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Papers

Evidence for Individual Differences in the Radiosensitivity of Human Skin

Susan L. Tucker, Ingela Turesson and Howard D. Thames

Previously published clinical data have been re-analysed to investigate individual differences in the radiosensitivity of human skin. In the clinical studies, acute and late skin reactions were recorded for 254 breast cancer patients receiving radiotherapy to the internal mammary nodes following simple or modified radical mastectomy. Each patient was treated bilaterally with different fractionation schedules to the right and left fields. Patients were assigned prospectively to 10 different treatment groups of 11–35 patients each, with all patients in a group receiving the same pair of fractionation schedules to the right and left fields. In the present study, correlations between the skin reactions in the two treatment fields per patient were investigated. For each of three different endpoints—peak reflectance measure of erythema, peak acute skin reaction score, and a ranking measure of the progression rate of telangiectasia—significant correlations were found between the levels of skin injury to the right and left treatment fields of the patients in most treatment groups. Although there were correlations between the absorbed doses in the right and left fields, statistical analyses indicated that dose effects were not sufficient to explain fully the patient-to-patient differences in skin response. Thus, these data provide evidence for the existence of individual differences in the radiation response of human skin, both for early and late effects. Whether these differences are dominated by heterogeneity in intrinsic cell radiosensitivity or by other factors has yet to be determined. However, there was no clear evidence of a correlation between the acute and late endpoints, suggesting that the individual differences in radiosensitivity are not dominated by a common genetic component expressed equally in all cells.
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INTRODUCTION

DURING THE past decade it has been recognised that human tumours differ in their intrinsic cell radiosensitivity and that *in vitro* radiosensitivity is correlated with clinical radioresponsiveness [1–3]. Heterogeneity in intrinsic tumour-cell sensitivity exists even among tumours of the same histologic type [4–7]. This recognition has led to the development of radiosensitivity assays that, it is hoped, will help to predict the response to radiotherapy of the individual tumour [4, 7–9].

More recently, attention has turned to the possibility that differences in normal tissue response among radiotherapy patients may also be due, at least in part, to differences in intrinsic cell sensitivity. It has been known for some time that individuals with ataxia telangiectasia, for example, are hypersensitive to radiation [10], but there may also be differences in inherent radiation sensitivity among apparently normal individuals.

The purpose of this paper is to present evidence for individual differences in the radiosensitivity of human skin, based on a reanalysis of previously published data. Since 1972, prospective studies of acute and late skin reactions have been carried out in

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Table 1. *Treatment schedules*

Series*	n	d (Gy)	D (Gy)	TLD (Gy)	n/week	n/day	Δt (h)	T (days)	N	Reference
1 (4BH)	16	2.59	41.4	37.2–40.3	5	1	24	22	35	†
2 (4BV)	4	6.74	27.0	24.0–26.8	1	1	168	22	35	†
3 (5AH)	17	2.52	42.8	40.3–41.4	5	1	24	23	11	[12,17]
4 (5AV)	50	1.11	55.5	53.6–55.1	15	3	4	23	11	[12,17]
5 (4AH)	16	2.59	41.4	37.4–41.3	5	1	24	22	27	[12,14]
6 (4AV)	4	7.46	29.8	26.2–31.0	1	1	168	22	27	[12,14]
7 (D3H)	4	7.89	31.6	27.1–29.3	1	1	168	22	25	[18]
8 (D3V)	12	2.63	31.6	26.8–28.9	3	3	0.25	22	25	[18]
9 (7BH)	35	2.00	70.0	60.7–66.6	5	1	24	68	30	[16,21,22]
10 (7BV)	14	4.00	56.0	48.6–52.8	2	1	72	67	30	[16,21,22]
11 (7CAH)	30	2.00	60.0	53.4–57.1	5	1	24	61	28	†
12 (7CAV)	12	4.00	48.0	42.6–45.2	2	1	72	60	28	†
13 (12BH)	25	2.00	50.0	43.4–47.2	5	1	24	33	29	[19]
14 (12BV)	25	2.00	50.0	43.2–46.6	10	2	4	17	29	[19]
15 (12CH)	25	2.25	56.3	46.0–52.3	5	1	24	33	27	[19]
16 (12CV)	25	2.00	50.0	42.9–46.9	10	2	4	17	27	[19]
17 (13AH)	25	2.10	52.5	44.8–49.2	5	1	24	33	29	[19]
18 (13AV)	25	1.80	45.0	39.6–42.9	15	3	4	11	29	[19]
19 (1AH)	21	2.62	55.0	45.9–50.4	5	1	24	29	13	[11,15]
20 (1AV)	9	5.00	45.0	37.4–41.9	2	1	72	29	13	[11,15]

* Series labels in parentheses indicate those used in earlier publications.

