Influence of length of interval between pulses in PDR brachytherapy (PDRBT) on value of Biologically Equivalent Dose (BED) in healthy tissues

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Abstract

Purpose: Different PDR treatment schemas are used in clinical practice, however optimal length of interval between pulses still remains unclear. The aim of this work was to compare value of BED doses measured in surrounded healthy tissues according to different intervals between pulses in PDRBT. Influence of doses optimization on BED values was analyzed.

Material and methods: Fifty-one patients treated in Greater Poland Cancer Centre were qualified for calculations. Calculations of doses were made in 51 patients with head and neck cancer, brain tumor, breast cancer, sarcoma, penis cancer and rectal cancer. Doses were calculated with the use of PLATO planning system in chosen critical points in surrounded healthy tissues. For all treatment plans the doses were compared using Biologically Equivalent Dose formula. Three interval lengths (1, 2 and 4 hours) between pulses were chosen for calculations. For statistical analysis Friedman ANOVA test and Kendall ratio were used.

Results: The median value of BED in chosen critical points in healthy tissues was statistically related to the length of interval between PDR pulses and decreased exponentially with 1 hour interval to 4 hours (Kendall = from 0.48 to 1.0; p = from 0.002 to 0.00001).

Conclusions: Prolongation of intervals between pulses in PDR brachytherapy was connected with lower values of BED doses in healthy tissues. It seems that longer intervals between pulses reduced the risk of late complications, but also decreased the tumour control. Furthermore, optimization influenced the increase of doses in healthy tissues.

Introduction

Brachytherapy with modern afterloading equipment offers three major advantages over interstitial and intracavitary insertions of separate needles, tubes, seeds or wires: 1. Isodose volumes in tissues can be created flexibly by a combination of careful placement of the catheter and adequate adjustment of the dwell times of the computerized stepping source. This process is usually called "dose optimization". 2. Automatic removal of radiation sources into a shielded safe whenever somebody enters the room, eliminates radiation exposure to the staff and visitors. 3. Radiation exposure to the staff is also eliminated where multiplicity of radioactive sources were formerly loaded and unloaded into the catheters, ovoids, tubes etc. [1-4].

Pulsed Dose Rate brachytherapy (PDRBT) is a new treatment that combines physical advantages of HDRBT technology (isodose optimization, planning flexibility and radiation safety) with radiobiological advantages of LDRBT brachytherapy (repair advantages) [5-8]. The single radioactive stepping source moves through all implanted catheters during each pulse. The resulting isodoses can be optimized by modulating the dwell-time of the source as a function of its trajectory within the implanted volume [6, 9-11].

In PDR brachytherapy each pulse delivers small doses followed by an interval which allows some repair 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 increased safety of the nursing staff. In principle, every removal from continuous exposure

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towards treatment with intervals carries a radiobiological disadvantage. This corresponds to fractionation with larger dose per fraction and theoretical and experimental evidence that leads to a relative increase in late normal-tissue reactions. The magnitude of this effect has been considered acceptable by Brenner and Hall who concluded that for intervals between pulses of up to 60 minutes the radiobiological deficit may be acceptable [12]. Nevertheless, the optimal length of interval between pulses remains unclear. To reproduce the biological effects of LDRBT using PDR remote afterloading Brenner and Hall [12] along with Fowler and Mount [13] have given the following four recommendations: 1) the same total dose, 2) the 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 repeated every hour, typically 0.4-1.0 Gy/hour. If these conditions are met, the biological effects of PDR brachytherapy should be equivalent to those of LDR brachytherapy for all tissues.

These conclusions were made on the basis 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 tumours and late reacted human tissues was estimated and is often consistent with a laboratory results using experimental animals. In contrast, caused by lack of clinical data, $T_{1/2}$ has been estimated mainly from experimental data [14]. However, it is likely that early-responding tissues – such as tumors – are repairing sublethal damage more rapidly than late-responding tissues [15-18]. In 1996, Brenner and Hall exploited this difference in order to design new therapeutic regimens. Using $T_{1/2}$ of 0.5 hours for early-responding tissues and 4 hours for late-responding, they estimated that PDR brachytherapy delivering series of pulses separated by 3-4 hours should generate better results than LDR brachytherapy [19-21].

