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Normal tissue complication probabilities (NTCP) for modified reverse hockey stick technique (MRHS)

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background Several treatment techniques are used for irradiation of patients with breast cancer after mastectomy. There is no one technique accepted as the "gold standard". In the Holycross Cancer Centre a novel technique – the modified reverse hockey stick technique – is used.

Aim Evaluation of the risk of heart and lung injury in patients treated with the MRHS technique. Comparison of the risk for MRHS and tangential techniques.

Materials/Methods The 3D CT based dose distributions for 25 left-sided and 25 right-sided patients after mastectomy were calculated. For each patient before the NTCP was calculated all physical doses were converted into biological doses according to an α/β model with an α/β value of 3Gy. The NTCP for the lung was for each patient calculated with generalized Lyman model with two parameters: the biological mean dose and the volume above a biological threshold dose of 13Gy (V13). For the heart the NTCP was calculated using the seriality model. The parameters of the models were taken from the literature. For the heart, for each patient the partial volume of the heart receiving more than 30Gy (V30) was also obtained. The correlation between NTCP and V30 for the heart and between the mean physical dose and the mean biological dose for the lungs were determined.

Results For all left-sided patients but two for the MRHS technique the NTCP for the heart was smaller than 0.01. For tangential technique, the calculated risk of heart injury was higher. A very high correlation between V30 and NTCP was obtained for both techniques. Larger NTCPs were obtained for both techniques for patients treated on the right side. About two times higher values of NTCP were obtained if calculated with the V13 parameter. Based on the mean dose on the left side NTCP is always smaller than 0.05. For some patients treated on the right side, NTCP exceeded 0.1. NTCP values for patients treated either on the left or the right lungs for both techniques were similar. There was a high correlation between the mean physical and biological doses.

Conclusions For left sided-patients, the MRHS technique is safe for the heart and is superior to the tangential technique. The risk of lung injury is higher for patients treated on the right side. Regarding the risk of lung injury, there is no difference between the two techniques. There is a very high correlation between NTCP and V30 for the heart and between the mean physical and biological doses for the lungs.

Key words NTCP • reverse hockey stick technique • tangential technique

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Background

In the last ten years, three large randomized trials have demonstrated benefit in survival in patients randomized to comprehensive postoperative loco-regional radiotherapy after systematic treatment in breast cancer patients [1–3]. Therefore, many radiotherapy centres performed routinely comprehensive postmastectomy radiotherapy. The close proximity of the clinical target volume (CTV) to the radiosensitive structures, the heart and the lungs, often necessitates highly individualized treatment planning with complex field arrangements. While several treatment techniques are used, there is no one technique accepted as the "gold standard" [4]. In the treatment planning procedure for patients treated for left-sided breast cancer it is of special importance to keep the dose to the heart as low as possible. The older treatment techniques involving orthovoltage X-rays and Co60 beams resulted in increased rates of pericarditis and radiation-induced ischaemic heart disease [5,6]. The modern treatment techniques in most cases result in lower cardiac dose than the older ones. However, still the risk of cardiac toxicity should always be taken into account for each single treatment plan. Radiation-associated pneumonitis is not a very common sequel of radiotherapy. However, it has been reported in several studies [7–10].

Aim

Quantitative evaluation of the normal tissue response to irradiation is typically performed by means of mathematical models. Normal tissue complication probability may be calculated using dose-volume histograms (DVHs) of organs at risk, and mathematical models. Several models that predict the incidence of radiation pneumonitis and heart injury have been developed [11,12]. To the best of the author's knowledge there is no publication in which the NTCP for the heart and the lung was calculated for postmastectomy patients treated with the reverse hockey stick technique [13]. Gagliardi used the data for calculations of lung pneumonitis for patients treated with a similar technique, but real 3D dose distributions were not available. The average dose distribution was calculated based on the calculation made for 10 patients and this average dose distribution was used for the NTCP calculations. In this study, the NTCP values for lung and heart for a group of patients treated for left-sided breast cancer and the NTCP values for lung for a group of patients treated for right-sided breast cancer were calculated. The NTCP values were compared with the NTCP values calculated with tangential techniques.