† Unpublished data.

n = Number of dose fractions; d = prescribed dose per fraction; D = prescribed total dose; TLD = absorbed dose to skin (range); n/week = fractions per week; n/day = fractions per day; Δt = minimum fractionation interval; T = overall treatment time; N = number of patients.

breast cancer patients receiving postmastectomy radiotherapy in Gothenburg, Sweden [11–23]. Patients were treated bilaterally to the internal mammary nodes with different fractionation schedules to the right and left fields, and skin reactions in both fields have been followed. Previous reports concerning these data have described the influence on early and late skin reactions of dose, dose per fraction, fractionation interval, and overall treatment time [11–23]. In this study, the paired data from the two treatment fields per patient were analysed to determine whether or not there were consistent differences in radiation response from patient to patient.

PATIENTS AND METHODS

Patient population and treatment schedules

The data analysed in this study are from 254 breast cancer patients treated with radiotherapy to the internal mammary nodes at the Department of Oncology in Gothenburg, Sweden, following simple or modified radical mastectomy. Patients were treated bilaterally with different fractionation schedules to the right and left fields.

Patients were assigned prospectively to 10 different treatment groups consisting of 11–35 patients each. Within each group, all patients were treated with a common fractionation schedule to the right field and a (different) common fractionation schedule to the left field. The 10 patient groups and the 20 distinct treatment series are described in Table 1. For convenience, the treatment series are identified in this paper by the numerals 1–20 as shown in Table 1. Series labelled with successive odd and even numerals (e.g. series 1 and 2, series 3 and 4, etc.) represent treatment schedules to the right and left fields of the same patients.

TL dosimeters were used to determine the absorbed doses at each treatment session, and Table 1 also shows the range of absorbed doses in each treatment series in this study. All doses are given as absorbed dose to water. Absorbed dose to muscle = 1.02 × absorbed dose to water for treatment series 1–6, and = 0.99 × absorbed dose to muscle for series 7–20. Further details of the irradiation procedures, field geometry and TL dosimetry have been presented elsewhere [11–19].

Acute skin reactions

Skin erythema was measured twice a week using reflectance spectrophotometry [13], and the peak value of the reflectance measure, expressed as the per cent deviation from the pre-irradiation value, was noted. Peak reflectance measures were unavailable for 18 patients (36 fields).

The level of acute skin injury was also assessed by photographing patients once or twice a week, starting before the first radiation treatment and continuing until the reaction faded away. Photographs were scored blindly by two observers according to an arbitrary 6-point scale: 0 = no reaction; 1,2,3 = mild, moderate or brisk erythema; and 4,5 = spotted or confluent moist reaction, respectively. The peak acute reaction score was used as a measure of acute response. The peak reaction scores were not available for 14 patients (28 treatment fields).

Late skin reactions

For all but one of the treatment groups, patients were photographed every 3 months until 5 years after treatment, and every 6 months thereafter, to follow the progression of late skin injury. In the remaining group (series 19 and 20), follow-up was less frequent. At each time point, the degree of skin telangiectasia was scored using an arbitrary 6-point scale: no, minimal, marked, very marked, partially confluent and totally confluent telangiectasia (score 0, 1, 2, 3, 4, 5, respectively). The data for the late reaction in each patient consisted, therefore, of a list of response times at which skin scores 1–5 were reached, if ever, together with a time of last follow-up or patient death. Times were measured in months from the start of treatment.

Average telangiectasia rank: a summary measure of late response

The following technique was used to quantify the late skin reactions of patients in each treatment series. First, a list of distinct time points was obtained by noting the times of the clinic visits at which an increase in the telangiectasia score occurred for one or more patients in the series, relative to the score observed at the previous clinic visit.

