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Comparison of PDR brachytherapy and external beam radiation therapy in the case of breast cancer

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Abstract

Pulsed dose rate brachytherapy (PDR) was compared to external beam radiation therapy (EBRT) in the case of breast cancer. The benefits were figured out by evaluation of dosimetric parameters and calculating the normal tissue complication probability (NTCP). PDR plans were set up for five randomly chosen left-sided breast cancer patients delivering a total dose of 50.4 Gy to the target (dose rate 0.8 Gy h^{-1}). For EBRT five left-sided breast cancer patients were planned using 3D-conformal tangential photon beams with a prescribed total dose of 50 Gy (2 Gy/fraction) to the total breast volume. For plan ranking and NTCP calculation the physical dose was first converted into the biologically effective dose (BED) and then into the normalized total dose (NTD) using the linear quadratic model with an α/β ratio of 3 Gy. In PDR the relative effectiveness (RE) was calculated for each dose bin of the differential dose volume histogram to get the BED. NTCPs were calculated for the ipsilateral lung and the heart as contoured on CT slices based on the Lyman model and the Kutcher reduction scheme. Dosimetric parameters as V_{th} (percentage of the total volume exceeding a threshold dose) and Jackson's f_{dam} (fraction of the organ damaged) were also used to figure out the benefits. The comparison of calculated NTCPs in PDR and EBRT showed no difference between these two modalities. All values were below 0.01%. f_{dam} derived from EBRT was always higher (mean value 8.95% versus 1.21% for the lung). The mean V_{10} and V_{20} of the lung related to BED were 6.32% and 1.72% for PDR versus 11.72% and 9.59% for EBRT. When using dosimetric parameters as V_{th} and f_{dam}, PDR was mostly superior to EBRT in respect of sparing normal tissues. NTCP calculation as a single method of modality ranking showed a lack of information, especially when normal tissue was exposed to low radiation doses.

1. Introduction

A feasible approach to rank competing treatment plans in radiation therapy is the calculation of normal tissue complication probability (NTCP). The evaluation of different external beam radiation modalities and treatment techniques is often based on NTCP calculation using different published models and parameter sets (Oetzel *et al* 1995, Ragazzi *et al* 1999, Moiseenko *et al* 2003, Cheung *et al* 2004, Johansson *et al* 2004).

Accelerated partial breast irradiation (APBI) using brachytherapy is tested in several trials with first promising results (Ott *et al* 2004, Polgár *et al* 2002, 2004). This study compares this new concept to the standard treatment of 3D-conformal radiation therapy (3D-CRT) using external beam radiation therapy (EBRT) in the case of breast cancer.

In addition to EBRT, APBI using brachytherapy has become an alternative to whole breast irradiation (Das *et al* 2004, Polgár *et al* 2004, Wazer *et al* 2006). In our study we limit APBI techniques to interstitial multicatheter brachytherapy. APBI using brachytherapy shows comparable clinical outcomes to whole breast irradiation, but might limit the dose to healthy tissues and reduce the overall treatment time (Polgár *et al* 2002, 2004). While EBRT is delivered during 5 weeks (2 Gy per fraction up to 50 Gy in our study), the entire brachytherapy procedure, including applicator insertion, planning, irradiation delivery and applicator removal, can be applied within 1 week.

In this study APBI with pulsed dose rate (PDR) brachytherapy was compared to whole breast EBRT. The benefits with regard to limiting the dose to normal tissues were worked out by evaluating dosimetric parameters and calculating normal tissue complication probability.

The main questions were

(1) Which modality results in a higher sparing of normal tissues, such as the ipsilateral lung and the heart?
(2) Does NTCP calculation allow such a ranking in the case of breast cancer?

2. Material and methods

PDR plans of five randomly chosen left-sided breast cancer patients delivering a total dose of 50.4 Gy to the target (dose rate 0.8 Gy h^{-1}) were provided by the Department of Radiotherapy, Medical University of Vienna. APBI planning with PDR was performed using the PLATO (Version 14.3, Nucletron B V Veenendaal, The Netherlands) treatment planning system (TPS). For EBRT, five left-sided breast cancer patients were planned on the TPS XiO (Version 4.33.02, CMS, St Louis, MO, USA) using 3D-conformal tangential photon beams with a prescribed total dose of 50 Gy (2 Gy/fraction) to the total breast volume. In EBRT the whole breast was irradiated with two tangential fields. Each field included a wedge to achieve a homogeneous dose distribution inside the breast volume. All ten plans were set up for patients after breast conserving surgery. The mean heart and ipsilateral lung volumes contoured on the CT slices were 562.02 cm^3 and 1044.88 cm^3 for the five patients in EBRT versus 451.48 cm^3 and 1129.91 cm^3 for the five patients treated with PDR brachytherapy, respectively. The heart volume included the muscular parts and the coronary vessels.