Materials and Methods

25 randomly selected postmastectomy patients treated for left-sided and 25 for right-sided breast cancer were used for this study. The treatment planning for each patient was performed by means of a CT-based 3D dose planning system (TMS, Nucletron). The CT images were acquired at 10mm thick intervals from the level of the mandible through the lung bases. The CTV including the chest wall (CW) and the axillary, parasternal and supraclavicular lymph nodes was delineated by a radiotherapist. The lung contours were defined by means of an automated density gradient tracing method, and if necessary corrected by the physicists responsible for treatment planning. The heart contours were delineated manually by physicians. The planning target volume (PTV) was defined by expanding the CTV of 5mm in the medio-lateral direction only.

In the RHS technique, the supraclavicular nodes and lateral chest wall were treated using an anterior 6MV photon field. The internal mammary nodes and medial chest wall were treated using an anterior field of 6, 9, 12 or 15MeV electrons. The energy was chosen to keep the minimum dose to the PTV to 85%. In some cases, an additional posterior 15MV photon field was used to keep the minimum dose to the supraclavicular and lateral chest wall to at least 85%. Other details of the dose planning for the reverse hockey stick technique are described in a former publication [5].

The treatment planning for tangential fields was performed with the same set of CT scans as for the MRHS technique but the patient's arm on the irradiated side, which would attenuate the medial tangential field, was removed from the calculation matrix. The tangential field technique was composed of two tangential fields directed to the chest wall and internal mammary nodes. The dorsal edges of both beams were made coplanar. The supraclavicular and axillary node region was irradiated with an anterior field. If the dose to the supraclavicular nodes was smaller than 90%, an additional posterior field was used. For the same reason, a 0.5-cm bolus was applied to the CW. For every beam, the individual blocks were designed to make the shape of the beam conform to the PTV as best as possible.

The patients were treated with a prescribed dose of 50Gy, 2Gy/fraction. In the case of the MRHS technique, the dose was specified to the dose at the maximum dose point at the central axis of the electron beam. In the case of tangential fields, the dose was specified at the middle point in the chest wall (ICRU reference point for the chest wall target). The weights of the beams were chosen to keep the mean dose to the PTV in the range 100–103% of the prescribed dose. In all cases the dose distributions in the PTV of tangential techniques were more homogeneous than the dose distributions of the MRHS technique. The standard deviations of the dose distributions to the PTV for tangential technique were in the range of 5–7%, and for the MRHS techniques in the range of 6–8% of the mean dose. The differences between techniques were small so there was no need to correct the total dose delivered to the PTV. The dose distributions were calculated based on CT data with tissue inhomogeneity correction.

NTCP calculations

For each patient, before the NTCP was calculated for either heart or lungs all physical doses were converted into biological doses according to an α/β model with an α/β value of 3Gy.

The NTCP for the heart was calculated using the relative seriality model. The response of the heart to a non-uniform dose delivery is given by:

$$NTCP=\left[1-\prod^{K}\left[1-P(D_k)^{s}\right]^{\Delta v_k}\right]^{1/s},$$

where K is the number of subvolumes in the dose-volume histogram, Δv_k is the partial volume of the heart, and the parameter **s** describes the relative seriality of the organ. The $P(D_k)$ function describes the dependence of the probability of injury of dose in the case of irradiating the whole organ with a homogeneous dose. The $P(D)$ function is given by:

$$P(D)=2^{-e^{e\cdot\gamma\cdot(1-\frac{D}{D_{50}})}}$$

where $D50$ is the dose corresponding to the 0.5 complication probability; the parameter γ is the maximum relative slope of the dose-response curve. The parameter values of the relative seriality model were chosen from Gagliardi [12]. They were D_{50}=52.4Gy, γ=1.28 and s=0.87. For the heart, values of the percentage of the heart that received more than 30Gy (V_{30Gy}) were also obtained. The V30Gy metric was chosen based on the data from Hancock and Gagliardi, who have demonstrated this dose to be the threshold for calculated risk of heart injury [14,15].

For lungs, the dose volume histogram was first reduced to a single parameter, T. Two single parameters were used: the "volume above a threshold dose V_{Dth}" and the mean dose to the lungs. The Dth value of 13Gy was used for calculations. The pneumonitis incidence is given by:

$$NTCP=\frac{1}{\sqrt{2\cdot\Pi}}\int_{-\infty}^{t} e^{\frac{-x^2}{2}}dx$$

$$t=\frac{T-TD_{50}}{m\cdot TD_{50}},$$

where $TD50$ is the value of parameter T for complication probability of 0.5, and m is the slope parameter (the smaller is the m parameter the larger is the steepness of the dose-response curve). The parameter values were taken from the paper of Seppenwolde et al. [11]. The parameters V_{Dth} and m were 77% and 0.44 respectively. TD_{50} and m were 30.8Gy and 0.37 respectively.

