Values of biologically equivalent doses in healthy tissues: Comparison of PDR and HDR brachytherapy techniques

Janusz Skowronek1,*, Julian Malicki2, Tomasz Piotrowski2

1Brachytherapy Department, Greater Poland Cancer Center, Poznan, Poland
2Medical Physics Department, Greater Poland Cancer Center, Poznan, Poland

ABSTRACT PURPOSE: The aim of this work was to compare the values of doses measured in healthy tissues in chosen pulsed-dose-rate (PDR) brachytherapy (PDRBT) and high-dose-rate (HDR) brachytherapy (HDRBT) fractionation schemas.

METHODS AND MATERIALS: 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 points in surrounded organs at risk (OaR). The biologically equivalent dose (BED) formula was used to compare doses in PDRBT and HDRBT.

RESULTS: One ascertained that in biologically equivalent (to PDR) HDRBT, the increase of fractional dose from 4 to 10 Gy caused the necessity to decrease the total dose in treatment target (p < 0.001). The use of HDR instead of PDR essentially caused lower physical and biologic doses in examined OaR. In many examined critical points in OaR where BED in the treatment area was the same, one ascertained the decrease of total physical HDR dose according to the growth of the fractional dose. Similar dependences were observed for BED.

CONCLUSIONS: The use of biologically equivalent HDRBT instead of PDRBT caused the decrease of physical doses in the treatment target and the decrease of physical doses and BEDs in OaR. Prolongation of intervals between pulses in PDRBT was connected with lower values of BED doses in healthy tissues. © 2010 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: BED; PDR brachytherapy; HDR brachytherapy; Healthy tissues; Optimization

Introduction

There have been several randomized trials that compared low-dose-rate (LDR) brachytherapy (LDRBT) and high-dose-rate (HDR) brachytherapy (HDRBT) in the treatment of gynecologic cancers and oral tongue cancer as well as some historical comparisons. However, no trial had met the criteria of modern randomized studies. In most of the trials, HDRBT and LDRBT produced similar results (1–4). Unfortunately, since introducing the new treatment modality (pulsed-dose-rate [PDR] brachytherapy [PDRBT]), similar trials comparing HDRBT and PDRBT have not been published.

PDR treatment is a new brachytherapy modality that combines physical advantages of HDRBT technology (isodose optimization, planning flexibility, and radiation safety) with the radiobiologic advantages of LDRBT (repair advantages) (5–8). The single radioactive stepping source moves through all the implanted catheters during each pulse. Most often, the source is located in a capsule 2.5 mm in length and 1.1 mm in diameter (depending on manufacturer). 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 PDRBT, each pulse delivers a small dose, followed by an interval that allows some repair of sublethal damage and small increase of radiobiologic effect compared with LDRBT. 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 toward treatment with intervals carries a radiobiologic disadvantage. Large fractional dose (in PDRBT pulse dose) should lead 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 radiobiologic deficit may be acceptable (12–14).

However, it is likely that early-responding tissues, such as tumors, repair sublethal damages more rapidly than late-responding tissues (15–18). 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 tissues, they estimated that PDRBT that delivers series of pulses separated by 3–4 hours should produce better results than LDRBT (19–21).

In clinical practice, there is now a possibility of choice between HDR and PDR techniques, but treatment schemas are not easily comparable. The aim of this work was to compare calculated doses in surrounded healthy tissues with various PDRBT fractionation schemas with different HDRBT schemas. We have chosen the biologically equivalent dose (BED) formula for dose calculations (22). Influence of dose optimization on BED values was analyzed.

## Materials and methods

### Materials

The first 51 patients treated with PDRBT in Greater Poland Cancer Center between 1999 and 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, with median value of 53 years. Values of doses and others physical and biologic data were analyzed in 15 patients with head and the neck cancer, 23 with breast cancer, 3 with soft tissues sarcoma, 1 with penis cancer, and 1 with rectal cancer. Radical PDRBT included two treatment courses—total dose 20 Gy each—separated by 3- to 4-day intervals (every course 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 the following applicators: interstitial, flexible 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.

PDRBT and HDRBT were applied in compliance with European recommendations (1, 2) using the following therapeutic equipments: integrated brachytherapy unit, PLATO planning system, and MicroSelectron’s PDR and HDR (Nucletron BV, Veenendaal, The Netherlands).

### Methods

The doses were calculated using PLATO planning system in prescribed reference point (clinical target volume [CTV]) and in some chosen so-called critical points in surrounded healthy tissues. In each group of patients, critical points were chosen separately for dose measurements in healthy critical tissues. The points are characterized in Table 2.

