Relationship between early and late normal-tissue injury after postmastectomy radiotherapy

Søren M. Bentzen and Marie Overgaard

Department of Medical Physics, Department of Oncology, and Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus C., Denmark

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**Key words:** Clinical radiobiology; Fractionation sensitivity; Mixture model; Relative biological effectiveness; Telangiectasia; Moist desquamation; Subcutaneous fibrosis

**Summary**

Factors of importance in the development of telangiectasia were investigated in a series of 229 patients who, between 1978 and 1982, received postmastectomy radiotherapy with two different fractionation schedules. Patients who developed moist desquamation had a statistically significantly increased risk of developing telangiectasia after a specific course of radiotherapy. As an example the estimated incidence of severe telangiectasia after 44 Gy in 22 fractions increases from 27% to 49% in patients who developed grade I> 2 moist desquamation as an early radiation reaction. A reanalysis of the Aarhus data with telangiectasia as the endpoint gave an \( \alpha/\beta \) ratio at 2.8 Gy (95% c.l. (0.1, 8.1) Gy) and a relative biological effectiveness (RBE) of high energy electrons relative to 8 MV photons at 0.89 (95% c.l. (0.85, 0.93)). Patients age or the occurrence of severe erythema did not predispose to telangiectasia. A similar predisposition after moist desquamation was not seen for subcutaneous fibrosis. The RBE of high energy electrons relative to 8 MV photons for this endpoint was estimated at 0.88 (95% c.l. (0.86, 0.91)).

**Introduction**

Historically, telangiectasia was an early recognized radiation sequela. In 1902 Teleky [15] recommended fractionated radiotherapy as a means of reducing the incidence of this radiation reaction. Holthusen [9] showed in 1936 a steep increase in the incidence of telangiectasia with increasing dose. Also Zuppingter [25] performed careful studies of this radiation reaction and described its long latent period, especially after low levels of tissue injury, and its tendency to continuously progress in severity in some patients. Furthermore Zuppingter noted the dissociation between this radiation reaction and the acute reactions, erythema and moist desquamation, with relatively worse telangiectasia after large dose fractions. This is probably the first mention of the difference in fractionation sensitivity between acute and late responding tissues [17]. Subsequently these studies have been continued by e.g. Cohen and Ubaldi [8] and through the comprehensive studies by Turesson and Notter [20,22-24].

Despite of the clinical interest in this endpoint, its radiation pathogenesis remains largely obscure. It has been proposed that the mechanism behind the formation of telangiectasia is an initial reduction of the vascular density due to radiation-induced killing of endothelial cells followed by a compensatory permanent dilation of the remaining capillaries, arterioles or venules [14,16]. These endothelial cells should have dose-fractionation and latent-time characteristics consistent with a late-responding normal tissue. However, a recent analysis of the Gothenburg telangiectasia data [24] showed, somewhat surprisingly, that the incidence of severe telangiectasia depended on overall treatment time. Speculations were made that this effect could be due to slow repair [24]. However, one concern in

*Address for correspondence: S. M. Bentzen, Danish Cancer Society, Department of Experimental Clinical Oncology, Norrebrodage 44, DK-8000 Aarhus C., Denmark.*
assessing the biological implications of this finding is that the radiation pathogenesis of telangiectasia may be rather complex, and that this endpoint may be partly consequent upon severe acute reactions. The present analysis was undertaken to test whether telangiectasia actually developed independently of the acute reaction in patients receiving postmastectomy radiotherapy at the Department of Oncology in Aarhus.

**Materials and methods**

**Patient group and treatment technique**

Details on the radiation field arrangement and the scoring of acute and late endpoints have been given by Overgaard et al. [13]. All patients were treated by an anterior 8 MV photon field covering the axillary and the infra- and supraclavicular areas. Individually shaped shielding blocks protected the humerus from the level of the caput humeri, the larynx, and the lung below the level of the second rib. The chest wall below the level of the second rib was treated by an abutted electron field. The surgical scar was covered by a 5 mm wax bolus with a margin of 3 cm. The bolus-covered area (referred to as the axillary field), the open photon field (the supraclavicular field), and the electron field produced three independent scores of early and late radiation sequelae. Data from 229 patients are included in this analysis. The series comprised 163 breast cancer patients who, from 1978 to 1980, received postmastectomy radiotherapy delivered in 12 fractions, with 2 fractions per week over a period of 37 to 46 days. In 88 patients the total dose was specified as a maximum absorbed dose of 51.36 Gy and in 75 patients as a minimum target dose of 36.6 Gy specified at the level of the mid-axilla. From 1981 to 1982, 66 patients received a minimum target dose of 40.92 Gy in 22 fractions administered as 5 fractions per week over 29 to 35 days. None of the patients analyzed here received adjuvant chemotherapy.