RESULTS

Figure 1 shows V_{30Gy} for all patients for both techniques treated for left-sided breast cancer. The results were sorted according to increasing values.

Figures 2 shows the NTCP and the correlation between V_{30Gy} and NTCP for patients treated with the MRHS technique.

Figure 3 shows the NTCP and the correlation between V_{30Gy} and NTCP for patients treated with the tangential technique.

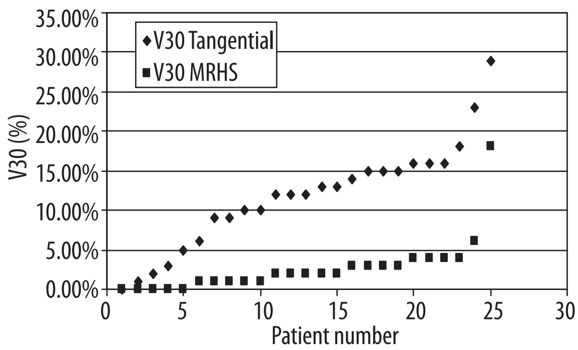

Figure 1. The V_{30Gy} for all patients for tangential and MRHS techniques treated for left-sided breast cancer.

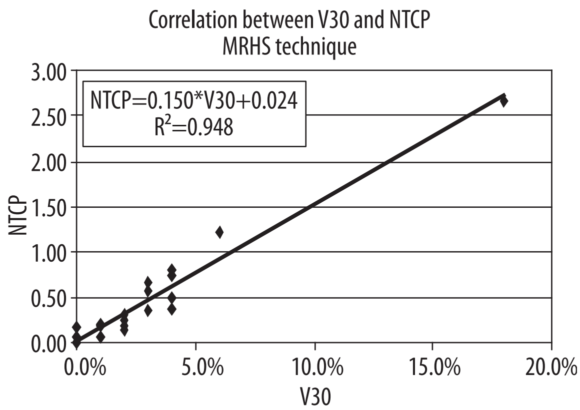

Figure 2. The NTCP and the correlation between V_{30Gy} and NTCP for patients treated with MRHS technique.

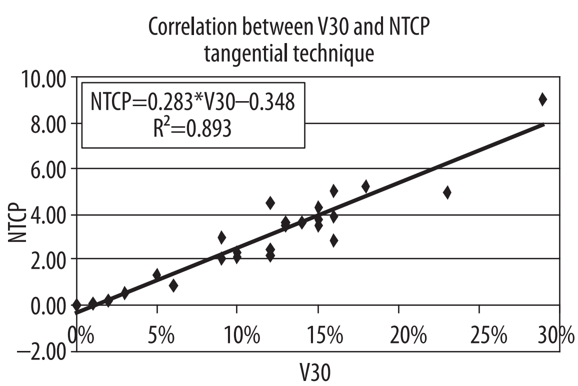

Figure 3. The NTCP and the correlation between V_{30Gy} and NTCP for patients treated with tangential technique.

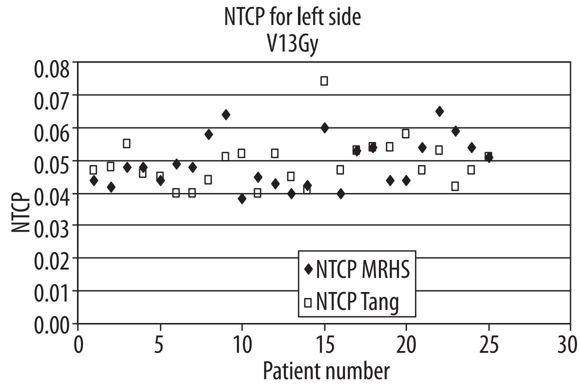

Figure 4. The NTCP for lung for left-sided patients calculated based on V_{13Gy} for MRHS and tangential techniques.

