Clinical radiobiology of malignant melanoma

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Summary

Tumor-control probability (TCP) was analyzed in a series of 121 patients having 239 histologically proven recurrent or metastatic malignant melanomas. These were treated with fractionated radiotherapy with various doses per fraction, total doses, and overall times. Cutaneous lesions (127, 53%) were treated with electron beams, and more deeply seated tumors (112, 47%) with ⁶⁰Co or 4–8 MV X-rays. The fraction size was highly variable, and this permitted determination of the $\alpha/\beta$ ratio in the multifraction linear-quadratic model, which was estimated at 0.57 Gy with 95% confidence limits [−1.07, 2.5] Gy. Treatment time had no demonstrable influence on TCP. Thus this tumor exhibits the fractionation sensitivity characteristic of a late-responding normal tissue, suggesting that an adequate fractionation schedule for malignant melanomas would be characterized by larger-than-conventional doses per fraction, possibly about 6 Gy per fraction. This is consistent with the conclusions of other authors. Tumor size, evaluated as mean tumor diameter, $S$, had a major impact on TCP: the number of target cells increased as a power function of $S$ with exponent 0.72 (95% confidence limits [0.49, 0.94]). In fact, a considerable amount of the heterogeneity in the dose-response data could be removed by accounting for size. Thus, the weak or absent dose response became highly significant. When a patient had multiple lesions, the responses of these to radiotherapy tended to be similar, thus implying that results were significantly influenced by a "hidden parameter" (such as inherent radiosensitivity or immunological status). A test of the predictive value of the TCP-model was performed in a different series of 183 cutaneous and lymph node malignant melanomas. The observed dose-response relationship in this data set was in good agreement with the model prediction. A chi-square test for goodness-of-fit showed that the variation between predicted and observed results could be explained by the binomial variation on quantal response data.

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Introduction

Malignant melanoma is a challenging disease from a radiotherapeutic point of view. For many years considered radioresistant, this tumor is now being recognized as potentially curable by irradiation if treated with hypofractionation, i.e. by doses per fraction greater than the standard 2.0 Gy. This treatment strategy, originally derived from in vitro radiobiological observations, is empirically supported by a number of clinical studies. However, most series have been too small to allow a quantitative radiobiological analysis.

Previous attempts to analyze both the present series and available data from the literature have suggested that malignant melanoma has a low $\alpha/\beta$ ratio and that the response to radiotherapy was highly dependent on tumor volume but surprisingly not on overall treatment time. However, the statistical methodology applied to support these conclusions is questionable.

This paper presents an analysis of the Danish experience in radiotherapy of malignant melanoma. The possible influence of total dose, dose per fraction, total treatment time, and tumor size is investigated in a Poisson model of tumor control.

Materials and methods

A total of 127 cutaneous and 112 lymph node lesions in 121 patients with histologically proven recurrent or metastatic malignant melanoma were treated with fractionated radiotherapy at varying dose per fraction and total dose (Table I).

Cutaneous lesions were treated with electron beams and more deeply seated tumors with $^{60}$Co or 4–8 MV X-rays. The tumor dose used in this analysis was evaluated as the maximum absorbed dose on the central axis of the beam. In case of skin involvement a wax bolus was applied. The lesions were treated with a broad range of dose per fraction as shown in Fig. 1. Overall treatment time ranged from 4 to 76 days (Table II).

Tumor size was evaluated as the mean tumor diameter. Patients with only microscopic disease and tumors in which the diameter could not be reliably estimated from the patient record were excluded. Table III shows the distribution of tumor sizes in the present series.

Many of the patients presented with advanced disease with a consequent short life expectancy. Therefore, complete response, i.e. complete tumor clearance after a minimal follow-up of 2 months, was taken as an indication of local tumor control (TC). A partial justification of this procedure is that previous analyses demonstrated a 71–87% persistent TC among patients with complete response [31,32]. If the number of sur-

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Number of fractions</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2–3</td>
</tr>
<tr>
<td>0–25</td>
<td>19</td>
</tr>
<tr>
<td>26–30</td>
<td>58</td>
</tr>
<tr>
<td>31–35</td>
<td></td>
</tr>
<tr>
<td>36–40</td>
<td></td>
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<tr>
<td>41–50</td>
<td></td>
</tr>
<tr>
<td>51+</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>77</td>
</tr>
</tbody>
</table>
viving clonogens after radiotherapy has a Poisson distribution (see Appendix) and tumors with one or more surviving clonogens will recur, these percentages correspond to an average of about 0.2 surviving clonogens in tumors showing complete remission. In other words, although complete response could be imagined in tumors with even a modest cell kill (e.g. a few decades), clinical clearance of malignant melanomas some months after treatment requires, in practice, an almost complete eradication of the viable clonogens.