Two late endpoints are used in this communication: subcutaneous fibrosis and telangiectasia. Scoring was done by the same physician on an ordinal 4 point scale (Table I). In patients treated with a 2 fractions per week schedule, scores of late sequelae from all three fields were used in the analysis. In the remaining patients scores from the supraclavicular field were discarded due to the extremely low frequency of moderate and severe radiation complications in this area.

Acute reactions were evaluated routinely in all patients by members of the staff or junior staff on the last day of treatment. Based on the clinical description of the skin reaction in the patient's record, a retrospective scoring of the grade of reaction was performed. While this may have introduced some uncertainty in the evaluation of erythema, any grade of moist desquamation was registered because special care for this skin reaction was often necessary.

A technical problem in this analysis is the low overall incidence of moist desquamation (Table II) in the radiotherapy regimens applied here, bearing with it a low statistical test strength i.e. a high probability of erroneously accepting the null hypothesis that moist desquamation does not alter the probability of developing severe telangiectasia. To help overcome this problem, the number of events was raised through a joint analysis of photon- and electron-field data. Furthermore both early and late endpoints will increase in incidence with increasing dose and dose per fraction. As a consequence both expressions of injury are more frequent in the bolus-covered axillary field and in the electron field compared to the incidence in the supraclavicular field. Thus the detection of a non-trivial association between these two must be based on multivariate statistical methods allowing simultaneous correction for dose-fractionation characteristics.

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**TABLE I**

**Definition of endpoints.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Moist desquamation</th>
<th>Erythema</th>
<th>Telangiectasia</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>&lt; 10% of field</td>
<td>Mild</td>
<td>&lt; 1/cm²</td>
<td>Mild (just palpably increased firmness)</td>
</tr>
<tr>
<td>2</td>
<td>10-49% of field</td>
<td>Moderate</td>
<td>1-4/cm²</td>
<td>Moderate (definitely increased firmness)</td>
</tr>
<tr>
<td>3</td>
<td>≥ 50% of field</td>
<td>Severe with dry desquamation</td>
<td>&gt; 4/cm²</td>
<td>Severe (very marked firmness, retraction and fixation)</td>
</tr>
</tbody>
</table>
TABLE II
Crude* incidence of moist desquamation and telangiectasia.

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Axillary field</th>
<th>Supraclavicular</th>
<th>Electron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moist desq.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade ≥ 2</td>
<td>22 fx</td>
<td>66</td>
<td>6 (9%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>22 fx</td>
<td>66</td>
<td>17 (11%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>grade 3</td>
<td>12 fx</td>
<td>163</td>
<td>10 (6%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

* No correction for total dose or observation time.

Dosimetry

A dosimetric reference depth of 4.1 mm was used for subcutaneous fibrosis. This depth was established by comparing isoeffective dose estimated from the axillary and supraclavicular fields as a function of the assumed (effective) depth of the target cell population. A reference depth of about 4 mm must be assigned in order to obtain consistent isoeffect estimates from these two areas [1]. For telangiectasia, moist desquamation, and erythema a dosimetric reference depth of 0.1 mm was used.

Physical dosimetry was based on phantom measurements in the actual treatment geometry using thermoluminescence and ion chamber dosimeters. Details on the dosimetry and the dosimetric field size corrections performed in individual patients have been given by Bentzen et al. [1]. Absorbed dose measurements during this period were performed according to the 1972 protocols of the Nordic Association of Clinical Physics [11]. Application of the revised Nordic recommendations [12] resulted in a 2.6% higher dose in the photon field and an approximately 1% lower dose in the electron field. This correction was applied in the estimation of the Relative Biological Efficiency (RBE*) of high energy (8–10 MeV) electrons relative to 8 MV photons.

Models

The data analysis was performed by so-called “direct analysis” [6,18] using maximum likelihood estimation of model parameters. The basic model for dose-response data was a single-follow-up mixture model [4,5] using the logistic formulation [18] of the multifraction linear-quadratic (LQ) model [19]. This is similar to the approach described previously [3]. In mathematical terms, the probability of response at long follow-up time is assumed to be given by the logit expression

\[ p_\infty = \exp(E)/(1 + \exp(E)) \]

where the level of effect, \( E \), for a patient treated with a total dose \( D \) in \( n \) fractions is assumed to be described by the multifraction LQ model:

\[ E = a_0 + a_1 \cdot D + a_2 \cdot D^2/n \]

The effect of moist desquamation is modeled as an additive term, \( \Delta \), modifying \( a_0 \). Effectively, this is equivalent to a reduction in the tissues capacity to overcome radiation injury. These expressions are used in a mixture model analysis as described in detail previously [4,5]. Latent times are assumed to have a Weibull distribution characterized by a shape parameter, \( \beta \), and a position parameter. The \( LT_{90} \), that is the time at which 90% of the ultimately expected damage is expressed, is chosen to characterize position of the latent-time distribution. Photon and electron field data are analyzed together after multiplication of the electron doses by the RBE relative to 8-MV photons. The RBE is included as a free parameter in the model and estimated jointly with the other parameters in the fit to all data.