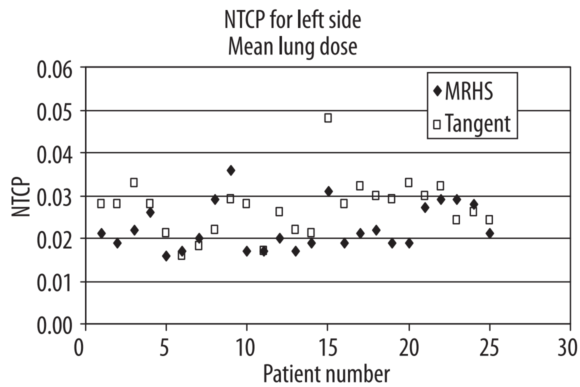

Figure 5. The NTCP for lung for left-sided patients calculated based on the mean dose for MRHS and tangential techniques.

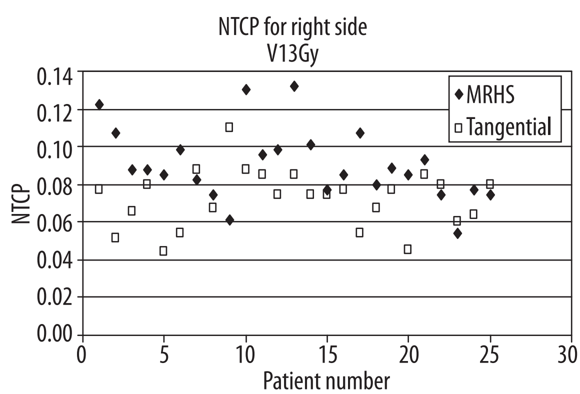

Figure 6. The NTCP for lung for right-sided patients calculated based on V_{13Gy} for MRHS and tangential techniques.

Figures 4 and 5 show the NTCP for lung for left-sided tumours calculated based on V_{13Gy} and the mean dose respectively for both techniques.

Figures 6 and 7 show the NTCP for lung for right-sided tumours calculated based on V_{13Gy} and the mean dose respectively for both techniques.

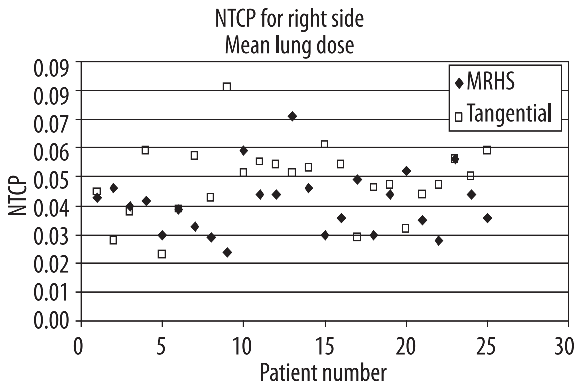

Figure 7. The NTCP for lung for right-sided patients calculated based on V_{13Gy} for MRHS and tangential techniques.

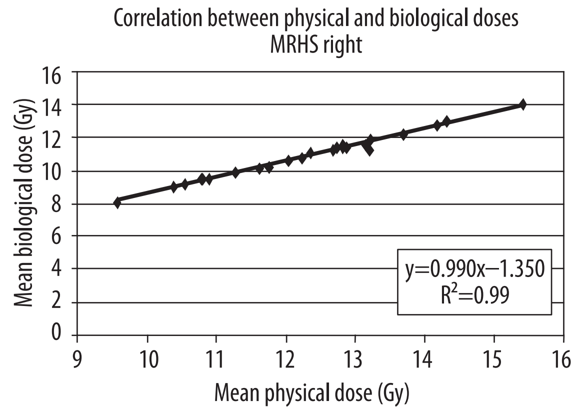

Figure 9. Correlation between the mean physical and biological doses for the MRHS technique for right side.

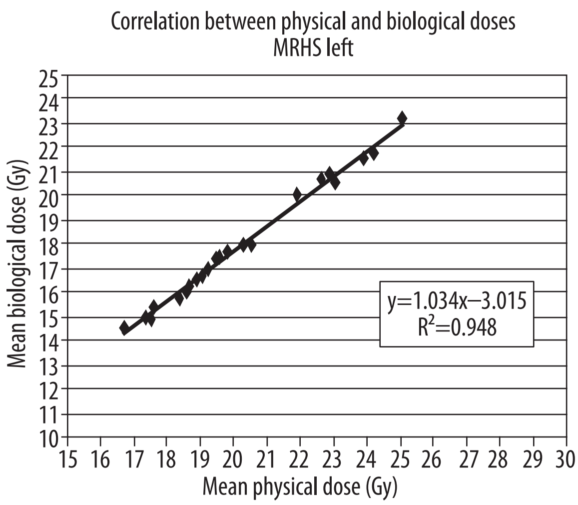

Figure 8. Correlation between the mean physical and biological doses for the MRHS technique for left side.