In all the cases, on the basis on PDRBT treatment plans, the influence of optimization on distance and on volume of doses in organs at risk (OaR) was examined. In OaR, the doses in chosen critical points were counted from the point of the risk of the late radiation complications. The model of the BED was used to calculate the doses and to compare the PDR doses. These data were then applied in the elaboration of hypothetical HDRBT treatment plans. One assumed a constant value of BED in reference point (in the treatment target) for hypothetical HDR plans and for real-treatment PDR plans. On this basis, the physical doses and BEDs in the reference point and in chosen critical points were calculated for four chosen treatment schemas with different HDR fractional sizes: 4, 6, 8, and 10 Gy given once daily. The differences among total doses and BED (PDRBT and dissimilar schemas of HDRBT) at critical points before and after distance and volume optimization were analyzed. The same dependences were examined for BEDs.

### Table 1: Clinical data of patients

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Number of patients, description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median: 53 years, Range: 22–85 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 22 (43.1%), Female: 29 (56.9%)</td>
</tr>
<tr>
<td>Tumor site</td>
<td>Head and neck cancer: 15, Brain tumor: 23, Breast cancer: 8, Soft tissue sarcoma: 3, Penis cancer: 1, Rectal cancer: 1</td>
</tr>
<tr>
<td>Doses</td>
<td>$1 \times 10$ Gy (breast cancer): 8, $1 \times 20$ Gy (palliative treatment): 39, $2 \times 20$ Gy (radical treatment): 4</td>
</tr>
</tbody>
</table>
advantage of using BED is its flexibility to compare different fractionation schemas (6, 23, 24). The values of $a/b$ and $T_{1/2}$ were chosen from the literature (6, 25, 26).

The comparison of the biologic effect of the total doses used the linear-quadratic formula and monoexponential repair models (25–27). One assumed that radiation-induced injuries would be incomplete during intervals between brachytherapy fractions, especially if $T_{1/2}$ is relatively high in relation to the length of the period. This incomplete repair decreases the BED and requires accounting in calculations. The irradiation is delivered over a period of time comparable to LDRBT, though not continuously. The dose is delivered in pulses that are repeated in this study of 1, 2, and 4 hours. Such intervals between fractions are 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 and the interval between fractions and $T_{1/2}$ (1).

The calculation was done using the following equation (22, 28):

$$\text{BED} = D[1 + d/(a/b) + H_m \times d/(a/b)],$$

where:

$$\Phi = \exp(-\mu \Delta T)$$

$$H_m = 2/m \times [\Phi/1 - \Phi] \times [m - (1 - \Phi_m/1 - \Phi)]$$

$D = \text{total dose}, d = \text{fractional dose}, m = \text{number of daily fractions},$ and $\Delta T = \text{interval between fractions (pulses)}$.

Values of $a/b$ were as follows: 10 Gy for tumors and early-reaction tissues and 3 Gy for late-responding tissues. The values of $T_{1/2}$ were 0.5 hours for tumors and early-reaction tissues and 1.5 hours for late-responding tissues. The mean time for repair was $\mu = 0.693/T_{1/2}$. In every treatment plan, the doses at the reference point and at critical points were calculated.

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 (1).

Optimization on volume was performed for applications (e.g., breast cancer applications) where the catheters lied in multiple planes, aiming for a homogeneous dose distribution inside the planning target volume and for minimizing the spread in the surrounded tissues. Only dwell positions that lied in the catheters other than the catheter for which the dwell times were calculated were taken into account (1). For statistical analysis, Friedman analysis of variance test and the Kendall tau rank correlation coefficient were used.

### Results

Dose value analysis in PDRBT showed undesirable increase of dose (from 1.9 to 13.4 Gy) at most of the points

