

Hyperfractionation of HDR brachytherapy – influence on doses and biologically equivalent doses in clinical target volume and healthy tissues

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Abstract

Purpose: The aim of this work was to compare value of doses calculated in healthy tissues according to chosen different HDR brachytherapy (HDRBT) fractionation schemas with doses given once and twice daily.

Material and methods: Fifty one patients with head and neck cancers, brain tumors, breast cancers, sarcoma, penile cancer and rectal cancer were qualified for calculations. Doses were calculated using PLATO planning system (Nucletron®) in chosen critical points in surrounded healthy tissues. For all treatment plans doses were compared using the BED (Biologically Equivalent Dose) formula. Data obtained from original PDR treatment plans were used for the elaboration of hypothetical HDRBT treatment plans – once and twice daily. For statistical analysis Wilcoxon test, Friedman ANOVA test and Kendall ratio were used.

Results: One ascertained that the increase of the fraction dose from 4 Gy to 10 Gy caused the necessity to decrease the total dose in the treatment area ($p < 0.001$), in the greater degree after fractionation twice daily. In many examined critical points in organs at risk when 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.

Conclusions: The increase of the HDR fraction dose or the use of two fractions daily instead of one fraction per day causes the need to decrease the physical dose in the treatment calculations using BED formula and it should be valuable in choosing fractionation schema.

J Contemp Brachyther 2009; 1, 2: 109-116

Key words: BED, HDR, brachytherapy, hyperfractionation, linear-quadratic.

Purpose

Fractionation of HDR requires selection of number of fractions or the fraction size. Frequently, in clinical practice, the best option is to lower the fraction size in order to reduce the biologic dose ratio of late-responding normal tissue to the tumor [1]. To overcome such extensive difference in overall treatment time between LDR, PDR and fractionated HDR that could allow tumor cells to repopulate, HDR regimens with multiple fractions per day are being used [2-5]. Generally, HDR is given as fractionated treatment to decrease normal tissue toxicity. The dose effect relationship in radiation therapy is not linear, but may be assumed to follow a linear-quadratic (LQ) function [6]. Hence, doses from different treatment modalities cannot be added linearly to determine the combined effect. Many radiation oncologists are not familiar with the fractionation schemes and its applicability

in HDR brachytherapy. Furthermore, there is a marked difference between the biological effects in the tumor and in those in late reacting normal tissue [6]. Besides, patients are often treated with external beam radiotherapy combined with HDR brachytherapy, which poses additional challenge to determine the combined effect of the two treatments [7]. One way to calculate the biologically equivalent doses (BED) of different dose fractionation schemes is the use the LQ equation [8,9]. In this equation, the α/β ratio is usually 10 Gy for tumor/early effects and 3 Gy for late effects [7,10].

The aim of this work was to compare value of doses measured in healthy tissues according to chosen different HDR brachytherapy (HDRBT) fractionation schemas with doses given once and twice daily. The BED formula was chosen for doses calculations [11]. Influence of doses optimization on BED values was analyzed.

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Received: 22.02.09

Accepted: 20.04.09

Published: 30.06.09

Material and methods

Material

The original data from the first 51 patients treated with PDR brachytherapy (PDRBT) in Greater Poland Cancer Centre were included in the study. Data obtained from original treatment plans were used for the elaboration of hypothetical HDRBT treatment plans – once and twice daily [12]. 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 neck cancer, 23 – with brain tumor, 8 – with breast cancer, 3 – with soft tissues sarcoma, 1 – with penis cancer and 1 – with rectal cancer. The PDR radical treatment included 2 fractions of 20 Gy with 3-4 days intervals (pulses 0.6 – 1 Gy hourly). In palliative PDR brachytherapy one fraction of 20 Gy was applied (pulses 0.6-0.8 Gy hourly). We used applicators such as: 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.

Methods

The doses were calculated using PLATO planning system in prescribed reference point (CTV) and in surrounded healthy tissues. In each group of patients critical points were chosen in order to measure the doses in healthy critical tissues. In organs at risk the doses in chosen critical

points were evaluated from the point of the risk of the late radiation complications. They are characterized in Table 2.