Figures 8 and 9 show the correlation between the mean physical and biological doses for the MRHS for left and right side respectively.

Discussion

In the case of the tangential technique the CT examinations for treatment planning were not made in the typical treatment position of a patient with hands raised over the head. Therefore the results obtained for the tangential technique should be treated with caution. However, in the author's opinion the change of position of hands influences only a little the dose distribution in the heart and lung.

For the MRHS technique the calculated probability of heart injury is in all but two cases smaller than 0.01. Therefore, the MRHS technique may be considered safe for patients with left-sided breast cancer. For the tangential technique in 4 cases only the NTCP values are smaller than 0.01. In three cases the probability is larger than 0.05. The mean values of the NTCP in the treated group of patients were 0.004 and 0.030 for the MRHS and tangential techniques respectively. The MRHS technique resulted in significantly lower NTCP than tangential technique (t test for average values of NTCP, $p<0.0001$). The result for the MRHS technique is very close to the result obtained by Pierce (0.005) for the RHS technique [23]. For the tangential technique, the result obtained in this work is a little worse than obtained by Gagliardi (0.02) [12].

For both techniques, there is a very good correlation between V_{30Gy} and NTCP (t test, $p<0.001$). In most commercially available treatment planning systems, NTCP calculations are not performed or are calculated at most according to only some mathematical methods, e.g. in the XiO treatment planning system only the Lyman method is implemented. V_{30Gy} may be easily obtained from DVH and the correlation enables NTCP to be estimated quite precisely. However, it should be remembered that the formulae for correlation obtained in this work may be applied for the tangential and MRHS techniques only. NTCP can be calculated using the formulae:

$NTCP = 0.151 \cdot V_{30Gy} + 0.024$ for the MRHS technique, and

$NTCP = 0.283 \cdot V_{30Gy} + 0.348$ for the tangential technique.

V_{30Gy} and $NTCP$ are given in percentages.

The dose delivered to the heart depends strongly on the position of the heart with respect to the PTV and the shape of the PTV itself. In the case of a very close position of the heart to the PTV, reduction of the cardiac volume may be obtained by applying a deep inspiration breath hold irradiation technique [16,17]. The shape of the PTV and its influence on the cardiac doses depends mainly on the decision whether, and if so which, internal mammary nodes should be included in the PTV. In the work of Pierce only those internal mammary nodal volumes in interspaces one to three were included in the PTV [23]. In this publication, the internal mammary nodes in the fourth interspaces were also delineated. Still there are controversies concerning the definition of the target volume with respect to internal mammary nodes. However, at least for patients receiving postamastectomy irradiation for advanced primary and nodal disease the irradiation of the internal mammary nodes appears justifiable [18]. The MRHS technique is very time consuming in preparation. At least three times more time is needed for preparation of the optimal plan with the MRHS technique than with the tangential technique. However, as shown in this work, for left-sided breast patients the MRHS technique is superior to the tangential technique, even though for some patients the difference is very small. Therefore a decision concerning the safe irradiation method at an early stage of planning would be important. Marks showed that for the tangential technique there is a very high correlation between the maximum heart distance and the risk of heart injury [7]. If the maximum heart distance is smaller than 17 mm the NTCP is smaller than 0.01. For the MRHS technique, the maximum heart distance may by identified with the heart distance in the 50% isodose. If such an interpretation is valid for the MRHS technique, for most plans for this technique the maximum heart distance is smaller than 17mm. If for the tangential technique the maximum heart distance is smaller than 17mm, this technique may be considered superior to MRHS because it is simpler than the MRHS technique. The virtual simulation enables a very quick evaluation of some geometrical parameters, such as the maximum heart distance [19]. It is important to make it during CT examination for treatment planning because a treatment position for the tangential technique is different from the position for the MRHS technique.

The estimated NTCP for lungs depends on the parameter used for calculations. NTCP calculated with V_{13Gy} are always about two times larger than those calculated with the MD. The mean values of NTCP in the group of patients are shown in Table 1.

Table 1. Mean values of the NTCP for both techniques.

	MRHS		Tangential	
	Mean dose	**$V1_{3Gy}$**	**Mean dose**	**V_{13Gy}**
Left	0.022	0.049	0.027	0.049
Right	0.041	0.090	0.048	0.072

Table 2. Confidence intervals for parameter values.