For plan ranking and NTCP calculation, the physical dose was first converted into the biologically effective dose (BED) and then into the normalized total dose (NTD) using the linear quadratic model with an α/β ratio of 3 Gy (Barendsen 1982, Maciejewski *et al* 1986, Fowler 1989, Van Dyk *et al* 1989):

$$\mathrm{BED} = \frac{E}{\alpha} = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

$$\mathrm{BED} = D \cdot \mathrm{RE}$$
$$\mathrm{NTD} = nd \frac{1 + \frac{d}{\alpha/\beta}}{1 + \frac{2}{\alpha/\beta}}.$$

The total physical dose D is given by the number of fractions n and applied dose d per fraction. In PDR the relative effectiveness (RE) was calculated using Dale's formula for each dose bin of the differential dose volume histogram to get the BED (Dale 1985, Dale and Jones 1998):

$$\mathrm{BED} = \mathrm{NRT}\left[1 + \frac{2R}{\mu(\alpha/\beta)}\left(1 - \frac{NY - SY^2}{N\mu T}\right)\right]$$
$$S = \frac{NK - K - NK^2Z + Z^N K^{N+1}}{(1 - KZ)^2}$$
$$Z = \exp(-\mu T)$$
$$Y = 1 - Z$$
$$K = \exp(-\mu x)$$
$$\mu = \frac{\ln(2)}{T_{1/2}},$$

where N is the number of pulses, R is the dose rate, T is the duration of each pulse and $T_{1/2}$ is the halftime for repair of sublethal damage. The value of $T_{1/2}$ was assumed to be 1.5 h.

NTCPs were calculated for the ipsilateral lung and the heart as contoured on CT slices based on the Lyman model and the Kutcher reduction scheme. It must be mentioned that NTCP models and their parameter sets were primarily derived from conformal photon therapy. Their validity for other treatment modalities such as brachytherapy has not been proven yet (Moiseenko 2008). The empirical Lyman model represents the NTCP for uniform organ irradiation by an error function of dose and volume using the power law relationship (Lyman 1985):

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(\frac{-u^2}{2}\right) \mathrm{d}u$$
$$t = \frac{D - \mathrm{TD}_{50}(v)}{m \cdot \mathrm{TD}_{50}(v)}$$
$$v = \frac{V}{V_{\mathrm{ref}}}$$
$$\mathrm{TD}_{50}(1) = \mathrm{TD}_{50}(v) \cdot v^n,$$

where TD_{50} gives the tolerance dose for the whole organ irradiation with 50% complication, m represents the steepness of the dose response function, V_{ref} is the reference volume, V is the irradiated organ volume and n defines the magnitude of the volume effect. To account for dose inhomogeneities the effective volume method proposed by Kutcher and Burman (1989) was used. This reduction scheme makes use of the differential dose volume histogram (d_i, v_i). The effective volume is the volume irradiated uniformly to the maximum dose $D_{\max}$ of the dose volume histogram, which would give the same probability of complication as that which results from the non-uniform dose distribution (Kutcher and Burman 1989):

$$V_{\mathrm{eff}} = \sum_i v_i \cdot \left(\frac{d_i}{D_{\max}}\right)^{\frac{1}{n}}.$$

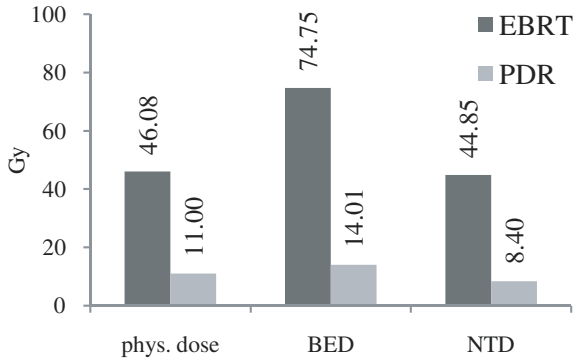

Figure 1. Averaged maximum doses to the heart in EBRT and PDR (phys. dose = physical dose, BED = biologically equivalent dose, NTD = normalized total dose).