In every case, on the basis of PDRBT treatment plans, the influence of optimization on distance and volume of doses in organs at risk was examined. The model of the biological equivalent dose (BED) was applied to calculate and to compare the doses. This data were used for the elaboration of hypothetical HDR brachytherapy treatment plans. One assumed the same value of BED in reference point (in the treatment area) 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 and twice daily (with 6 hour interval between fractions). Differences among total doses in critical points before and after distance and volume optimization were analyzed. The same dependences were examined also for biological equivalent doses. One of the BED formula advantages is its relative application facility in different fractionation schema [12,13]. Basing on literature data constant values of α/β ratio and $T_{1/2}$ ratio were chosen [12,14,15].

The comparison of biological effect of total doses were fulfilled by using the linear-quadratic formula and mono-exponential repair models [10,14,15]. 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 partial repair increases BED and requires adequate correction in calculations. The irradiation is delivered over a period of time comparable to low dose rate brachytherapy. The PDRBT dose is delivered in repeated pulses with 1-4 hours intervals. However, 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 $T_{1/2}$ [16].

For all treatment plans and all critical points doses were compared using BED (Biologically Equivalent Dose) formula, then HDRBT doses for different schemas were calculated. This formula was presented earlier by Thames and Hendry [17], justified by Steel [11]:

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

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 per day, 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, the treatment plan contained doses distribution in reference point and in critical points calculated for following dwell times. Doses distributions were calculated using real treatment plans for all 51 patients treated with PDRBT.

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

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 in central plane of applicator 4. point located on level in the middle of applicator 5. point located in nearest distance from applicator 6. point ocated on base of the skull, lying in nearest distance from applicator
Brain tumor	1. orbit 2. sella 3. chiasma 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	1 and 2 – points located every 2 cm, center point located in 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 in medial level of applicator
Penis cancer	1. pubic symphysis 2. epididimis 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

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. Optimization on volume was prepared 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 the other catheters that differ from the ones for which the dwell times were calculated, were taken into account [16].

Doses in Clinical Target Volume (CTV)

It has been established that BED in reference point in every HDRBT fractionation schema will be the same as calculated in PDRBT. From that reason physical doses (D) in reference point would be different for all fraction size because BED depends on the D and on fractionation schema.

Eight chosen dissimilar fractionation schemas were compared with fraction size of 4, 6, 8 and 10 Gy, given once and twice daily. The meaning of abbreviations in presented figures: PDR – PDRBT; HDR4, HDR6, HDR8, HDR10 – HDR brachytherapy once daily with fraction size 4 Gy, 6 Gy, 8 Gy i 10 Gy, respectively, and 2HDR4, 2HDR6, 2HDR8, 2HDR10 – HDR brachytherapy

twice daily with fraction size 4 Gy, 6 Gy, 8 Gy i 10 Gy, respectively.

Differences between median total doses in nine fractionation schemas (PDR, HDR4, HDR6, HDR8, HDR10, 2HDR4, 2HDR6, 2HDR8, 2HDR10) were examined. The ANOVA Friedman statistical analysis was used, permitting investigation of dependent variables. For examination of differences between two groups: fractionation once and twice daily, non parametric Wilcoxon test was used. Difference between median total doses in HDRBT given once and twice daily was defined as follows:

$$\Delta D^S_{1HDR - 2HDR} = \frac{\sum_{i=N}^i \{D_{1HDR} - D_{2HDR}\}_i}{N}$$

where N means number of analyzed group, $\{D_{1HDR}-D_{2HDR}\}_i$ – variance between *i-case* of HDRBT given once and twice daily.

Doses in critical points (OaRs)

The assumption of the same biological effect in reference point resulted in changing the doses in critical points depending on fractionation schema. Physical total doses in all critical points were calculated for all nine (PDR, HDR4,

HDR6, HDR8, HDR10, 2HDR4, 2HDR6, 2HDR8, 2HDR10) schemas. Correlation between doses before and after optimization was also analyzed. For statistical analysis Wilcoxon test, Friedman ANOVA test and Kendall ratio were used.

For analysis of differences in doses factors like: the median total doses ($D^{S,N}$ [%]) in critical points and standard deviations (SD [%]) before optimization ($D^{S,N}_K$ [%]), after optimization on point ($D^{S,N}_{KP}$ [%]) and on volume ($D^{S,N}_{KV}$ [%]) were taken into consideration. Doses before the comparison were normalized for PDRBT dose according to formula $D^{S,N} = D_M / D_{PDR} * 100\%$, where M means brachytherapy method, D_{PDR} - total dose of PDRBT. For statistical analysis, groups of patients of more than 8 were taken into account. Remaining groups were omitted.