Model	TD50	m
V_{13Gy}	62–107	0.31–0.51
MD	27–42	0.36–0.54

There may be two reasons for such a difference. The first is the uncertainty of parameters used in both models. Table 2 shows the 95% confidence intervals for parameter values for two models used for calculations of risk of lung injury taken from Seeppenwoolde [11].

The second one is that the V_{13Gy} parameter – volume above a threshold dose – is sensitive to uncertainty of dose distribution calculations. The mathematical model of dose-response relationships was based on the dose distributions calculated with a tissue inhomogeneity correction, according to the equivalent path length method which is the simplest correction method [20]. Therefore, the results based on the MD parameter seem to be more reliable and they will be discussed. It should be also emphasized that even though in the present study widely accepted mathematical models for NTCP calculations were used, all models are more phenomenological than mechanistic. This means that the validity of the models is proved by fitting parameters of a model to clinical data. Moiseenko et al. analyzed the influence of the choice of several mathematical models on NTCP estimation for the liver [21]. They found considerable variability in predicted NTCP values depending on what model and what parameters were used. One may also expect large uncertainties in NTCP estimation for the lung and heart.

The risk of lung injury is higher for irradiation on the right side (t test for the average value of NTCP in the group of patients irradiated on the left and right side, p<0.001). On the left side the irradiated volume of the lung with a high dose is smaller, because of the position of the heart. On the left side for the MRHS technique for all patients the risk is very small. For 23 of 25 patients the NTCP is smaller than 0.03. For the tangential technique, the average value of the risk in the group of patients is close to the risk for the MRHS technique. For one patient the NTCP is close to 0.05. Both techniques seem to be very safe. Gagliardi et al. published data of clinical incidence of lung complications for 138 patients treated with the RHS technique [9]. The clinical incidence was 22.0% (NTCP=0.22), which is much higher than the value obtained in this work. In this paper, there were no details concerning the technique so it is difficult to compare dose distributions for the RHS and MRHS technique used in our case. The individually designed bolus applied in the MRHS technique diminishes the dose delivered to the lung and decreases the NTCP. In the same paper for a group of patients treated with the tangential technique the NTCP was 0.0018. This result is close to the result obtained in this work. Marks reported a 2.6% risk of clinical pneumonities in patients treated with so-called partially wide tangent fields [22]. The NTCP for the lung for left-sided patients calculated by Pierce for the RHS technique was 0.05, which is almost 0.03 larger than in this work [23]. The difference may be attributed to the additional preventing influence of the individually designed bolus. For right-sided tumours the NTCP is higher. The average value of the NTCP in the group of patients for the MRHS and tangential techniques is 0.041 and 0.048 respectively. For the tangential technique for 12 patients the NTCP is larger than 0.05. For the MRHS technique the NTCP is larger than 0.05 for only 3 patients. For irradiation on both sides, there is a very high correlation between the mean physical dose and biological dose for the MRHS techniques. Also a very high correlation was obtained for the tangential technique but because the dose distributions were calculated based on the CT made not in the typical treatment position for this technique it is likely that the relationship between the mean physical and biological dose would be slightly different. Therefore, the author decided not to present these data. The biological dose with the α/β model with the α/β parameter of 3Gy may be calculated from:

$Mean_{biol} = 1.034 \cdot Mean_{physical} - 3,015$ for the MRHS technique for the left side

$Mean_{biol} = 0.990 \cdot Mean_{physical} - 1,350$ for the MRHS technique for the right side

The relationship is a straight line but not going through the origin, so using it for doses much smaller than the smallest mean dose value in Figures 8 and 9 should be done with special caution. The correlations were highly significant (t test, p<0.0001).

Conclusions

For patients irradiated on the left side, the MRHS technique enables smaller heart toxicity. The risk of lung injury is similar for both techniques and sides. However for some patients irradiated on the right side in the case of the tangential technique the risk of lung injury may be larger than 5%. For the MRHS and tangential techniques there is a very high correlation between V_{30Gy} and NTCP and between the physical mean dose and the biological dose. The relationship between V_{30Gy} and NTCP enables very fast estimation of the risk of heart injury. The relationship between the mean dose and biological dose enables easy calculation of the biological mean dose, which is an input parameter for calculation of NTCP for the lungs. For the tangential techniques these correlations should be confirmed based on the dose distributions calculated with CT data acquired in the treatment position used for this technique.

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