The volume effect is described by n, such as used in the Lyman model. To figure out the influence of the volume effect on the NTCP results, the calculation was based on two different model parameter sets published by Burman *et al* (1991) and Martel *et al* (1998). Following parameter sets were used for the heart: $TD_{50} = 48$ Gy, $n = 0.35$ and $m = 0.1$ (Burman) and $TD_{50} = 50.6$ Gy, $n = 0.636$ and $m = 0.13$ (Martel) with pericarditis as endpoint. For radiation pneumonitis Burman proposed $TD_{50} = 24.5$ Gy, $n = 0.87$ and $m = 0.18$. Dosimetric parameters such as V_{th} (percentage of the total organ volume exceeding a threshold dose) (Graham *et al* 1999) and f_{dam} (fraction of the organ damaged) proposed by Jackson and Kutcher (1993) were also used to work out the benefits for PDR and EBRT. The fraction of the organ damaged is calculated from the differential dose volume histogram (d_i, v_i) expressed in terms of biologically equivalent doses:

$$f_{dam} = \sum_i v_i \cdot p(d_i)$$

$$p(d_i) = \frac{1}{1 + \left(\frac{d_{1/2}}{d_i}\right)^k},$$

where $p(d_i)$ describes the probability of damaging a subunit at a given biologically equivalent dose and can be expressed by a logistic function (Jackson *et al* 1995). $d_{1/2}$ is the dose at which 50% of the subunits are damaged and k determines the slope parameter of the dose response function. $d_{1/2}$ was assumed to be 48 Gy for the heart and 24.5 Gy for the lung.

3. Results

The comparison of calculated NTCPs in PDR and EBRT showed no difference between these two modalities. All values were below 0.01%. To work out the benefits the focus was placed on dosimetric parameters. The averaged mean and maximum doses (physical dose, BED and NTD) among all patients are shown in figures 1–4 for the heart and the lung in PDR and EBRT.

The figures demonstrate that PDR was superior to EBRT, especially in the case of sparing the lung. In the case of the heart the averaged mean doses were higher in PDR compared to EBRT; however, the difference was negligible. The fraction of the organ damaged derived from EBRT was always higher than the values resulted from PDR, which is shown in table 1 for each patient.

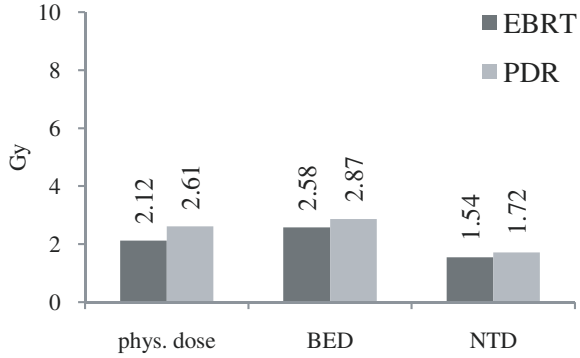

Figure 2. Averaged mean doses to the heart in EBRT and PDR (phys. dose = physical dose, BED = biologically equivalent dose, NTD = normalized total dose).

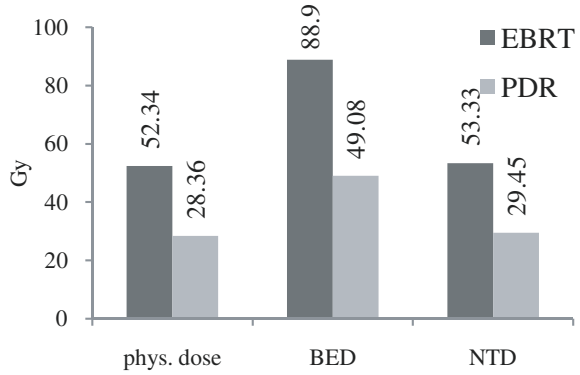

Figure 3. Averaged maximum doses to the lung in EBRT and PDR (phys. dose = physical dose, BED = biologically equivalent dose, NTD = normalized total dose).