Next, the telangiectasia score at each of these time points was recorded for each patient in the series. The telangiectasia scores associated with the list of time points were approximate in the sense that the response times of individual patients were known only to within 3–6 months, due to the spacing of the follow-up clinic visits. Also, the scores of some patients were unknown at some time points because of patient loss to follow-up.

The unknown telangiectasia scores were next extrapolated by using the larger of two values: the median of the known scores for the corresponding time point or the highest score already reached by the patient in question at some previous time point in the list. This extrapolation procedure assigns values to the unknown telangiectasia scores that are as 'typical' as possible for each time point, while still taking into account the fact that telangiectasia is a strictly progressing endpoint.

Finally, the observed and extrapolated telangiectasia scores at each time point in the list were ranked from 1 to N (N = number of patients in the treatment series) with appropriate adjustments made for ties, and the average rank over all time points was calculated for each patient in the series.

The ranking technique outlined above is illustrated in Results for one of the treatment series.

RESULTS

Early skin reactions

Within each subgroup of patients treated to the right and left fields according to a common pair of fractionation schedules, a range of acute skin reactions was observed. To determine whether this variation might reflect individual differences in sensitivity, the correlations between the acute reactions from the right and left fields of individual patients were investigated. These analyses were done within treatment groups to avoid the necessity of selecting a suitable mathematical model to adjust for the large differences in dose, dose per fraction, fractionation interval, and overall treatment time between treatment groups (cf. Table 1).

Reflectance spectrophotometry

Table 2 lists the correlation coefficients calculated using the peak reflectance measures of erythema from the right and left fields of patients in each treatment group. In all 10 groups, there was a significant positive correlation between the reflectance measures from the right and left fields ($P \leq 0.006$; Table 2). Figure 1 shows the distribution in paired reflectance measures from the treatment groups having the lowest (series 13 and 14) and highest (series 11 and 12) correlation coefficients, as well as from one with an intermediate value (series 3 and 4).

Table 2. Correlations between the reflectance measures of erythema from the right and left fields of individual patients

Treatment series*	Raw data†	Corrected for dose†‡
1,2	0.733 (< 0.001)	0.745 (< 0.001)
3,4	0.785 (0.002)	0.734§ (0.005)
5,6	0.823 (< 0.001)	0.815 (< 0.001)
7,8	0.877 (< 0.001)	0.802 (< 0.001)
9,10	0.908 (< 0.001)	0.904‖ (< 0.001)
11,12	0.940 (< 0.001)	0.919 (< 0.001)
13,14	0.617 (< 0.001)	0.617** (< 0.001)
15,16	0.867 (< 0.001)	0.829 (< 0.001)
17,18	0.854 (< 0.001)	0.854** (< 0.001)
19,20	0.672 (0.006)	0.699 (0.004)

* cf. Table 1.

† Pearson correlation coefficient and P value (one-tailed test).

‡ Reflectance measures (y) were corrected for dose within treatment series by: $y - (b_0 + b_1 \cdot D)$, where $b_0 + b_1 \cdot D$ is the best-fitting regression line for the data in that series.

§ Dose coefficient (b_1) was negative for series 4; dose correction not made for that series.

‖ Dose coefficient was negative for series 9; dose correction not made for that series.

** Dose coefficients were negative for both series; no dose corrections made.

Although the patients in each treatment group received the same pair of prescribed radiation doses to the right and left fields, there were some differences in absorbed dose from patient to patient as determined by TL dosimetry (Table 1). Moreover, a correlation analysis revealed that in all 10 of the treatment groups there was a significant positive correlation between the TL doses to the right and left fields ($P \leq 0.035$). This suggested that the observed differences in peak reflectance measures within treatment groups, as well as the correlations between the reflectance measures from the right and left fields of individual patients, could potentially be due to dose effects rather than to individual differences in sensitivity.