Parts of the present series have been analyzed previously [30–33] but a qualitative approach was used in those analyses. It has been shown [39] that a more statistically satisfactory analysis may be done using maximum likelihood estimation of the model parameters. Furthermore, to obtain accurate (unbiased) estimates of fractionation sensitivity, simultaneous correction for other important clinical factors must be performed. It is the aim of the present paper to present a re-analysis of this series using adequate statistical methods. Technical details of these methods may be found in the Appendix.

A test of the predictive power of the derived model was performed on an independent data set of 183 cutaneous and lymph node malignant melanomas with available mean tumor diameter. One hundred twenty-nine of these were extracted from a data base of published treatment results, the remaining 54 lesions were treated at the Maria Sklodowska-Curie Institute in Warsaw.

**Results**

Tumor size had a strong negative influence on tumor control probability (TCP). When tumor size was not accounted for, the TCP was clearly underestimated in small lesions and over-

### TABLE II

Distribution of treatment times.

<table>
<thead>
<tr>
<th>(t) (days)</th>
<th>No. of lesions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–10</td>
<td>76</td>
<td>31.8</td>
</tr>
<tr>
<td>11–20</td>
<td>10</td>
<td>4.2</td>
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<tr>
<td>21–30</td>
<td>65</td>
<td>27.2</td>
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<tr>
<td>31–40</td>
<td>59</td>
<td>24.7</td>
</tr>
<tr>
<td>41–50</td>
<td>17</td>
<td>7.1</td>
</tr>
<tr>
<td>51–60</td>
<td>6</td>
<td>2.5</td>
</tr>
<tr>
<td>61–70</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>71–80</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

### TABLE III

Distribution of tumor sizes.

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>No. of lesions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1–2.0</td>
<td>70</td>
<td>29.3</td>
</tr>
<tr>
<td>2.1–4.0</td>
<td>67</td>
<td>28.0</td>
</tr>
<tr>
<td>4.1–6.0</td>
<td>46</td>
<td>19.2</td>
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<tr>
<td>6.1–8.0</td>
<td>18</td>
<td>7.5</td>
</tr>
<tr>
<td>8.1–10.0</td>
<td>13</td>
<td>5.4</td>
</tr>
<tr>
<td>10.1–12.0</td>
<td>18</td>
<td>7.5</td>
</tr>
<tr>
<td>12.1–14.0</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>14.1+</td>
<td>4</td>
<td>1.7</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

Fig. 1. Frequency distribution of fraction sizes in 239 malignant melanomas. The large variation in fraction size and the relatively low number of lesions in most fraction-size groups makes direct analysis attractive.
clonogens with tumor diameter was mathematically represented by a power law with an exponent to be estimated from the observed data. There was no significant anatomical-site dependence of the exponent, and in all further analyses a common exponent was assumed in the model. Figure 3 shows a scatter-plot of TC as a function of total dose and tumor size in the 5 Gy per fraction group. The distribution of points in this diagram is in good agreement with the predicted TCPs. The predicted increase in total dose to control 80% of the tumors as a function of their

estimated in large lesions (Fig. 2a). After inclusion of tumor size in the model, no residual effect of this parameter was detectable (Fig. 2b). There was no difference in the size effect for cutaneous and nodal lesions. The increase in number of

Fig. 2. Influence of tumor size on the deviation between observed and predicted responses in models (a) without and (b) with tumor-size correction. The number beside each point is the number of lesions represented. Positive or negative deviations, i.e. points located above or below the stippled line, indicate a higher or lower observed frequency of tumor control than that predicted.

Fig. 3. Scatter plot showing the results in individual lesions in the 5 Gy/fx group as a function of total dose and tumor size. Filled circles indicate lesions in which tumor control was obtained, open triangles indicate local failure. Straight lines represent iso-tumor control probability (TCP) lines for various levels of tumor control from 20 to 80%. The observed frequencies of responders in each of the bands between iso-TCP lines are specified in the right-hand margin of the figure. When the relatively low number of lesions in each band is taken into account, the agreement between predicted and observed results is good.
size is shown in Fig. 4 for doses per fraction of 2, 5, and 9 Gy [Appendix, Eqn. (6)].