Total doses in chosen critical points for all nine fractionation schema are presented in figures. For brain tumors the critical point was meninx, for head and neck cancer - external jaw surface.

BED in critical points (OaRs)

Biologically equivalent doses in all critical points were calculated for all nine (PDR, HDR4, HDR6, HDR8, HDR10, 2HDR4, 2HDR6, 2HDR8, 2HDR10) schemas. Correlation between doses was also analyzed for doses before and after optimization. The same parameters were used as for the physical doses.

Statistical analysis

Wilcoxon test (non parametric test) for two dependent tests was applied for analysis of correlation between value of doses in critical points in healthy tissues. It was concer-

ning 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 schema (given once or twice daily). The correlation between doses for every critical point was also analyzed. ANOVA Friedman and Kendall ratio for statistical analysis was used in order to permit the examination of dependent variables (several groups). $\alpha = 0.05$ significance level was accepted.

Results

Total physical doses in CTV according to different fractionation schemas

Results presented in Figs. 1 and 2 suggests the decrease of total doses in CTV with increase of HDR fraction dose with doses given twice daily. This could indicate certain changes in total doses prescribed to a patient. In Fig. 1 the decrease of HDR total dose (CTV) in connection with the increase of HDR fraction dose in function of PDR total dose is presented. In Fig. 2 the correlation between total doses (after normalization PDR total dose - continuous red line - 100%) and HDR (median doses and respondent stan-

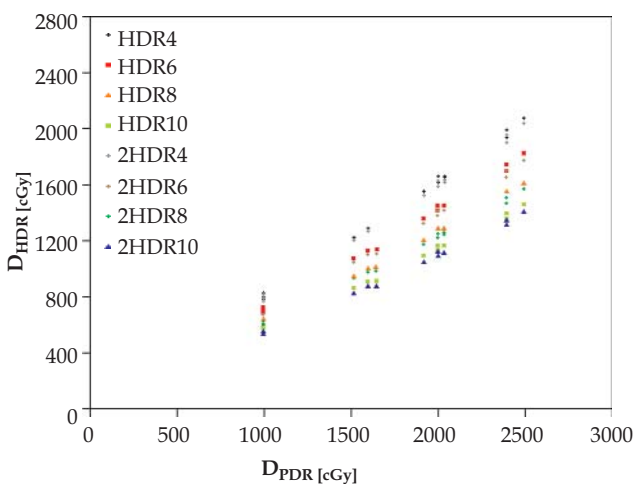


Fig. 1. Correlation between total doses in reference point (CTV) D_{PDR} [cGy] in PDRBT and doses calculated for different HDR treatment schemas - D_{HDR} [cGy], on the assumption of identical BED. HDR4, HDR6, HDR8, HDR10 - means HDRBT fractionated once daily with fraction size 4 Gy, 6 Gy, 8 Gy, 10 Gy and 2HDR4, 2HDR6, 2HDR8, 2HDR10 - HDRBT fractionated twice daily with fraction size 4 Gy, 6 Gy, 8 Gy, 10 Gy