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Critical point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck cancer</td>
<td>1. External jaw surface</td>
<td>1 and 2—Points located in central plane of applicator</td>
</tr>
<tr>
<td></td>
<td>2. Internal jaw surface</td>
<td>3—Point located in nearest distance from applicator</td>
</tr>
<tr>
<td></td>
<td>3. External ear</td>
<td>4—Point located in the middle of applicator</td>
</tr>
<tr>
<td></td>
<td>4. Spinal cord</td>
<td>5—Point located in nearest distance from applicator</td>
</tr>
<tr>
<td></td>
<td>5. Orbit</td>
<td>6—Point located on base of the skull, lying in nearest distance from applicator</td>
</tr>
<tr>
<td></td>
<td>6. Brain</td>
<td></td>
</tr>
<tr>
<td>Brain tumor</td>
<td>1. Orbit</td>
<td>Points located at nearest distance from applicator</td>
</tr>
<tr>
<td></td>
<td>2. Sella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Chiasma opticum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. External ear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Epipharynx</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1. Three points on external surface of pleura</td>
<td>1 and 2—points located every 2 cm, center point located on medial level of applicator</td>
</tr>
<tr>
<td></td>
<td>2. Three points on skin</td>
<td></td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>1. Three points on bone surface</td>
<td>1 and 2—Points located every 2 cm, center point located on medial level of applicator</td>
</tr>
<tr>
<td></td>
<td>2. Three points on skin</td>
<td></td>
</tr>
<tr>
<td>Penis cancer</td>
<td>1. Pubic symphysis</td>
<td>Points located at nearest distance from applicator</td>
</tr>
<tr>
<td></td>
<td>2. Epidydimes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Ischiadic tuber</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4—6. Three points on skin surface</td>
<td></td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1. Femoral bone head</td>
<td>Points located at nearest distance from applicator</td>
</tr>
<tr>
<td></td>
<td>2. Sacra bone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Pubic symphysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Obturator foramen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Urinary bladder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Mons pubis</td>
<td></td>
</tr>
</tbody>
</table>
in OaR after optimization, depending on the length of interval between pulses and localization of the critical point in every analyzed patient. Values of doses in critical points differed in every case. These doses presented in Tables 3 and 4 and Figs 1–3 were calculated on the basis of 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 to 10 Gy should cause the necessity to decrease the prescribed total dose in the treatment target. The median BED value at the chosen critical points in healthy tissues was statistically related to the length of intervals between PDR pulses decreasing exponentially as the interval increased from 1 to 4 hours (Kendall tau rank correlation = 0.48–1.0, \(p = 0.002–0.00001\)).

The optimization influenced the increase of doses in all measured points in healthy tissues. Similar dependences were observed in calculations for BED doses before and after optimization on distance. Summarized BED values—different interval length, HDR fractional dose, and optimization status—are presented in Tables 3 and 4.

BED values for different lengths of intervals between pulses were compared with four chosen HDR fractionation schemas. The comparison of BED between PDR and HDR (fractions of 4, 6, 8, and 10 Gy) for a chosen critical point (e.g., “internal jaw surface”) before and after optimization are presented in Figs. 1–4. It seems that BED boundary values (the highest and the smallest) for PDRBT were smaller than BEDs for different HDRBT fractionation schemas.

### Discussion

Although the PDR approach has been the subject of numerous theoretical articles, and afterloading units...
modified for PDR treatments have been commercially available for several years, only a few data have been published regarding clinical experience with these techniques (7, 29–31). Our results show that the prolongation of intervals between pulses in PDRBT, and thus the total duration, was linked to the decrease of BED values in healthy tissues, represented by chosen critical points. These observations were similar before and after optimization of treatment plans. The prolongation of the interval length was related to better protection of healthy tissues that surrounded the treated tumor. In clinical practice, such prolongation may mean decreasing the number of treated patients.

There are only few data indicating a reliable use of radiobiologic models for the purpose of comparing different brachytherapy techniques and fractionation schemas (32–34). We analyzed the existing radiobiologic models and chose BED formula for calculating the biologically effective doses in HDRBT and PDRBT. The results depend on the mathematical model chosen for calculations. In our work, the use of HDRBT instead of PDRBT resulted in lower physical and biological doses in examined OaR. In many examined critical points in OaR when the BEDs in the treatment area were the same, one ascertained the decrease of the total physical HDR dose according to the growth of the fractional dose. Similar dependences appeared also for BEDs. At all critical points, the increase of the HDR fractional dose caused the decrease of BED. It implies the necessity for considering unexpected values of physical doses after change of HDR fractionation schemas. Especially in some critical tissues, we cannot be sure of values of doses without practicable calculations. This dependence advises the necessity of choosing adequate HDR fractional doses for specific tumor locations and careful choosing of treatment method (PDRBT or HDRBT). Nowadays, in clinical practice, we use “physical doses,” not the BED. Physical value of HDR fractional dose should be decreased after calculations in critical healthy tissues (OaRs) when OaRs are nearby. In such cases, the mathematical models are useful with the notification of all the limitations.

The lack of literature about equivalence of HDRBT and PDRBT causes really important limitation; hence, the conclusions should be made carefully, and they do not lead directly to introduce new treatment schemas. Both methods can be used convertibly in clinical practice after taking into account differences in dose efficiency and after suitable and adequate calculations. In doses calculations, special attention should be paid to healthy critical tissues (OaR) surrounding the tumor (CTV). Doses in such OaRs should be calculated as a routine part of preparing the treatment plan, especially in case of using routine optimization procedures. Our observations should be continued in randomized trials comparing HDRBT and PDRBT techniques.

Conclusions

The model of BED and proposed locations of critical points in OaR were useful for comparative analysis of the biologic equivalence of PDRBT and HDRBT. The use of
biologically equivalent HDRBT instead of PDRBT caused the decrease of physical doses in the treatment area and the decrease of physical and BEDs in healthy OaR. Prolongation of intervals between pulses in PDRBT was associated with lower values of BED doses in healthy tissues.

References