Analysis of residuals was used to look for an effect of factors not already included in the model [2,3]. A model without the factor in question was fitted to all data. In each individual patient the difference between the observed response (0 or 1 depending on whether or not the endpoint was reached) and the model-predicted response was calculated. With the mixture-model the predicted response is a function of dose-fractionation details as well as the observation time in that particular

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* Following the terminology of the ICRP/ICRU RBE committee [10] the term RBE should be reserved for situations in which the depth-dose curves of the two radiations are identical, which is not the case here. In all other situations the term Equivalent Effect Ratio is recommended. Here the term RBE will be used, but with the explicit warning that it refers to a specific treatment technique and to specific radiation beams using telangiectasia or subcutaneous fibrosis as late endpoints.
Patient. These differences, the residuals, are averaged over patients having a particular characteristic to test if this characteristic influences the probability of developing the complication. Positive residuals correspond to patients doing worse than expected, negative residuals to patients doing better than expected.

While the analysis of residuals is a powerful tool in the explorative data analysis, the final test of the significance of a given parameter was to see whether its inclusion in a direct analysis improved the fit of the model to the data significantly. To this end the likelihood-ratio test was used.

Results

Direct analysis of all data showed a RBE of high energy electron relative to photons estimated at 0.86. Figure 1 shows dose-response relationships for telangiectasia scored in the photon or electron fields. A clear separation between the two curves is seen when an RBE of one is assumed (Fig. 1a). However, all data points fit closely to a common dose-response curve after correcting the total dose in the electron field by means of an RBE = 0.86 (Fig. 1b).

A predisposition to telangiectasia after moist desquamation was sought for in an analysis of residuals. When the average deviations between observed and predicted responses for grade 3 telangiectasia were plotted as a function of the grade of moist desquamation, a clear trend was seen (Fig. 2): patients without moist desquamation did slightly better than expected, patients with grade 1 moist desquamation did worse than expected, and this was even more pronounced for patients with grade 2 and 3 moist desquamation. The two highest grades were analyzed together due to the low incidence of these. The impression from the analysis of residuals was supported by the direct analysis (Table III) where inclusion of previous moist desquamation improved the fit significantly ($p = 0.04$; likelihood-ratio test). The electron field data were included in the analysis with the RBE taken into account as a free parameter in the model. The RBE of high energy electrons relative to 8-MV photons with telangiectasia as the endpoint was estimated at 0.86 [95% confidence limit (c.l.) (0.82, 0.90)].
Mixture-model parameter estimates with 95% confidence limits for telangiectasia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% c.l.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_0$</td>
<td>-8.6</td>
<td>(-12.9, -4.2)</td>
</tr>
<tr>
<td>$a_1$ (Gy$^{-1}$)</td>
<td>0.099</td>
<td>(-0.02, 0.22)</td>
</tr>
<tr>
<td>$a_2$ (Gy$^{-2}$)</td>
<td>0.036</td>
<td>(0.022, 0.051)</td>
</tr>
<tr>
<td>LT$_{90}$ (yrs)</td>
<td>4.7</td>
<td>(2.8, 6.5)</td>
</tr>
<tr>
<td>$\Theta$</td>
<td>2.8</td>
<td>(1.1, 4.6)</td>
</tr>
<tr>
<td>RBE$^a$</td>
<td>0.86</td>
<td>(0.82, 0.90)</td>
</tr>
<tr>
<td>$\Delta a$</td>
<td>1.04</td>
<td>(-0.1, 2.2)</td>
</tr>
</tbody>
</table>

Derived quantities with 95% confidence limits for telangiectasia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% c.l.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBE$^b$</td>
<td>0.89</td>
<td>(0.85, 0.93)</td>
</tr>
<tr>
<td>$\alpha/\beta$ (Gy)</td>
<td>2.8</td>
<td>(-0.1, 8.1)</td>
</tr>
</tbody>
</table>

$^a$ Dosimetry according to the NACP 1972 recommendations [11].
$^b$ Dosimetry according to the NACP 1980 recommendations [12].