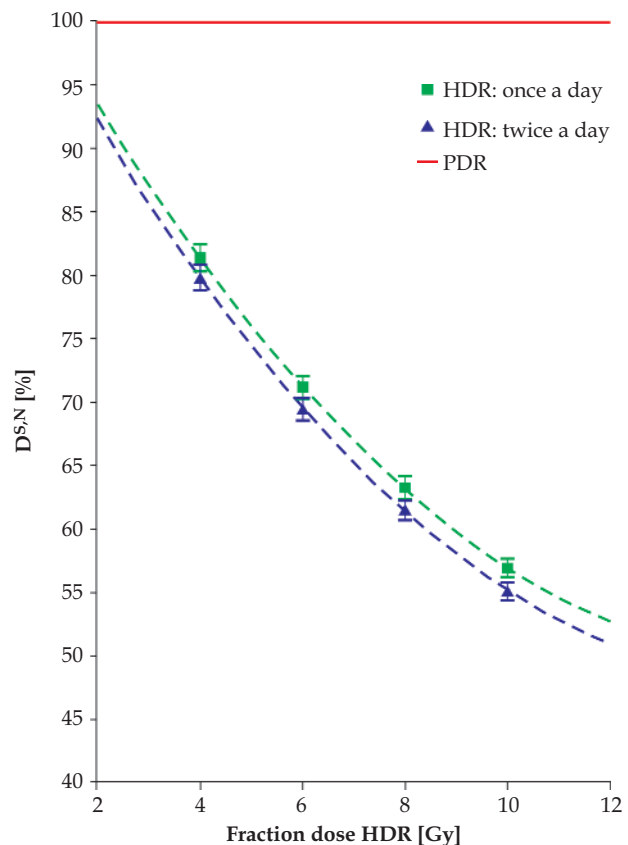


Fig. 2. Correlation between median total doses $D^{S,N}$ (after normalization of PDRBT total doses i.e. $D^{S,N} = D_M / D_{PDR} * 100\%$, where M means method of brachytherapy) obtained in PDRBT (continuous red line) and calculated total doses for alternative HDRBT fractionation schemas (Gy) (square - once daily, triangle - twice daily) and different HDR fraction sizes (horizontal axis)

standard deviations) calculated for alternative fractionation schemas (quadrate – once daily, triangle – twice daily) is presented.

The tendency that are visible in Figs. 1 and 2 was confirmed using Friedman ANOVA test. For obtaining similar biological effect in CTV the total doses should be diminished along with the increase of HDR fraction size and – in every case – replacement of PDRBT by HDRBT. For example replacing PDRBT by HDRBT (fraction size $d = 4$ Gy given once daily) requires reduction of total dose to 81.4% of PDR dose. Reduction of total doses is necessary also in case of replacing once daily fractionation schema by twice daily schema. Differences between total doses in reference point (CTV) in analyzed fractionation schemas (PDR, HDR4, HDR6, HDR8, HDR10, 2HDR4, 2HDR6, 2HDR8, 2HDR10) are presented in Table 3. In Table 4 two fractionation schemas (doses given once and twice daily) are compared. The difference in total doses were confirmed with statistical importance (51 patients, 4 different fraction size, 204 measurements).

Total physical doses in critical points

Total doses for different HDR fraction size in all patients and in chosen critical points were analyzed. In Figs. 3A and 3D the total doses in chosen critical points, median total doses and standard deviation depending on fractionation schema are presented. Representative critical points for patients with brain tumor (meninx-1) and head and neck tumor (external jaw surface) were chosen for investigation.

In every case, the total dose was decreasing along with growing HDR fraction size in both schemas: once and twice daily. Some deviation from this schema were observed – for example in point – external jaw surface with PDRBT replaced by HDRBT caused the increase of dose for one of HDR4 fraction size, but in critical point – meninx-1

the decrease of dose was ascertained. Dose increase was observed for all critical points after changing the fractionation schema from once to twice daily. Despite of great standard deviations statistically important differences between median PDR and HDR doses in critical points were observed, regardless of HDR fraction size.

Biologically equivalent doses in critical points

Values of BED were analyzed for chosen critical points similarly to physical total doses. In Fig. 4 we present results that suggests the decrease of total BED in critical points with the increase of HDR fraction dose, more visibly while doses were given twice daily. In critical point – external jaw surface with PDRBT replaced by HDRBT caused increase of BED, more clear than for physical dose, but in critical point – meninx-1 we observed decrease of BED. That advises great caution when choosing fractionation schemas because of possibility of unexpected dose growth depending on catheter position. BED increase was observed for all critical points after changing the fractionation schema from doses given once to twice daily. Similarly to physical doses, in spite of great standard deviations and statistically important differences between median PDR and HDR doses in critical points were observed, regardless of HDR fraction size. Tendency visible on Fig. 4 was confirmed using Friedman ANOVA test.

One ascertained that in biologically equivalent (to PDR) HDR brachytherapy the increase of the fraction dose from 4 Gy to 10 Gy caused the necessity to decrease the total dose in the treatment area ($p < 0.001$). These results suggest that the use of HDR brachytherapy instead of PDR brachytherapy indicates reducing the physical doses given to the treatment area, greater in case of higher fraction doses.