A dose dependence of the TCP was demonstrated by plotting the frequency of TC as a function of the volume-corrected dose [Appendix, Eqn. (5)]. Figure 5 shows the observed and expected dose-response curves in the 5 Gy/fx and the 9 Gy/fx groups. When no account was taken of tumor size, the results were scattered, producing no significant dose-response relationship (Fig. 5a). When the same data were analyzed but the effect of tumor size was accounted for, a strong dose-response relationship emerged (Fig. 5b). The same was true for the 9 Gy/fx group (Fig. 5c).

Proliferation of tumor cells during treatment was modeled either as simple exponential growth or as accelerated regeneration. When the time factors representing these two effects [Appendix, Eqn. (6) and (7)] were included, neither had statistical significance. Further support for the conclusion regarding the lack of treatment-time im-

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**Fig. 4.** Estimated total dose to control 80% of tumors (TCD_{80}) as a function of tumor size. Lines are given for 2, 5, and 9 Gy/fx. Note that even small lesions require very high dose levels to obtain a TCP of 80%.

**Fig. 5.** Dose-response relationships in the 5 Gy/fx group (a) without and (b) with correction for tumor size and (c) in the 9 Gy/fx group with correction for tumor size. The solid lines represent dose-response curves predicted from an analysis of the entire series. The strong confounding effect of tumor size is illustrated by the 5 Gy/fx data where the dose-response relationship is lacking when no size correction is performed (a) but evident after such correction (b).
Fig. 6. Lack of treatment-time influence. Average residuals as a function of treatment time in a model without treatment-time correction. Number of lesions represented by each data point is specified. See also legend to Fig. 2.

Importance for the TCP was obtained from an analysis of deviation of observed from the predicted responses (Fig. 6). A treatment-time influence would have appeared as a perceptible trend in which points representing short treatment times would tend to lie above the line, and those representing larger treatment times below the line. No such trend was seen.

The resulting estimates of the parameters in the model [Appendix, Eqn. (4)] are given in Table IV together with their 95% confidence limits. From the directly estimated values of \( \alpha \) and \( \beta \) the \( \alpha/\beta \) ratio was found to be 0.57 Gy with 95% confidence limits \([-1.07, 2.5]\) Gy.

**TABLE IV**
Final parameter estimates.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( c_1 )</td>
<td>2.92</td>
<td>[1.5, 6.0]</td>
</tr>
<tr>
<td>( c_2 )</td>
<td>0.72</td>
<td>[0.49, 0.94]</td>
</tr>
<tr>
<td>( \alpha(\text{Gy}^{-1}) )</td>
<td>( 5.3 \times 10^{-3} )</td>
<td>([-7.4, 17.9] \times 10^{-3})</td>
</tr>
<tr>
<td>( \beta(\text{Gy}^{-2}) )</td>
<td>( 9.2 \times 10^{-3} )</td>
<td>([6.5, 11.9] \times 10^{-3})</td>
</tr>
</tbody>
</table>

\( \alpha/\beta = 0.57 \text{ Gy} \) \([-1.07, 2.5] \) Gy.

Multiple lesions were present in 48 patients who had a total of 158 cutaneous and lymph node lesions. In 23 of these patients, with a total of 87 lesions, the different lesions in each patient were treated with essentially different treatment schedules. Using methods described in the Appendix it was found that the outcomes of treatment in multiple lesions were correlated beyond what could be explained by tumor size and treatment characteristics. This effect was highly significant \((p = 0.008)\).

A cross-validation of the derived model was performed on a different data set of 183 cutaneous and lymph node malignant melanomas for which mean tumor diameter was available. For each lesion the volume-corrected total dose was calculated and this dose was subsequently converted into the isoeffective dose in a 5 Gy/fx schedule by the standard linear-quadratic (LQ) isoeffect formula. One patient, in whom 8 out of 9 lesions failed, was excluded as he seemed to be an outlier with an unusually poor result. All nine lesions had diameters between 0.8 cm and 1.2 cm and were treated with equivalent biological doses at 5 Gy/fx between 39 and 45 Gy. The resulting
dose-response relationship for the remaining 174 lesions is shown in Fig. 7 and compared to the model-predicted dose-response curve.

