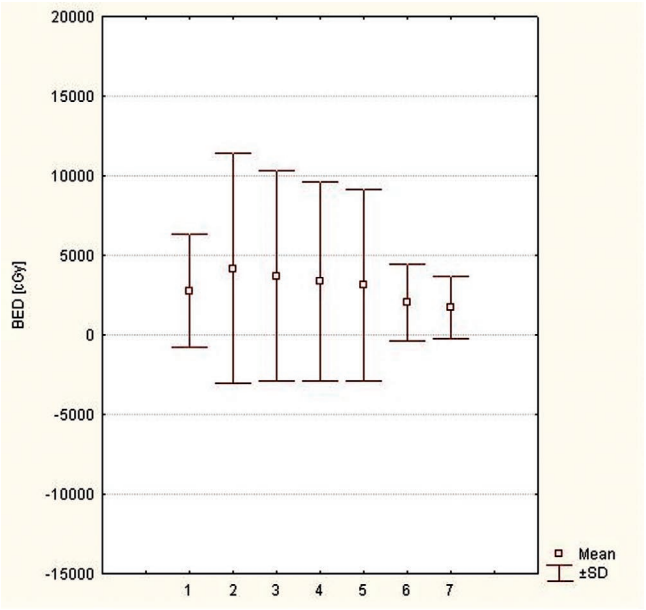

Figure 1 BED value dependent on treatment method in critical point „internal jaw surface" – data before optimization:1 - D PDR (1h interval between pulses), 2 - .D HDR (fraction 4 Gy), 3 - D HDR (fraction 6 Gy), 4 - D HDR (fraction 8 Gy), 5 - D HDR (fraction 10 Gy) 6 – D PDR (2h interval between pulses), 7 - D PDR (4h interval between pulses)

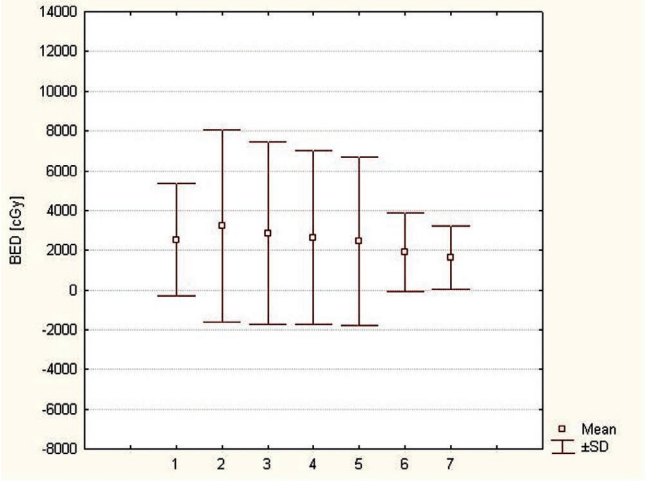

Figure 2 BED value dependent on treatment method in critical point „internal jaw surface" – data after optimization on distance: 1 - D PDR (1h interval between pulses), 2 - .D HDR (fraction 4 Gy), 3 - D HDR (fraction 6 Gy), 4 - D HDR (fraction 8 Gy), 5 - D HDR (fraction 10 Gy) 6 – D PDR (2h interval between pulses), 7 - D PDR (4h interval between pulses)