Table 3. Correlation between median total doses in reference point (CTV) for PDRBT and different HDRBT fractionation schemas (ANOVA Friedman, $p < 0.001$)

1	2		3		4		5		6		7		8		9		10		11
N	PDR [%]		HDR4 [%]		HDR6 [%]		HDR8 [%]		HDR10 [%]		2HDR4 [%]		2HDR6 [%]		2HDR8 [%]		2HDR10 [%]		ANOVA Friedman P
	$D^{5,N}$	SD	$D^{5,N}$	SD	$D^{5,N}$	SD	$D^{5,N}$	SD	$D^{5,N}$	SD	$D^{5,N}$	SD	$D^{5,N}$	SD	$D^{5,N}$	SD	$D^{5,N}$	SD	
51	100.0	–	81.4	1.1	71.2	0.9	63.3	0.8	56.9	0.7	79.8	1.0	69.4	0.9	61.5	0.8	55.1	0.7	< 0.001

N – group number, $D^{5,N}$ – median total doses (after normalization), SD – standard deviation

Table 4. Differences between total doses in reference point (CTV) in analyzed fractionation schemas for fractions given once (column 2) and twice (column 3) daily (Wilcoxon test, $p < 0.001$)

1	2		3		4		5
N	HDR once daily [%]		HDR twice daily [%]		Dose difference (median + SD) [%]		Wilcoxon p
	$D^{5,N}$	SD	$D^{5,N}$	SD	$D^{5,N}_{1HDR} - D^{5,N}_{2HDR}$	SD	
204	68.2	9.2	66.5	9.3	1.7	0.1	< 0.001

N – number of analyzed cases, $D^{5,N}$ – median total dose, SD – standard deviation, $D^{5,N}_{1HDR} - D^{5,N}_{2HDR}$ – median difference between doses calculated for 1HDR – fractionated once daily, and 2HDR – fractionated twice daily