The chi-square goodness-of-fit statistic had a value of 4.5 with 8 degrees of freedom. The corresponding p-value was 0.80, thus indicating that the variation between predicted and observed results was not larger than expected from the binomial distribution of the quantal response data.

**Discussion**

Three factors characterize the radiobiological behavior of malignant melanomas: the low $\alpha/\beta$ ratio, the lack of treatment-time influence, and the importance of tumor size in the prediction of radiotherapeutic outcome. Thus malignant melanomas proliferate slowly, have a high capacity for repair of sublethal damage [41] and show negligible regeneration during the course of a typical radiation treatment. Qualitatively these findings agree with the results from previous analyses of parts of this series [31,32].

**Alpha/beta**

While considerable data exist for the values of $\alpha$ and $\beta$ for human melanomas irradiated in vitro [35], the present material provides the first statistically rigorous quantitation of $\alpha/\beta$ in a clinical series. Direct comparison between in vitro and clinical $\alpha/\beta$ ratios is problematical [47], and the predictive value in the clinic of in vitro parameter estimates is controversial. Although the present $\alpha/\beta$ estimate clearly is at the low end of the broad range in vitro values between 0 and 60 Gy, it is noteworthy that 9 out of 40 in vitro $\alpha/\beta$ values reviewed by Rofstad [35] are below the upper 95% confidence limit of the clinical estimate.

Few data are available on $\alpha/\beta$ values for human tumors. The only available value for a tumor originating from a late-responding tissue is from an analysis [40] of data on a highly heterogeneous group of 60 liposarcomas. The $\alpha/\beta$ ratio for this tumor was estimated at 0.4 Gy with 95% confidence limits [−1.4, 5.4] Gy. Despite the rather wide 95% confidence limits the upper limit is still low.

The absolute values of $\alpha$ and $\beta$ are much lower than those characteristic of human melanoma cell lines assayed in vitro [35]. It is likely that a contributing factor to this discrepancy is inter-lesion heterogeneity of dose response [40,46]. Thus the dose response for the population as a whole, which is shallow, is composed of those of its constituent parts, each of which may be quite steep. As a result of this the estimate of log (clonogen number) will be unrealistically low [46]. Now the TED$_{37}$ for a given fraction size $d$ is determined by the data, and is given by [Eqn. (6)] log (clonogen number) divided by $(\alpha + \beta d)$. Therefore, the factor by which log (clonogen number) is unrealistically low will be the same factor as that by which $\alpha$ and $\beta$ are unrealistically low. Although there seems to be no reliable way of estimating the magnitude of this effect, a comparison between the current values and the values obtained from in vitro studies [35] suggest that our estimates may be too low by a factor of 6 to 60. Note, however, that the ratio $\alpha/\beta$ estimated from this analysis will be the best estimate of fractionation sensitivity for the population.

**Dose response**

Interestingly, the first published dose-response curve for human tumors was for skin cancer [27]. For malignant melanomas as well there was a strong dependence of TCP on total dose, but this was clear only after correction for the effect of tumor size (see below). Figure 5a shows how the dose-response curve in the 5 Gy/fx group is confounded by tumor size. The Poisson model presents a natural way to correct for tumor size, namely by Appendix, Eqn. (5). After correcting the dose for the effect of tumor size the increased effect of larger total dose becomes evident (Fig. 5b,c). This predicted dose-response curve fits the observed data quite closely and displays
the expected increased steepness when the fraction size is increased (cf. Fig. 5b,c).

Tumor size

Tumor size is crucial to predicting the outcome of radiotherapy in malignant melanoma. Nevertheless the absolute magnitude of the exponent for the mean tumor diameter is only 0.72 [0.49,0.99]. This is significantly lower than the simple volume predictions of the exponents, 2 for a discoid tumor, 3 for a spheroid tumor. However, as noted above there is probably a considerable bias in the absolute magnitude of $a$ and $b$. As the predicted and observed TCPs agree, the size exponent must be biased downwards to the same extent as $a$ and $b$ [cf. Appendix, Eqn. (6)]. In other words, the true value of the exponent may be well above 3, thus indicating that the increase in apparent number of clonogens with tumor volume is actually higher than expected from volume measurements.