The $\alpha/\beta$ ratio for telangiectasia was estimated at 2.8 Gy with 95% c.l. (-0.1, 8.1) Gy. This value was only marginally lower than what was found when the effect of moist desquamation was omitted from the model: $\alpha/\beta = 3.0$ Gy with 95% c.l. (-0.1, 8.3) Gy. Figure 3 compares the observed dose-response relationships for grade 3 telangiectasia in patients with or without moist desquamation with the prediction from the fitted model. As an example of the magnitude of the effect of previous moist desquamation, the estimated incidence of severe telangiectasia after 44 Gy in 22 fractions increases from 27% to 49% in patients who developed grade $\geq$ 2 moist desquamation as an early radiation reaction.

Because of the low incidence of moist desquamation in this study, it was not possible to investigate whether increasing grade of moist desquamation implied an increasing probability of developing telangiectasia, or whether the latent time for telangiectasia subsequent to moist desquamation was shorter than in patients who did not develop moist desquamation.

Subcutaneous fibrosis was found to be unaffected by a previous history of moist desquamation. The plot of residuals (Fig. 2) showed no convincing trend as a function of the grade of moist desquamation and in a direct analysis of subcutaneous fibrosis, the parameter describing the effect of moist desquamation did not improve the fit of the model to the data judged from the likelihood-test statistics. The RBE was found to be 0.88 (0.86, 0.91) in good agreement with the value of 0.84 (0.79, 0.89) estimated from a previous analysis [1] based on isoeffect doses. The potential influence of dosimetric uncertainties is hard to quantify. However, the estimated RBE is relatively robust against random patient-to-patient variations in the actually absorbed doses. Using Monte Carlo simulations, Bentzen et al. [1] estimated that a 5% standard deviation on the distribution of individual absorbed doses in both the photon and the electron fields yielded a slightly wider 95% confidence interval for the RBE: 0.84 (0.77, 0.92).

Erythema, even in the severe cases, did not predispose to telangiectasia or to subcutaneous fibrosis. As the scoring of acute reactions was performed retrospectively on basis of the patient records, the reporting of erythema is probably less reliable than the reporting of...

Radiobiological characteristics of telangiectasia and subcutaneous fibrosis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Telangiectasia</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha/\beta$</td>
<td>2.8 Gy (−0.1,8.1) Gy</td>
<td>1.7 Gy (0.6,2.6) Gy</td>
</tr>
<tr>
<td>LT$_{90}$</td>
<td>4.7 years$^a$ (2.8,6.5) years</td>
<td>3.2 years$^b$ (2.3,4.0) years</td>
</tr>
<tr>
<td>RBE of high energy $e^−$</td>
<td>0.89$^c$ (0.85,0.93)</td>
<td>0.88$^c$ (0.86,0.91)</td>
</tr>
<tr>
<td>Moist desq. predisposition</td>
<td>Yes</td>
<td>No significant influence</td>
</tr>
<tr>
<td>Erythema predisposition</td>
<td>No significant influence</td>
<td>No significant influence</td>
</tr>
</tbody>
</table>

$^a$ Depends on grade of reaction and on biological dose [7,21]. Current value is for grade 3 telangiectasia.
$^b$ Depends on grade of reaction and (possibly) on biological dose. Current value is for grade $\geq$ 2 fibrosis.
$^c$ Dosimetry according to the NACP 1980 recommendations [12].
the moist desquamation. Table IV summarizes the radiobiological properties of the two late endpoints.

In a previous study [3] an attempt was made to identify factors, other than dose-fractionation characteristics, predisposing to telangiectasia and subcutaneous fibrosis. Patient's age, the number of lymph nodes excised from the axilla, surgical complications, and a lateral tumor location were tested, but none of these had any statistical significance as predisposing factors.

**Discussion**

In accordance with our previous findings for subcutaneous fibrosis the RBE of high energy (8–10 MeV) electrons relative to 8-MV photons is significantly lower than one. Note that the high-energy electron RBE discussed here applies to telangiectasia and subcutaneous fibrosis after treatment with anterior radiation fields. The reference depth for these two endpoints are 0.1 mm and 4.1 mm for telangiectasia and fibrosis, respectively. This is close to the surface compared to the maximum-absorbed-dose depth for 8-MV photons at 18 mm. At these depths, electron equilibrium is not established yet and the RBE estimated here does not apply to points located deeper in the tissue.