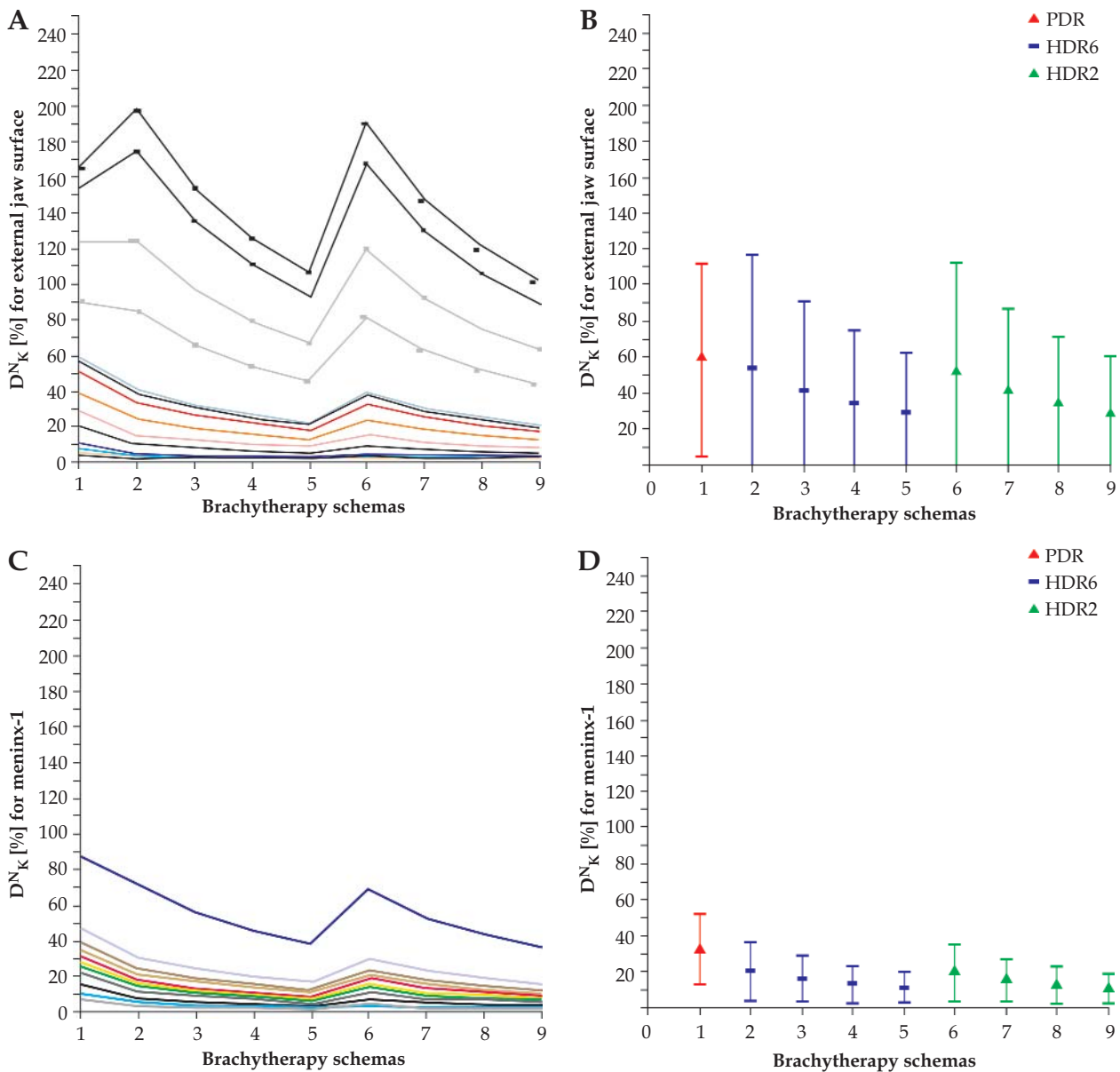


Fig. 3. Total doses D^{N_K} [%] in critical points depending on brachytherapy schemas separately for every patient (A, C, E) and median total doses D^{S,N_K} [%] and standard deviations SD for all patients (B, D, F): A and B – external jaw surface, C and D – meninx-1. All doses calculated before optimization. In the Figs. 3A, 3C points are assessed in the same patients and connected with continuous line. Intermittent line indicates change between fractionation once and twice daily. On the horizontal line following brachytherapy schemas are indicated: 1 – PDR, 2 – HDR4, 3 – HDR6, 4 – HDR8, 5 – HDR10, 6 – 2HDR4, 7 – 2HDR6, 8 – 2HDR8, 9 – 2HDR10

Discussion

The original treatment plans of patients treated in Greater Poland Cancer Centre were used for the calculations. There are only single 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 [18-20]. We analyzed existing radiobiological models and chose the BED formula for calculations of biologically effective doses in HDRBT and PDRBT. Results suggests that the use of HDRBT instead of PDRBT indicates reducing the phy-

sical doses given to the treatment area, greater in case of higher fraction doses. The use of HDR instead PDR essentially lowered physical and biological doses in examined organs of risk (OaR) while the biological equivalence dose in the treatment area was the same. In many examined critical points in organs of risk 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.

This dependence show necessity of choosing adequate HDR fractions doses for specific tumor locations and pos-