The aim of this work was to compare BED doses calculated in surrounded healthy tissues according to different intervals between pulses in PDR brachytherapy. We have chosen BED formula for doses calculations [22]. The influence of doses optimization on BED values was analyzed.

Material and methods

Material

Original data of 51 patients treated with PDR brachytherapy (PDRBT) in Greater Poland Cancer Centre were included into the study. Values of doses and remaining physical and biological data were analyzed in patients with different cancers presented in Table 1. The PDR radical treatment included 2 fractions of 20 Gy with 3-4 days intervals (pulses of 0.6-1 Gy hourly). In palliative PDR brachytherapy one fraction of 20 Gy was used (pulses of 0.6-0.8 Gy hourly). The lengths of pulses differed due to pulse dose value, tumour volume and number of applicators used in treatment, also depended on Ir-192 source activity. We used applicators: interstitial, elastic ("blind-end") in breast cancer, head and neck cancer, sarcomas, rectal cancer, and penis cancer, French 6 endoluminal applicators in 2 patients with nasopharyngeal cancer and steel needles in 2 patients with lip cancer. Clinical data of patients are presented in Table 1.

PDRBT was applied in compliance with European recommendations [1, 2], using therapeutic line (Nucletron®): IBU (Integrated Brachytherapy Unit), PLATO planning system and microselectron PDR.

Methods

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

In all cases, on the basis of PDRBT treatment plans, the influence of optimization on distance and volume of doses in organs at risk was examined. Organs at risk were chosen from the point of the increased risk of the late radiation complications. The model of the biological equivalent dose (BED) was used to calculate BED dose and to compare PDRBT doses. One of the BED formula advantages is its relative facility to use it in different fractionation schemas [6, 23, 24]. On the basis of literature data, the constant values of α/β ratio and $T_{1/2}$ ratio were chosen [6, 25, 26]. One assumed the same BED value in reference point (in the treatment area) for different PDR interval lengths. On the basis of biological equivalent, doses in critical points were calculated. Differences among biologically corresponding doses in PDR brachytherapy in critical points before and after optimization on distance and volume were analyzed.

Table 1. Patients characteristic

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 the 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 × 10 Gy (breast cancer)	8
1 × 20 Gy (palliative treatment)	39
2 × 20 Gy (radical treatment)	4

Gy – Grey

The comparison of biological effect of total doses were made by using the linear-quadratic formula and mono-exponential repair models [25-27]. One assumed that radiation induced injuries during interval between brachytherapy fractions could be incompletely repaired, especially if $T_{1/2}$ is relatively high in relation to length of this period. This incomplete repair increases BED and requires adequate correction in calculations. The irradiation is delivered over a period of time comparable to low dose rate brachytherapy, however it is not continuous. The dose is delivered in pulses that are repeated in intervals of 1-4 hours. This 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, the interval between fractions, and $T_{1/2}$ [1].

For all treatment plans and all critical points the doses were compared using BED (Biologically Equivalent Dose) formula with three interval lengths of 1.2 and 4 hours. This formula was presented earlier by Thames and Hendry [28], justified by Steel [22]:

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

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 daily fractions, ΔT – interval between fractions (pulses).

We choose values of α/β: 1) for tumors, early reactions tissues $\alpha/\beta = 10$ Gy, 2) for late reaction tissues $\alpha/\beta = 3$ 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 out 1.386, and for $T_{1/2} = 1.5$ h – 0.462, respectively. In every case of a treatment plan the contained doses distribution in reference point and in critical points were calculated for following dwell-times. Dose distribution were calculated using real treatment plans of all 51 patients treated with PDRBT. 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. Optimization on volume was done for applications where the catheters lied in multiple planes, aiming at a homogeneous dose distribution inside the PTV, i.e. and minimized the spread of the local doses. Only dwell positions that lied in catheters other than the catheter for which the dwell limes were calculated, were taken into consideration [1].