A similar conclusion, albeit as a result of a completely different analysis, was reached by Dutrex [10]. Dutrex’s analysis is based on a decomposition of the clinical dose-response curve for malignant melanomas into (hypothetical) subgroups with varying inherent radiosensitivities. Without entering a discussion of the details of this approach, it turns out to be subject to the same type heterogeneity effect (see above) in the transition from clinical data to dose vs. cell-survival data. In Dutrex’s paper this was controlled not by comparison with in vitro values of dose-response parameters but rather by assuming a lower bound on the realistic number of clonogenic cells in a 1-cm diameter tumor.

If the apparent number of clonogens increases faster than predicted from the scaling with tumor volume, this may be an indication of a hypoxic fraction in large tumors. Data on the hypoxic fraction in human melanomas are not available, but values have been published for a few human melanoma xenografts reviewed by Rofstad [35]. The hypoxic fractions covered a broad range but were occasionally very high. Dische [8] found the preliminary results with the hypoxic cell radiosensitizer Ro 03-8799 in malignant melanoma encouraging thus providing indirect support that hypoxic cells may be a problem in this disease. It should be noted, however, that the reported response rate of 71% was observed in a group of only seven patients thus having a wide 95% confidence interval [29,96]%. The role of hypoxic-cell radiosensitizers in malignant melanomas has yet to be defined.

The importance of tumor size has been demonstrated in other tumors as well. Miescher [28] provided a demonstration of this effect in a series of 96 squamous cell carcinomas of the skin. He found that 67/74 (90%) tumors with a diameter not exceeding 2 cm were controlled after initial radiotherapy, compared to 10/22 (45%) for larger tumors. Also for neck nodes [4,14], squamous cell carcinoma of the head and neck [14], and adenocarcinoma of the breast [14], the TCP has been shown to decrease significantly with increasing tumor size.

Treatment time

Regeneration, either with or without the acceleration of growth rate as a response to injury, is a phenomenon in tumor biology that has drawn increasing attention in recent years. Our analysis indicates that for malignant melanoma there is no quantifiable effect of normal or accelerated growth even when the treatment was protracted over 6–7 weeks (Fig. 6).

Fraction size and treatment time tend to be correlated so that small fraction sizes are associated with relatively long treatment times. Indeed, the present series does show a highly significant correlation coefficient of $-0.6$ ($p < 0.001$). Consequently, appropriate correction for other important parameters (in this case dose per fraction) is necessary to investigate an independent effect of treatment time. An adequate tool is the average residual plot. Various hypotheses on the influence of treatment time or other background variables may be tested by including the appropriate term in the model and testing for statistical significance of the corre-
sponding parameter. However, graphical methods are useful in generating alternative hypotheses, i.e. to screen the data against unexpected dependency on a given parameter.

The observed correlation between fraction size and overall treatment time may give rise to some concern that a possible deleterious effect of long treatment time is described in the model as a disadvantage of small dose per fraction (L. Peters, pers. commun.). To investigate this hypothesis, a subset of 152 tumors was selected by excluding all tumors treated with less than 5 Gy/fx in more than 5 weeks or with more than 5 Gy/fx in less than 2 weeks. In this subset the sign of the correlation was inverted as short treatment time was correlated with small dose per fraction \( r = 0.17, p = 0.02 \). The analysis of this subset gave an \( \alpha/\beta \) estimate at \(-0.9 \) Gy with 95\% confidence limits \([-5.8, 3.5]\) Gy. The wider 95\% confidence limits reflect the lower number of tumors and the diminished variation in treatment parameters. The agreement is good between this interval and that obtained from the analysis of all lesions. The parameter describing regeneration was not statistically significant.