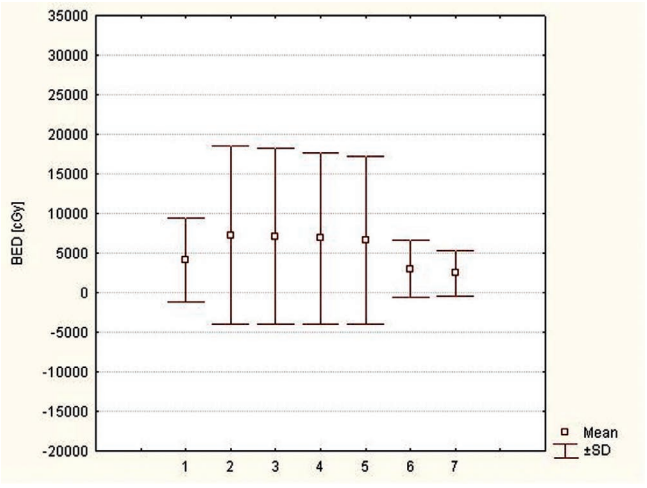

Figure 3 BED value dependent on treatment method in critical point „internal jaw surface" – data after optimization on volume: 1 - D PDR (1h interval between pulses), 2 - .D HDR (fraction 4 Gy), 3 - D HDR (fraction 6 Gy), 4 - D HDR (fraction 8 Gy), 5 - D HDR (fraction 10 Gy) 6 – D PDR (2h interval between pulses), 7 - D PDR (4h interval between pulses)

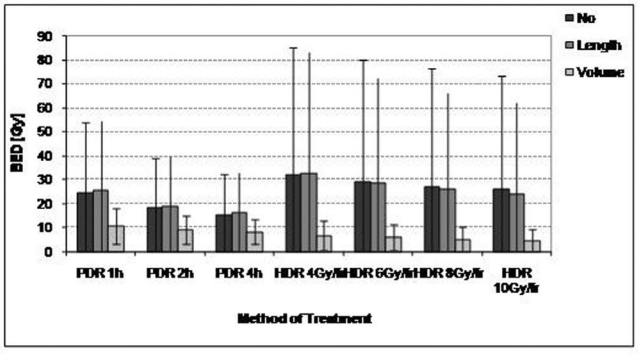

Figure 4 BED value dependent on treatment method in critical point „internal jaw surface" – summary. Data before, after optimization on distance and volume. 1 - D PDR (1h interval between pulses), 2 – D PDR (2h interval between pulses), 3 - D PDR (4h interval between pulses) 4 - .D HDR (fraction 4 Gy), 5 - D HDR (fraction 6 Gy), 6 - D HDR (fraction 8 Gy), 7 - D HDR (fraction 10 Gy)

for an interstitial implant that can be formulated as the basis for an optimization algorithm can be as follows: 1. minimize the spread in the individual minimum doses. These individual minimum doses are used to calculate the Mean Central Dose (MCD) inside the PTV. 2. minimize the size of the volume inside the PTV that receives more than 150% of the MCD. 3. maximize the dose homogeneity index value. This index is defined as the ratio of the MTD and the MCD. It is always smaller than 1 and should therefore be as close as possible to the value 1. 4. minimize the conformity index value. The CI is larger than 1 and should be as close as possible to the value 1. 5. maximize the uniformity index value. 6. maximize the COIN index value. The COIN is smaller than 1 and should be as close as possible to the value 1. 7. comply with dose and volume constraints on critical organs. 8. maximize the

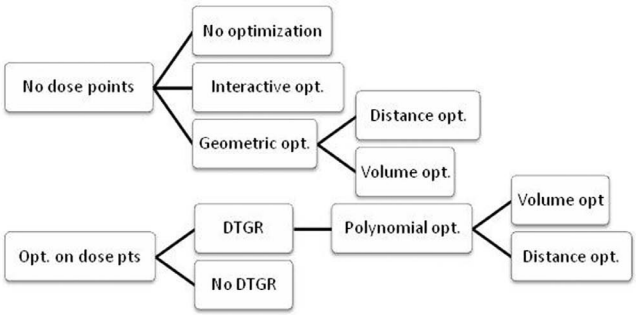

Figure 5 Optimization approaches in HDR Brachytherapy. The Stepping Source Dosimetry System SSDS (DTGR: Dwell Time Gradient Restriction)

Tumor Control Probability (TCP) for the PTV. 9. minimize the Normal Tissue Complication Probability (NTCP) or keep the NTCP below a certain maximum value [10]

Two techniques are distinguished:

1. *Optimising on distance***.** This is done for applications where the catheters lie in a single plane (slab volume) and where an isodose surface is required at a given distance from the catheters. All dwell positions in all catheters are taken into account.
2. *Optimising on volume***.** This is done for applications where the catheters lie in multiple planes, aiming at a homogeneous dose distribution inside the PTV, i.e., minimize the spread in the local minimum doses. Only dwell positions that lie in the other catheters than the catheter for which the dwell times are calculated, are taken into account (Fig. 5).