For statistical analysis Friedman ANOVA test and Kendall ratio were used.

Results

Analysis of doses values in PDR brachytherapy indicates the undesirable increase of the dose (from 1.9 to 13.4 Gy) in most of the points in organs at risk after the optimization. It shows the probability of undesirable increase of the risk of late complications in these healthy

Table 2. Critical points in healthy tissues chosen for calculations

Tumor	Critical point	Description
Head and the 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 in central plane of applicator 4 – point located in 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	points located in nearest distance from applicator
Breast cancer	1) three points on external surface of pleura 2) three points on skin	1 and 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	1 and 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

organs after standard use of optimization. The median value of BED in chosen critical points in healthy tissues was statistically related to the length of interval between PDR pulses and reduced exponentially with the increase from 1 hour interval to 4 hours (Kendall = from 0.48 to 1.0, p = from 0.002 to 0.00001). The optimization has influenced the increase of doses in all measured points in healthy tissues. Summarized BED values with different interval length and optimization status are presented in Table 3.

Comparison of BED values for different interval length – before optimization

Median BED value in each critical point was statistically significant and was depending from interval length, declined exponentially with interval growth – from 1, to 2 and 4 hours (Kendall ratio = from 0.48 to 1.0, p = from 0.002 to 0.00001). Exemplary BED values for critical point "external jaw surface" carried out: 1 h – 24.4 Gy, 2 h – 18.3 Gy, 4 h – 15.6 Gy, for critical point "internal jaw surface": 1 h – 27.6 Gy, 2 h – 20.4 Gy, 4 h – 17.1 Gy, for point "sella": 1 h – 21.9 Gy, 2 h – 16.1 Gy, 4 h – 13.5 Gy. Results testify that with the growth of interval length, the BED value decreases in healthy tissues. Comparison of BED values [cGy] PDRBT (1-h interval) and PDRBT (2-h, 4-h interval) in whole group of patients for all critical points before optimization presents Fig. 1.

Comparison of BED values for different interval length – after optimization on distance

Median BED value in each critical point was statistically significant and was depending from interval length, declined exponentially with interval growth – from 1, to 2 and 4 hours (Kendall ratio = from 0.43 to 1.0, p = from 0.0002 to 0.00001). Exemplary BED values for critical point "external jaw surface" carried out: 1 h – 25.4 Gy, 2 h – 19.1 Gy, 4 h – 16.3 Gy, for critical point "internal jaw surface": 1 h – 25.2 Gy, 2 h – 19 Gy, 4 h – 16.2 Gy, for point „sella": 1 h – 36 Gy, 2 h – 24.9 Gy, 4 h – 19.8 Gy.

Table 3. Summarized BED values – different interval length 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

Similar dependences were observed in calculations of BED doses before the optimization and after volume optimization. Comparison of BED values [cGy] PDRBT (1-h interval) and PDRBT (2-h, 4-h interval) in whole group of patients for all critical points after optimization on distance presents Fig. 2.

Comparison of BED values for different interval length – after optimization on volume