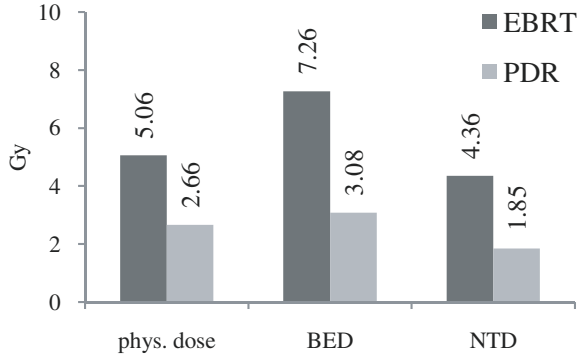

Figure 4. Averaged mean doses to the lung in EBRT and PDR (phys. dose = physical dose, BED = biologically equivalent dose, NTD = normalized total dose).

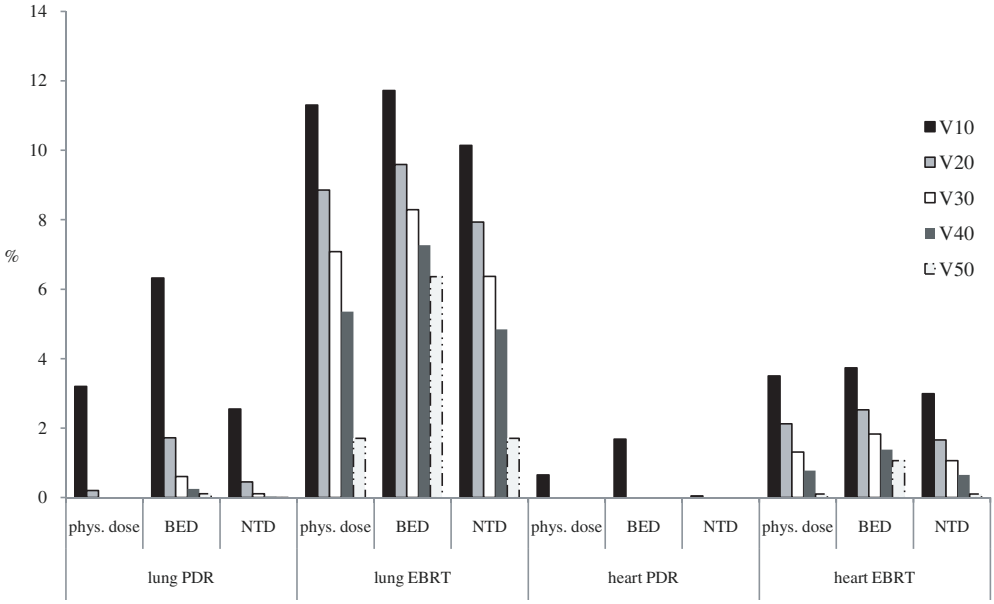

Figure 5. Averaged lung and heart volumes (%) exceeding 10–50 Gy in PDR and EBRT.

Table 1. Fraction of the organ volume damaged (f_{dam}) for the lung and the heart resulting from PDR and EBRT.

Patient ID	Lung	Heart
PDR f_{dam}(%)		
A	0.05	0
B	0.32	0
C	1.74	0
D	0.44	0
E	3.49	0
Mean f_{dam}	1.21	0
EBRT f_{dam} (%)		
F	8.39	3.17
G	6.03	0.03
H	5.18	0
I	14.40	0.13
J	10.76	2.29
Mean f_{dam}	8.95	1.12

The percent of the total organ volume exceeding the threshold doses from 10 to 90 Gy showed that external beam radiation therapy resulted in a higher dose exposure to both the lung and the heart. The mean values of V_{10}–V_{50} are demonstrated in figure 5 for EBRT and PDR. Concerning the pair of values NTD_{max} and V_{eff} resulting from the Kutcher reduction scheme (Burman parameter), the heart showed on average a higher NTD_{max} in EBRT but with a lower corresponding V_{eff} compared to PDR (44.85 Gy and 0.76% versus 8.40 Gy and 2.56%). In EBRT 7.22% of the lung volume was irradiated to 53.33 Gy (the averaged value among all five patients). For the patients treated with PDR both the dose and volume were lower, which is shown in figure 6.