In the current series, 82\% of the patients were treated in 5 weeks or less, 95\% in 7 weeks or less. A natural question is: will we expect to detect an influence of treatment time in the interval from 1 to 7 weeks? At present, only sparse clinical and experimental data are available for the analysis of this problem. The median tumor-volume doubling time in a series of 45 malignant melanomas has been estimated at 54 days [36]. Therefore, acceleration of regeneration must be assumed if treatment time should have any importance. This may occur in three ways: from a reduction of the cell-cycle time, from an increase in the growth fraction, or from a decrease in the cell-loss factor. Diverse opinions exist on the relative importance of these three factors for reducing the clonogen doubling time [42, 44, 48]. If the predominant mechanism is a change in the cell-loss factor [42, 48], then the potential doubling time for malignant melanoma with a median of 11 days [36] is a lower limit to the volume doubling time after acceleration of repopulation. Withers et al. [48] estimated that this acceleration starts at about 4 weeks after onset of treatment for squamous cell carcinoma of the head and neck. If this value is accepted for melanomas as well, and at present there seems to be no reason why this delay should be shorter for melanomas, these tumors will probably be subject to only 3 or 4 doublings of the clonogenic cell number within a 7 week treatment course. This effect will most likely be masked by the observed variation in tumor volume of approximately a factor of 1000 (equivalent to 10 doublings).

The present finding of a lack of treatment-time influence is supported by the sparse in vitro measurements of the potential doubling time in malignant melanoma which also indicate that this is a slowly proliferating tumor [42]. In the clinical series reported by Trott et al. [43], a marked importance of treatment time in predicting local control was demonstrated. Unfortunately, these data are not suited for re-analysis by the present model, as no measures of tumor sizes have been published, and as shown in Fig. 5a, b, considerable heterogeneity can be attributed to variability in tumor size. The variation in dose per fraction was relatively modest with two thirds of the patients receiving between 1.8 Gy and 3.0 Gy/fx and only three patients (7\%) receiving more than 4.6 Gy/fx. Moreover, the analysis by Trott et al. [43] relied on a modified Ellis's NSD formula. The time factor in this type of model is biologically unrealistic as it predicts decreasing regeneration rate with increasing time after the onset of treatment [38]. Interestingly, the series by Trott et al. did not show correlation between fraction size and overall treatment time \( r = -0.11, p > 0.1 \), and the reasons for prolonged treatment in some patients were not stated.

Choi et al. [5] claimed that shortening the overall treatment time from 2 weeks to one week significantly prolonged survival after radiotherapy of metastatic melanoma in the brain. However, serious doubt is cast on the relevance of survival as the endpoint for measuring the effect of radiotherapy as only half the number of observed
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deaths had intracranial disease as their major cause and no dose-response relationship could be demonstrated with survival as endpoint. Both of the presumably most important prognostic factors, major symptoms and extracranial metastasis, were more frequent in the group treated in longer overall times. Furthermore, 32/59 (54%) of the patients had a complete resection before radiotherapy. Of the remaining 27 patients, radiotherapy failed to control the disease in 25, all of whom had an intracranial recurrence at the time of death. Finally, even if survival is accepted as a relevant endpoint, the interpretation is hampered by the fact that all short treatments were given with larger-sized fractions (3.0–3.75 Gy) than the longer treatments (1.88–2.4 Gy).

Also, Von Rottkay [45] has advocated predominantly accelerated fractionation with 1.5–3.0 Gy/fx in malignant melanomas based on the results in a relatively small and heterogeneous series of 14 patients treated with radiotherapy in typically 3–6 weeks overall time. Results from a total of 25 treatment fields were reported. Eight of these received post-operative irradiation. The series also included metastases in other organs, e.g. brain and bone, all of which were excluded from the Danish series in order to achieve a biologically more homogeneous material. The dosimetry in Von Rottkays series is complicated by the fact that some patients were treated with conventional X-rays with a RBE differing from that of $^{60}$Co. The present TCP model estimates a 40–65% tumor control probability for typical fractionation schedules given in the German series. Taking the above caveats into consideration, the result of the German trial seems to be consistent with the Danish experience.

**Treatment strategy**

Radiocurability of solid human tumors is often limited by the late radiation damage tolerable in the surrounding normal tissue. In the case of cutaneous malignant melanoma the dose-limiting late-reacting tissue is generally the skin and subcutis. The quantitation of the relevant radiobiological parameters for both tumor and normal tissue allows, at least in principle, an optimization of the fractionation schedule employed. Owing to the very limited influence of treatment time as shown in the present analysis, acceleration of the treatment is unlikely to improve tumor control. Thus the treatment time should be chosen mainly to insure an acceptable level of acute normal-tissue response.

When this is said, it is true that characteristic overall treatment times in the current series were about one week with the 9 Gy/fx, 4–5 weeks with the 5 Gy/fx and 6–7 weeks with the 2 Gy/fx schedules. The derived model for TCP must be expected to be more accurate for combinations of treatment time and fraction size similar to these.