In case of no dose points we have – 1. interactive optimization: manually changing dwell times and visually evaluating the resulting dose distribution, 2. geometrical optimization: dwell positions are also used as dose points. Optimization on distance is obtained by taking all dwell points into account, optimization on volume uses only the dwell position in the other catheters. In case of optimizing on dose points we have – 1. without the dwell time gradient restriction DTGR negative dwell times may result, 2. with DTGR: solving the equation results in optimization on distance. Polynomial optimization approximates the dwell times along a catheter as a function of the distance to the first dwell position in that catheter. When the total time of each catheter obtained by geometrical optimization, is added as an additional constraint to the polynomial optimization, a dose distribution optimized on volume results. In addition to the physical dose distribution, there is also the effect of the large dose gradients that are associated with large variations in dose rate. Therefore as well as absolute dose, these large variations in dose rate will also affect the overall biological effect and in the future may become part of the optimization procedure [10].

Although the PDR approach has been the subject of numerous theoretical papers, and afterloading machines modified for PDR treatments have been commercially available for several years, only small amount of data has been published regarding clinical experience with these techniques [37–46]. PDRBT fractionations schedules with 3 different length of intervals (1, 2 and 4 hours, respectively) between pulses were analyzed. The results show that the prolongation of intervals between pulses in PDRBT was linked to the decrease of BED values in healthy tissues, presented by chosen critical points. These observations were similar before and after optimization of treatment plans. The prolongation of the interval length influenced better protection of healthy tissues that surrounded the treated tumor, simultaneously prolonged treatment time (the same total dose given to the patient but in a longer time). In clinical practice it means decreasing the number of treated patients.

There are only few data available that indicating a reliable use of one from many radiobiological models for the purpose of comparing different brachytherapy techniques and different fractionation schema [17, 47–49]. We analyzed existing radiobiological models and chose the BED formula for calculating the biologically effective doses in HDRBT and PDRBT. Results suggest that the use of HDRBT instead of PDRBT (taking account of the same value of BED in reference point) shows reducing the physical doses given to the treatment area in greater case of higher fraction doses. By all means it's a result of chosen mathematical model for calculations. The use of HDR instead PDR essentially lowered physical and biological doses in examined organs of risk. In many examined critical points in organs at risk (OaR) where the biological equivalence dose in the treatment area was the same, one ascertained the decrease of the total physical HDR dose according to the growth of the fraction dose. Similar dependences appeared also for biologically equivalent doses. In all critical points the increase of the HDR fraction dose caused the decrease of BED. It shows necessity for considering unexpected differences in physical doses after change of HDR fractionation schedules. This dependence show necessity of choosing adequate HDR fractions doses for specific tumor locations and change of treatment method. Nowadays in clinical practice we use „physical doses", not the biologically equivalent doses (BED). Real values of HDR fractions dose should be decreased more than may get out of the routine dose calculations in CTV (reference point) when critical healthy tissues (OaRs) are nearby. In such cases the mathematical models are useful with the notification of all the limitations.

When discussing our observations the lack of literature about equivalence of HDRBT and PDRBT causes really important limitation, so, the conclusions should be made carefully and do not lead directly to introduce a new treatment schedules. Both methods can be used convertibly in clinical practice after taking into account differences in dose effectivity and after suitable and adequate calculations. In doses calculations special attention should be given to critical points in healthy tissues (OaRs) surrounded the tumor (CTV). Doses in such OaRs should be calculated as a routine part of preparing the treatment plan, especially in case of routine optimization.

Our observations should be continued in randomized trials comparing HDRBT and PDRBT techniques.

In conclusion, the model of biologically equivalent dose and proposed locations of critical points in organs at risk are useful for comparative analysis and the definition of conditions of the biological equivalence of PDR and HDR brachytherapy. Prolongation of intervals between pulses in PDR brachytherapy was connected to lower values of BED doses in healthy tissues. The optimization process in PDR brachytherapy improved the dose homogeneity in the treatment area, but simultaneously was able to induce unprofitable (statistically essential) increase of dose in some healthy organs at risk, what made for increase of the risk of radiation-induced complications.

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