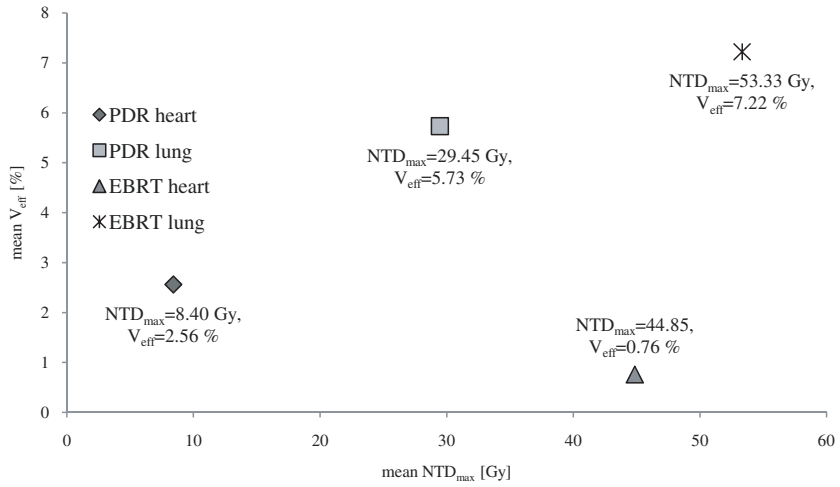

Figure 6. Averaged pairs of values (NTD_{max}, V_{eff}) in PDR and EBRT for the lung and the heart (NTD_{max} = maximum normalized total dose, V_{eff} = effective volume).

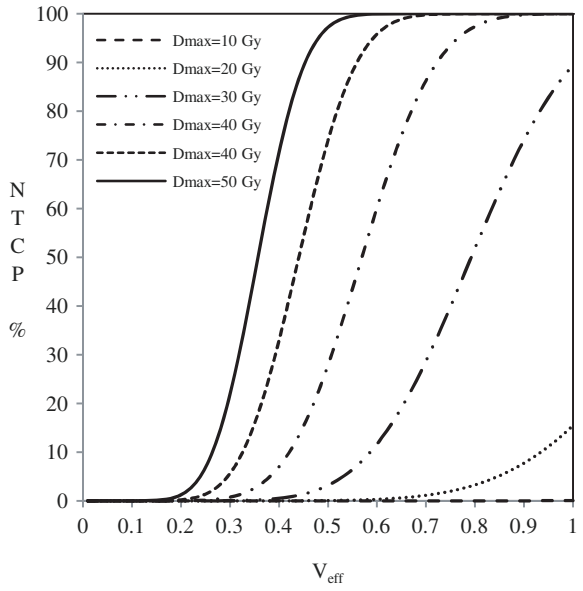

Figure 7. Effective volume versus calculated NTCP for the lung.

4. Discussion

In this study the benefits and the difference in the dose distribution between APBI using PDR and EBRT could not be worked out by means of NTCP. Figures 7 and 8 show the dependence of V_{eff} on the calculated NTCP value for different maximum normalized total doses to the heart and the lung based on the Lyman model. Both organs at risk represent a threshold type behavior, which means, that for a given dose, the complication probability does not vary with

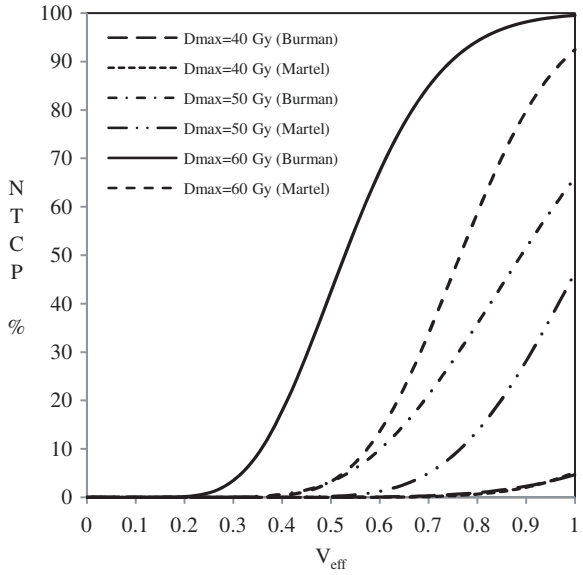

Figure 8. Effective volume versus calculated NTCP for the heart using Burman's and Martel's parameter sets.

the partial volume until a certain part of the volume is irradiated. After exceeding this threshold the probability rises rapidly depending on the dose. Among all ten patients the maximum effective volume for the lung was 11% (i.e. $V_{\text{eff}} = 0.11$) with a NTD_{max} equal to 56 Gy. For the heart it was 3% using Burman's parameter and 11% using Martel's parameter with a NTD_{max} equal to 12 Gy. According to figures 7 and 8 both normal tissues did not exceed their thresholds in this study. The NTCP calculation as a single method of modality ranking showed a lack of information, especially when normal tissue was exposed to low radiation doses. In the treatment plan study of Bovi *et al* (2007) comparing three accelerated partial breast irradiation techniques (3D-conformal radiation therapy versus brachytherapy) all NTCP values for normal breast tissue and for the lung were low for all three methods. Similar to our study higher doses to normal tissues in EBRT compared to brachytherapy did not translate into significantly higher calculated NTCP values. The evaluation was based on the concept of equivalent uniform dose (EUD).