The $\alpha/\beta$ ratio for telangiectasia was estimated at 2.8 Gy with 95% c.i. (0.1,8.1) Gy. While the estimate of $\alpha/\beta$ is not significantly different from that of a previous analysis of grade $\geq 2$ telangiectasia in the photon field (3.7 Gy with 95% c.i. (0.2,47) Gy [4]), the 95% c.i. are considerably narrower here. Most likely this is the combined effect of less uncertainty in the scoring of grade 3 reactions and the increase in the number of data points resulting for the inclusion of the electron-field data.

Patients with moist desquamation have a considerably increased risk of developing severe telangiectasia after a given radiotherapy regimen. As an example, the estimated incidence of grade 3 telangiectasia after 44 Gy in 22 fractions increases from 27% to 49% in patients with moist desquamation grade 2 or 3. The picture emerging from the present analysis is supported by clinical experience from other institutions (G. H. Fletcher, personal communication, 1989).

The predisposition to telangiectasia after grade 2 and 3 moist desquamation indicates that this endpoint is partly consequent upon severe early skin damage. This is important as the target cells of relevance in developing moist desquamation are the stem cells of the basal layer [14] which on their side would have the fractionation characteristics of an acute responding tissue. Biologically, a direct mechanism behind this predisposition could be the temporary lack of epidermal protection of the endothelial cells in patients developing moist desquamation (J. Hopewell, personal communication, 1990). This is also consistent with the observations that subcutaneous fibrosis was unaffected by previous moist desquamation and that erythema did not change the probability of developing telangiectasia. Another possibility would be that moist desquamation predominantly occurred in patients with a high general normal-tissue radiosensitivity and that these patients, despite the different target-cell populations, also had an increased probability of developing telangiectasia. Again, this hypothesis is weakened by the fact that severe erythema did not predispose to telangiectasia, and neither did moist desquamation imply an increased risk of developing subcutaneous fibrosis.

Comparison of the results from different clinical radiobiological studies should be done with some reservation as differences in definition of endpoints, in treatment technique, and in the detailed dosimetry could hamper a direct comparison. First of all, when comparing the present dose-response relationships with those of other clinical series, it is important to note that all doses in the present analysis are specified at the relevant tissue reference depth, for telangiectasia and moist desquamation at 0.1 mm, for subcutaneous fibrosis at 4.1 mm. Thus for a single anterior 8 MV photon field an absorbed dose of 44 Gy at a tissue depth of 0.1 mm would correspond to maximum absorbed doses of 51 Gy in the axillary (5 mm bolus covered) and 130 Gy in the supraclavicular field.

The endpoint used in the Gothenburg study [24] was defined as spotted moist desquamation. When the dose-response model derived by Turesson and Thames [24] was applied to the Aarhus fractionation schedule the expected incidence of this radiation reaction in the axillary field was 11–12% after the average (with respect to total dose) treatment schedule in the 12 and the 22 fractions groups of this study. This is in good agreement with the observed incidence (Table II) of moist desquamation at 11% and 9% in the 12 and the 22 fractions groups, respectively. Thus the two definitions of moist desquamation apparently correspond to comparable levels of biological injury. While the overall incidence of significant moist desquamation is low in the Aarhus series, about 6%, this is not the case in several of the treatment regimens used in Gothenburg [24]. Among 204 fields, treated with a dose per fraction lower than or equal to 2.0 Gy, 32% (95% c.i. (26,39) %) had spotted moist desquamation [24]. Among the fields treated with more than 5.0 Gy per fraction, the incidence of spotted moist desquamation was 7% (3,14)%.

In view of the findings in the present analysis, the relative advantage of low doses per fraction could
be partly masked by the high incidence of moist desquamation among these fields. This again might also influence the evaluation of the time factor for telangiectasia in that series. A reanalysis of the Gothenburg data with explicit correction for acute toxicity would be interesting to throw light on these problems.

Subcutaneous fibrosis is an important late endpoint. A correlation between the occurrence of subcutaneous fibrosis and impaired shoulder movement has been demonstrated in a previous analysis [3] of the Aarhus postmastectomy-radiotherapy series.

Although telangiectasia is of interest to the clinician, its role as a model for late radiation reactions is questioned by the apparently complex radiation pathology which may not be explained by cell kill in a single target-cell population.

In spite of the low incidence of moist desquamation in this study a statistically significant predisposition to severe telangiectasia was found in patients with this acute radiation reaction. In some schedules, this predisposition may almost double the probability of developing severe telangiectasia, thus some of the dose-fractionation characteristics of moist desquamation may be "inherited" when telangiectasia is used as a late endpoint. A similar predisposition to subcutaneous fibrosis after moist desquamation was not found.

References