Median BED value in each critical point was statistically significant and was depending from interval length, declined exponentially with interval growth – from 1, to 2 and 4 hours (Kendall ratio = from 0.44 to 1.0, p = from 0.001 to 0.00001). Similar dependences were observed like in calculations for BED doses before optimization and after optimization on distance. Comparison of BED values [cGy] PDRBT (1-h interwal) and PDRBT (2-h, 4-h interval) in whole group of patient for all critical points after optimization on volume is presented in Fig. 3.
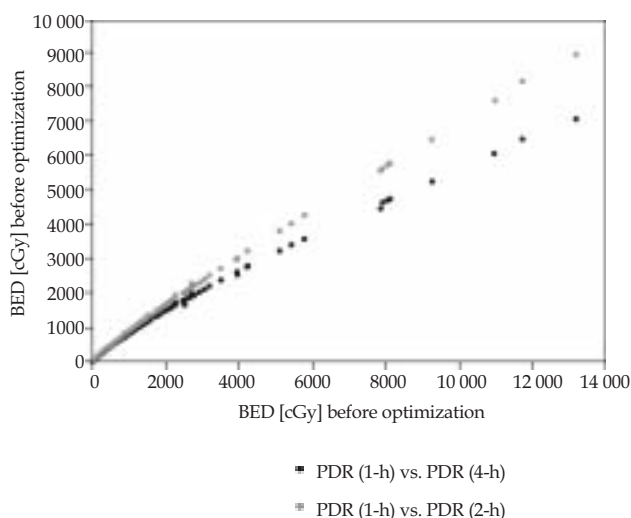

Fig. 1. Comparison of BED PDR (1-h interval) with BED PDR (2- and 4-h interval) of all patients (before optimization)
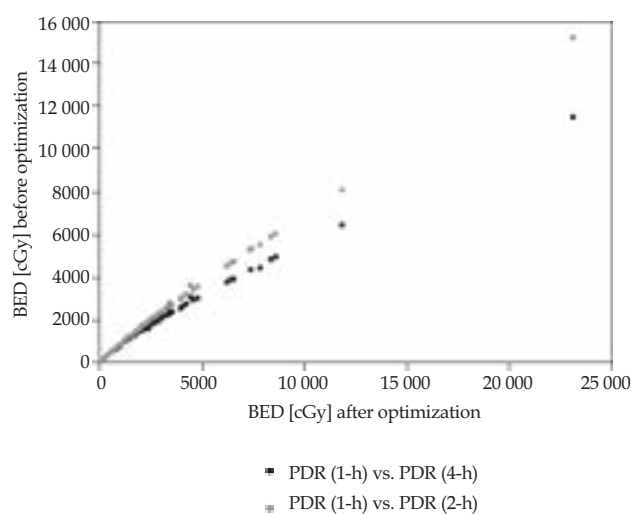

Fig. 2. Comparison of BED PDR (1-h interval) with BED PDR (2- and 4-h interval) of all patients (data after optimization on distance)
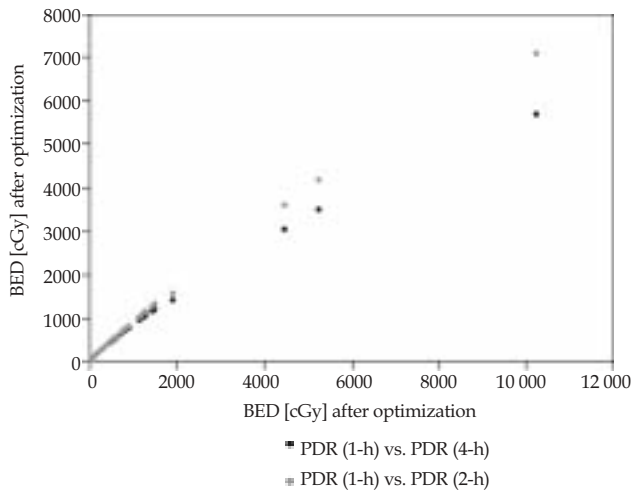
Fig. 3. Comparison of BED PDR (1-h interval) with BED PDR (2- and 4-h interval) of all patients (data after optimization on volume)
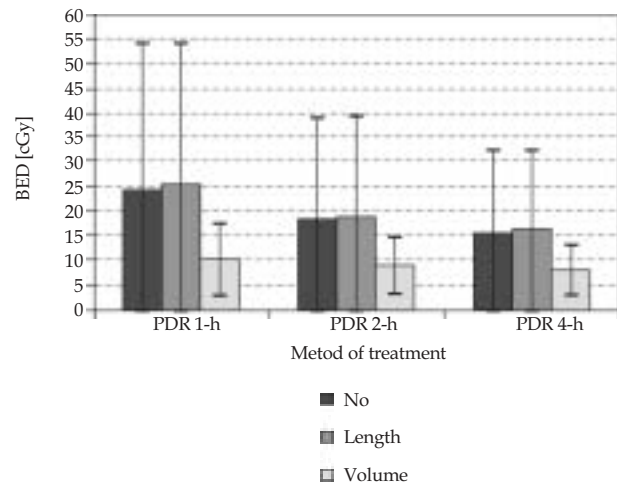