Among other prognostic factors the calculated NTCP derived from the Lyman model was significantly correlated with the incidence of pneumonitis in the studies of Hernando *et al* (2001) and Yorke *et al* (2002). Tsougos *et al* (2007) also found a good correlation of the calculated NTCP values with the clinical outcomes. The mentioned studies were based on conformal photon therapy. Important factors, which put the use of NTCP models for brachytherapy in question, are completely different dose distributions and high dose gradients in brachytherapy compared to conformal photon therapy. In the study of Dale *et al* (2000) the Lyman–Kutcher model was applied to calculate NTCP values for a combined high dose rate (HDR) brachytherapy and EBRT treatment in the case of uterine cervix cancer. The calculated NTCPs were compared with clinical complication frequencies. The Lyman model used in that study provided a reasonable NTCP for the rectum, whereas the calculated complication probability for the bladder was too high compared to the clinical complication frequency. Dale also pointed out that it is still an open question whether the NTCP models

need modifications before incorporating extremely heterogeneous dose distributions such as those in brachytherapy.

To draw a comparison between APBI with PDR and EBRT and to perform a first evaluation, NTCP values were calculated in this study. For brachytherapy plans, the relative effectiveness and the BED were assessed for each physical dose bin resulting from the differential dose volume histogram. Due to the high dose gradients around the sources in brachytherapy, any BED or relative effectiveness value is valid only at the point at which it is calculated (Dale *et al* 2000). After determining the biologically effective dose volume histogram in brachytherapy the use of the subsequent steps for NTCP calculation mentioned in section 2 is questionable for this modality. This includes the validity of tolerance doses and DVH (dose volume histogram) reduction schemes which were primarily derived from conformal photon therapy.

With regard to figures 1, 3 and 4, PDR was superior to EBRT in sparing normal tissues. In figure 2 the mean doses to the heart are lower in external beam radiation therapy; however, the difference between these two modalities is negligible. One reason for this could be the larger heart volumes contoured on the CT slices of randomly chosen patients used in EBRT compared to those in PDR (mean value: 562.02 cm^3 versus 451.48 cm^3). Relating to the mean physical doses shown in figure 2 and the mean heart volumes for both modalities, a reduction of nearly 20% in the mean volume resulted in an increase in the mean dose of 23% (562.02 cm^3 and 2.12 Gy in EBRT versus 451.48 cm^3 and 2.61 Gy in PDR). Hence, we assume that APBI using PDR could probably result in a better sparing of the heart in a study with more patients, particularly because the dosimetric parameters, such as f_{dam} and V_{th} shown in table 1 and figure 5, point out the benefits of this modality in the case of limiting the dose to the heart. Figure 5 shows the volumes (%) exceeding threshold doses of 10 to 50 Gy. The use of DVH parameters has been proposed as a sophisticated method to report the dose to organs at risk in brachytherapy (Berger *et al* 2008).

According to figure 6, PDR showed a higher mean irradiated effective volume (2.56%) compared to EBRT (0.76%); however, this volume corresponded to a lower NTD_{max} in PDR (8.40 Gy versus 44.85 Gy). Based on the values NTD_{max} and V_{eff}, the question arises whether the heart can tolerate a large dose to a small irradiated volume or vice versa. EBRT definitely resulted in a lower sparing of normal lung tissue, which was a consequence of the tangential photon fields irradiating higher volumes in contrast to PDR.

5. Conclusions

NTCP calculation as a single method of modality ranking showed a lack of information, especially when normal tissue was exposed to low radiation doses. It must be taken into account that the validity of NTCP models, model parameter sets and DVH reduction schemes has not been proven yet for brachytherapy.

When using dosimetric parameters, pulsed dose rate brachytherapy was mostly superior to external beam radiation therapy in respect of sparing normal tissues.

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