Fraction size should be selected to increase the therapeutic differential between the tumor and the associated late-responding normal tissue. Figure 8 shows the therapeutic ratio defined as the ratio between the isoeffect dose for 50% chance of subcutaneous fibrosis and the isoeffect dose for 80% TC. The $\alpha/\beta$ value used for subcutaneous fibrosis (1.8 Gy, 95% confidence limit [0.9,2.7] Gy) is determined from the Aarhus series of post-mastectomy radiotherapy in breast cancer.

![Fig. 8. Estimated therapeutic ratio as a function of fraction size (full line). The therapeutic ratio is the quotient between the (predicted) isoeffect dose for 50% probability of severe subcutaneous fibrosis and for 80% probability of complete tumor response. Stippled lines are the 95% confidence limits calculated by standard propagation of error techniques.](image-url)
patients [3]. The rather large confidence intervals for both $\alpha/\beta$ for fibrosis and CR of melanoma result in a broad confidence interval on the predicted therapeutic ratio (Fig. 8), and so the possibility that the therapeutic ratio is independent of fraction size cannot be ruled out. However, based on the present experience, hypofractionation may actually increase the therapeutic differential between tumor response and subcutaneous fibrosis. Other late skin reactions, e.g. telangiectasia, seem to have higher $\alpha/\beta$ ratios, thus lending further support to the probable advantage of hypofractionation for malignant melanoma. The gain from increasing the dose per fraction above 6 Gy is expected to be minimal, and at present 5–6 Gy/fx seems to be a reasonable choice.

Finally, an adjustment of the total dose for tumor size is indicated (Figs. 3 and 4). The accuracy of the present estimates of the parameters in Appendix, Eqn. (5) does not justify its general application in the clinic. Further data collection is necessary, and an investigation of the predictive value of size measures other than mean diameter would be desirable. It is clear from this analysis, however, that the dose should be increased as the size of the lesion increases.

**Multiple lesions**

About 40% of the patients had multiple lesions. A Kruskal-Wallis test of residuals (see Appendix) showed a highly significant correlation between the deviations from the radiobiological model in individual patients, thus indicating the existence of a "hidden parameter" that affects response to radiotherapy. This could be a host effect, for example the immunological status of the patient could influence the outcome of therapy [26]. Another possibility is that the inherent radiosensitivities of multiple lesions are correlated. Indeed, the radiosensitivity of human malignant melanoma cell lines, quantitated by the surviving fraction at 2 Gy, $SF_2$ [12], do span a broad range [6,13], which could account for the observed differences between individuals. Numerous parameters have been considered possible determinates for the outcome of radiotherapy [34], and host-tumor dependent correlation between the values of one of these could explain the present finding.

The demonstration of a correlation between treatment responses of multiple malignant melanomas casts some doubt on the design philosophy of clinical trials in this disease, where the allocation of different treatments to multiple lesions is used in an attempt to balance treatment groups. In the presence of correlation, this procedure increases the chance of type-II errors, i.e. the chance of erroneously accepting the null-hypothesis of no difference between treatments. The reason is that multiple lesions in a specific patient either tend all to respond or all not to respond. In this situation random treatment allocation is superior.

The host effect suggested by the present analysis should be cross-validated in a series with random treatment allocation to each lesion or be verified directly, for example by demonstrating correlation between the $SF_2$ of multiple lesions.

**Predictive value of the model**

Published data from the literature together with the previously unpublished data from the Maria-Sklodowska-Curie Institute in Warsaw constituted an independent data set for cross-validation of the TCP-model. The decision to analyze the Danish data separately was made to improve the homogeneity of the treatments and the evaluation of response. It turned out that the derived model provided a good average description of observed response rates in the independent series as well. The deviation between the observed and expected complete response rates was no larger than expected from the binomial distribution of quantal response data.

An analysis of the pooled data set of all 422 lesions gave only slight changes in the parameter estimates. The point estimate of the $\alpha/\beta$ was 0.0 Gy with 95% confidence limits [-1.3,1.6] Gy, thus reinforcing the conclusion concerning the low $\alpha/\beta$. 
Conclusions

Quantitation of the relative importance of radiobiological parameters in a clinical series of 239 malignant melanomas was accomplished using a Poisson model of probability of local tumor control. This type of direct analysis, where individual observations may be entered in a combined overall analysis, is especially attractive in a series with a great diversity of treatments. The biological behavior inferred is characterized by negligible proliferation, no treatment-time influence, and large sublethal damage repair capacity (low α/β ratio). Tumor size is of major importance in predicting radiotherapeutic outcome.