Fig. 4. BED values in exemplary critical point "internal jaw surface" – before and after optimization on distance and volume

BED values in exemplary critical point "internal jaw surface" are presented in Fig. 4. Prolongation of interval length was connected with BED value decrease.

Discussion

Modern computer planning systems permits much better possibilities in achieving requested dose levels at specified points or volumes of clinical interest (such as organs at risk) than manual methods. In general, such a match is attained by optimizing the source configuration (positions and/or strengths). The adjustment of the source configuration may be performed intuitively by a planner or automatically by computer. The computer with the use of algorithms incorporates a set of decision criteria that resembles the criteria used by the physician [1]. Ideally there should be zero dose outside the treated tumor (PTV) i.e. and no dose deposited to critical structures, which in our work is called as critical points. For normal tissue damage there is a strong correlation between dose, volume and the occurrence of certain end-points. We observed that an addition to the optimization influenced the increase of doses in healthy tissues that were independent on the length of the interval between pulses.

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 now, very little data has been published regarding clinical experience with these techniques [7, 29, 30]. Theoretical calculations indicate that pulsed dose rate irradiation should be approximately as effective as continuous low dose rate with the same total dose given in unchanged overall time [1, 14]. In case of small doses per pulse (< 0.5 Gy) with repair times larger than 10 min, the differential effect to continuous LDRBT is less than 10%. This is, however, not the case if large doses per pulse (> 2 Gy) are used and/or there is a non-exponential or very short $T_{1/2}$ (< 0.5 h) [31-35].

Experimental data are available from a variety of animal experiments [1]. In a mouse jejunum, Mason *et al.* [36] found continuous LDRBT at 0.7 Gy/h and PDR with 0.7 Gy hourly pulses to be of equal effectiveness. Pulse duration was around 10 min. Shortening the pulse down to 1 min marginally increased the effectiveness by 3-4%. This is caused by fast repair kinetics of the jejunum. Armour *et al.* [37] investigated different PDR schedules in a rat rectum, where the endpoint resulted as a late rectal stenosis. The reference LDR protocol used dose rate of 0.75 Gy/h. The PDR schedules were similarly effective when pulses of 0.375, 0.75 and 1.5 Gy were given at 30 min, 1 h or 2 h intervals, respectively. Larger pulses of 3 Gy every 4 h resulted in 15% increase in efficiency and pulses of 6 Gy every 8 h resulted in 30% increase in effectiveness. This reference dose rate of 0.75 Gy/h is high. In a clinic it would correspond to 3 days and 8 h treatment with a total dose of 60 Gy, i.e. Lower reference dose rate of 0.4-0.5 Gy/h would have been more clinically relevant, although probably not relatively feasible with this model [1]. Brenner *et al.* [20] have compared LDR and PDR schedules in a rat cataract model. A dose of 15 Gy was delivered to a rat eye: 1) continuously over 24 h (0.625 Gy/h) or 2) with hourly pulses of 10 min, 3) with 10 min pulses every 4 h, and 4) with hourly pulses of about 1 min. All schedules were found to be isoeffective. Haustermans *et al.* [38] attempted to define a pulsed dose rate of isoeffective protocol with a continuous low dose rate irradiation of a rat cervical spinal cord. Two different schedules were used, delivering pulses of 0.69 Gy at 1 h repetition (9 pulses/day) and of 2 Gy at 3 h repetition (4 pulses/day), with overnight intervals of 12-15 h. The reference LDR exposure used a range of dose rates up to 0.94 Gy/h. Pulsed dose rate irradiation was more effective than low dose rate by a factor of 10 to 17%. The most probable explanation was that was a substantial component of repair with very short $T_{1/2}$ in the spinal cord. Multi-exponential repair has been shown to offer a better fitting to spinal cord repair