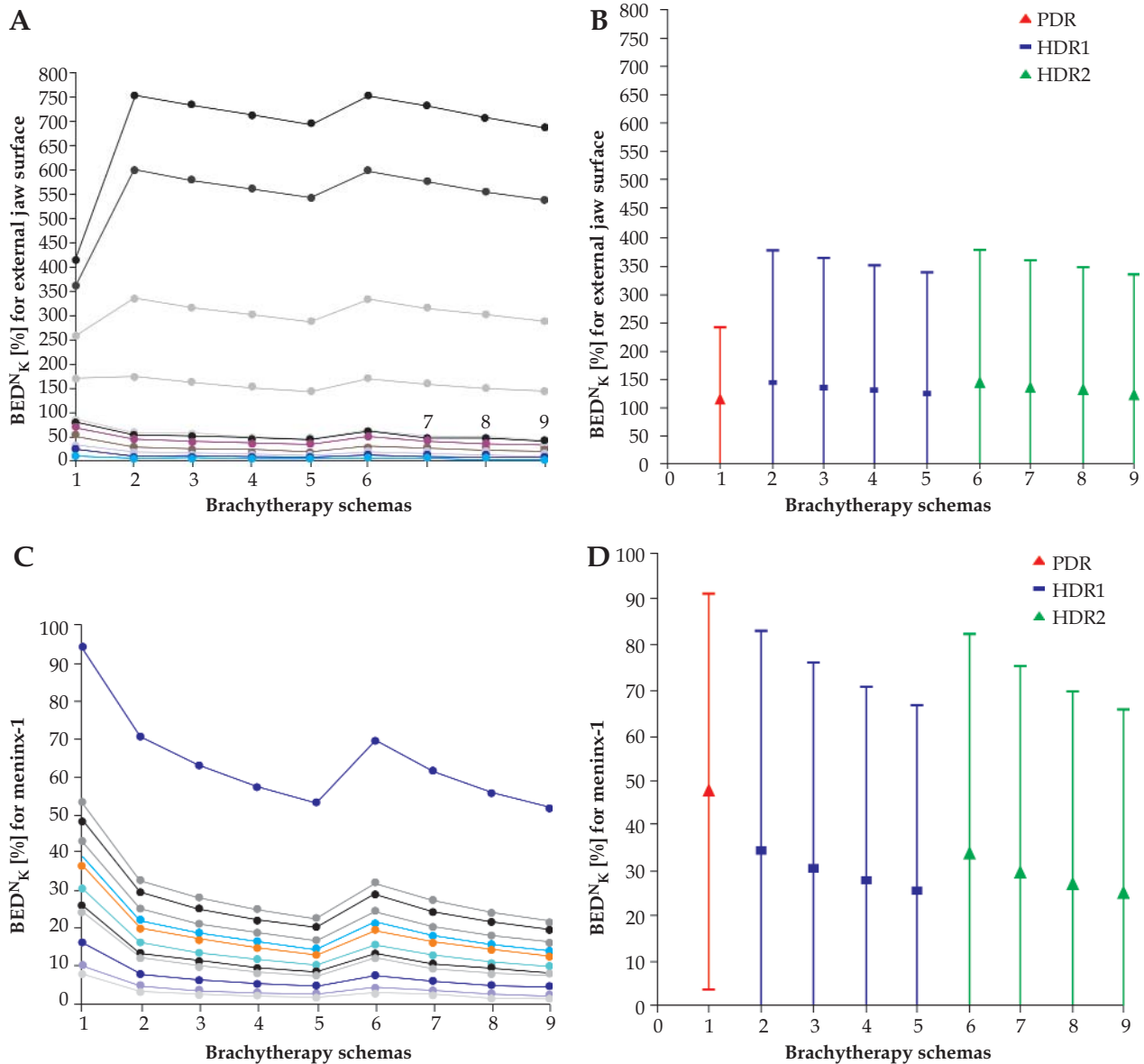


Fig. 4. Total BED (BED^N_K [%]) in critical points depending on brachytherapy schemas separately for every patient (A, C, E) and median of total doses and standard deviations SD for all patients ($BED^{S:N_K}$ [%]) (B, D and F): A and B – external jaw surface, C and D – meninx-1. All doses calculated before optimization. In the Figs. 4A, 4C points assessed in the same patients are connected with continuous line. Intermittent line indicates change between fractionation once and twice daily. On the horizontal line following brachytherapy schemas are indicated: 1 – PDR, 2 – HDR4, 3 – HDR6, 4 – HDR8, 5 – HDR10, 6 – 2HDR4, 7 – 2HDR6, 8 – 2HDR8, 9 – 2HDR10

sible alteration of treatment method. Nowadays in clinical practice we use “physical doses” in clinical target volume (CTV) instead of the biologically equivalent doses (BED). The real values of HDR dose should be decreased more than routine dose calculations in CTV (reference point) with close location of critical health tissues (OaR). Mathematical models are useful in such cases, remembering all the limitations.

In our paper the conditions of the biological equivalence of PDRBT and HDRBT were examined. Basing on literature data constant values of α/β ratio and $T_{1/2}$ ratio were chosen. One assumed the same value of BED in refer-

ence point (in the treatment area) for hypothetical HDR plans and for real treatment PDR plans. On this base 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 per day. When discussing our observations the important limitation is lack of literature in relation to equivalence of HDRBT and PDRBT. Therefore, conclusions must be analyzed carefully and should not lead directly to introduce new treatment schemas. Both methods can be used convertibly in clinical practice taking into account differences in dose efficacy, followed by

appropriate calculations. In doses calculations special attention should be given to healthy critical tissues (OaR) circumjacent a tumor (CTV). Doses in such OaR's should be calculated as a routine part of preparing correct treatment plan, especially in case of routine optimization. Our observations should be continued in randomized trials comparing HDRBT and PDRBT techniques.

Conclusions

The model of the biologically equivalent dose and proposed locations of critical points in organs of risk are useful for the comparative analysis and the definition of conditions of the biological equivalence of PDR and HDR brachytherapy. The increase of the HDR fraction dose or the use of two fractions daily instead of one fraction per day causes the decrease of the physical dose in the treatment area and decreases physical doses and biological equivalent doses in organs at risk. Calculations using BED formula should be useful in choosing the fractionation schema.

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