Analysis of TCPs in patients with multiple lesions points to the existence of a "hidden parameter" influencing the outcome of radiotherapy. It is not possible to identify this parameter based on the data available in this series, but inherent radiosensitivity or immunological status are obvious candidates.

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References


Appendix

Models and analysis

The number of surviving target cells after radiotherapy is assumed to be described by a Poisson distribution. TC is
achieved in tumors with zero target cells surviving. Let \( N \) be the average number of surviving target cells. Then the TCP is [29]:

\[
p(\text{TC}) = e^{-N}.
\] (1)

The number of target cells surviving a dose \( D \) delivered in \( d \) Gray per fraction is assumed to be described by the multi-fraction linear-quadratic (LQ) model:

\[
N(D,d) = N_0 \cdot \exp\left(-\frac{\alpha D + \beta d}{\alpha \beta d}\right)
\] (2)

where \( N_0 \) is the initial number of target cells. \( N_0 \) is assumed to be a power function of the mean tumor diameter, \( S \):

\[
N_0 = c_1 \cdot S^{c_2}.
\] (3)

Combining Eqns. (1-3) yields the final expression for the TCP:

\[
p(\text{TC}) = \exp\left(-c_1 \cdot S^{c_2} \cdot \exp\left(-\frac{\alpha D + \beta d}{\alpha \beta d}\right)\right)
\] (4)

The four parameters \( c_1, c_2, \alpha \) and \( \beta \) are to be determined from observed quantal response data by the maximum likelihood method [39]. The log likelihood is maximized using the optimization routines by Gay [15].

For the purpose of displaying the dose-response relationship, a tumor-size corrected dose (\( D_\ast \)) is calculated as

\[
D_\ast = D - \frac{c_2 \ln S}{\alpha + \beta d}
\] (5)

where \( D \) is the dose delivered in fractions of size \( d \) to a tumor of size \( S \). The second term on the right hand side of Eqn. (5) is the dose required to reduce the number of target cells in a tumor of diameter \( S \) to the number present in a 1 cm diameter tumor.

The relationship between dose to cure a fraction \( p \) of the tumors (\( \text{TCD}_p \)) and size \( S \) is obtained by rearranging Eqn. (4):

\[
\text{TCD}_p = \frac{\ln c_1 + c_2 \ln S - \ln(-\ln p)}{\alpha + \beta d}
\] (6)

Tumor growth during treatment was modeled in two ways. Firstly, a simple exponential growth model was tested, multiplying the right-hand side of Eqn. (2) by

\[
g_1(T) = e^{k_1T}.
\] (7)

where \( T \) is the overall treatment time in days and \( k_1 \) is a constant to be estimated by the maximum likelihood method. Secondly, accelerated regeneration during treatment was tested in a threshold model by putting

\[
g_2(T) = \begin{cases} 1 & \text{if } T < 28 \\ e^{k_2(T-28)} & \text{if } T \geq 28 \end{cases}
\] (8)

The 4-week threshold was selected on the basis of available experimental data in other tumors [48].

The possible dependency between the TCP and a clinical variable \( x_j \) was investigated graphically by plotting the average residual as a function of \( x_j \). The residual is defined for the \( i \)th lesion as

\[
R_i = r_i - p_i
\] (9)

where \( r_i \) is the observed result (equal to one if TC is obtained, zero if not) and \( p_i \) is the TCP determined from the model. Thus a positive residual \((R_i > 0)\) indicates a better-than-expected result. Conversely a negative residual indicates a worse-than-expected result. Values of \( R_i \) were averaged over lesions with values of \( x_j \) within a specific range and plotted as a function of the mean \( x_j \) in that group.

The possible correlation between the outcome of treatment in multiple lesions was tested by means of a non-parametric one-way analysis of variance. For each lesion the residual [Eqn. (9)] was calculated and the analysis of variance was conducted to test whether the interpatient variation of the residual was explained by the intra-patient variation. The Kruskal-Wallis H statistic [24] had a value of 41.2 with a corresponding \( p \)-value of 0.008, indicating that the average residual differed significantly among patients.