in more recent experiments [39]. These data emphasize some inadequacies of using mono-exponential repair models as an approximation to multi-exponential repair, which is particularly critical in pulsed dose rate isoeffect calculations. Data on normal tissue repair in humans are unfortunately extremely limited [1]. The radiobiological modeling of pulsed dose rate is difficult, due to numerous uncertainties regarding DNA repair parameters [40-43]. Theoretical pulsed dose rate protocols, which could simulate a continuous low dose rate treatment, have been worked out [12, 13, 20, 33, 34, 36, 44]. Several of the conclusions were rather similar regarding the necessity to deliver pulses of at least 10 minutes per hour using a source with the lowest possible activity. It must be emphasized once more that these calculations are based on a hypothesis concerning the half time repair for early and late responding normal tissues as well as tumors [13, 33, 34]. As stated previously, the available data on the kinetics of DNA repair are quite insufficient [1].

An important, yet often forgotten element in theoretical calculations of isoeffects is the reference low dose rate used in the model. Conventional low dose rate in Paris or Manchester system delivers 10 to 12 Gy per day (0.4-0.5 Gy/h). Higher dose intensity, for instance 15 or 17 Gy/day, has much greater biological effectiveness [45]. Therefore, the reference low dose rate is very critical for isoeffect calculations, as critical as the α/β and $T_{1/2}$ values [1]. In addition to its limitations as a biological model, the linear-quadratic isoeffect model does not account for the peculiar, stepwise accumulation of absorbed dose throughout the target volume with current PDR afterloading equipment. In order to build up, over 10 minutes, a dose distribution that mimics linear sources, the point source needs to cover a large number of consecutive steps, each one being only briefly, but intensely exposed. Therefore, the dose is accumulated in very small volumes, and ultimately at the cellular level, delivered at a much higher dose rate than the average dose rate calculated for the entire exposure. This has been called the "golf ball" effect by Fowler and Van Limbergen [14]. Biological equivalent doses calculated without accounting for this effect are usually overestimating the tissue tolerance and pulsed dose rate appears "hotter" than expected [1].

In summary, whenever pulsed dose rate brachytherapy departs from its original hourly pulse without interruption at night, it becomes biologically closer to a HDRBT than a continuous LDRBT [14, 46].

There is no data available for authors indicating a reliable use of one from many radiobiological models for the purpose of comparing different brachytherapy techniques and different fractionation schema. We analyzed existing radiobiological models and chose the BED formula for calculations of biologically effective doses. Three PDRBT fractionations schemas with different length of intervals (1.2 and 4 hours, respectively) between pulses were analyzed. Original treatment plans of patients treated in Greater Poland Cancer Center were used for calculations. The results show that prolongation of intervals between pulses in PDRBT was connected with the decrease of BED values in healthy tissues, presented by chosen critical points. Critical points were chosen as the nearest points from the applicator surface. Those observations were similar before and after optimization of treatment plans. Prolonging the interval length influenced better protection of healthy tissues circumjacent treated tumor, but simultaneously prolonged treatment time (the same total dose given to the patient but in a longer time). In clinical practice it means the decrease of number of treated patients.

Conclusions

1. Prolongation of intervals between pulses in PDR brachytherapy is connected with lower values of BED doses in healthy tissues.
2. It seems that longer intervals between pulses reduce the risk of late complications, but also decreases number of cured patients.
3. Addition of optimization influenced increase of doses in healthy tissues.

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