This issue was investigated by performing a linear regression of the peak reflectance measure against absorbed dose within each treatment series. For 15 of the 20 treatment series, the coefficient of dose did not differ significantly from zero, indicating no detectable influence of TL dose on reflectance measure over the relatively narrow ranges of absorbed dose in those treatment series. In two additional series the dose coefficients, though statistically different from zero, were negative. That is, there was a decrease in the average peak reflectance measure with increasing absorbed dose, suggesting that the observed correlations between TL dose and reflectance in those two cases were merely coincidental. However, for the remaining three series, there were statistically significant positive correlations between absorbed dose and peak reflectance measure of erythema. Therefore, the correlation analyses between the reflectance measurements from the right and left fields were repeated after correcting for positive dose effects within treatment series

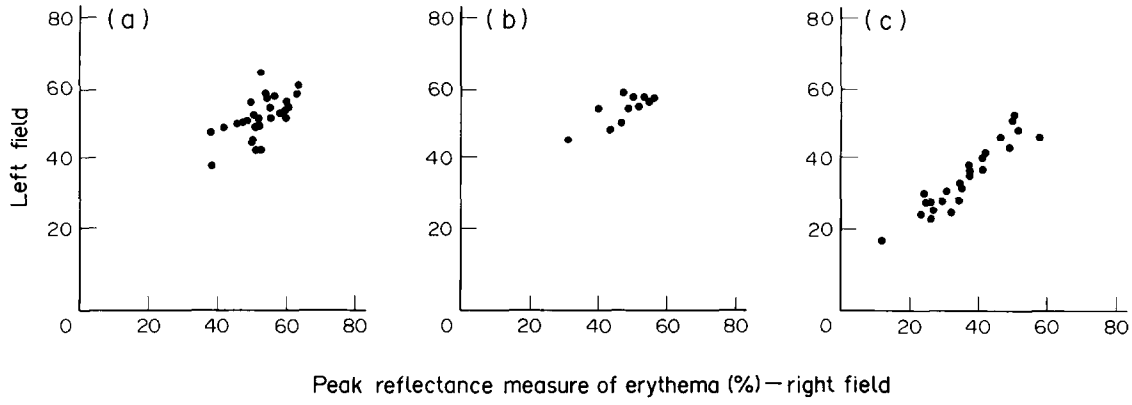

Fig. 1. Distribution of peak reflectance measures from the right and left fields of patients in treatment series 13 and 14 (panel A), series 3 and 4 (panel B) and series 11 and 12 (panel C). Pearson correlation coefficients are 0.617, 0.785 and 0.940 ($P < 0.001$, $P = 0.002$ and $P < 0.001$) for panels A–C, respectively (cf. Table 2). Reflectance measures are expressed as per cent deviations from pre-irradiation values.

on the basis of the regression fits. As shown in Table 2, highly significant correlations were still found between the responses in the right and left fields of individual patients. That is, the most severe acute reactions in the right and left treatment fields, as measured by reflectance spectrophotometry, tended to occur in the same patients, and similarly for the least severe reactions.

Acute reaction scores

Significant correlations were also found between the peak acute reaction scores from the right and left treatment fields of individual patients in nine of the 10 groups of patients ($P \leq 0.001$; Table 3). In fact, for two of these nine groups, the correlation was perfect (correlation coefficient = 1.000). The lack of correlation in the remaining group (series 3 and 4) was due to the fact that all but two of the 11 fields treated with series 3 exhibited the same acute reaction score. Figure 2 illustrates the distribution of acute scores from this pair of series, as well as from one of the treatment groups in which scores were perfectly correlated (series 11 and 12) and from a group with an intermediate correlation coefficient (series 17 and 18).

Table 3. Correlations between the acute skin reaction scores from the right and left fields of individual patients

Treatment series*	Spearman rank-order correlation coefficient (and P value†)
1,2	0.633 (< 0.001)
3,4	0.000 (0.500)
5,6	0.798 (< 0.001)
7,8	0.596 (0.001)
9,10	1.000 (< 0.001)
11,12	0.885 (< 0.001)
13,14	0.826 (< 0.001)
15,16	0.714 (< 0.001)
17,18	0.652 (< 0.001)
19,20	1.000 (< 0.001)

* cf. Table 1.
† One-tailed test.

For the acute reaction scores, the possible influence of slight dose differences in producing individual differences in response was investigated by fitting the proportional-odds model [24] with a single covariate (TL dose) to the data in each treatment series. This model, described in the Appendix, allows a statistical test of the significance of TL dose in determining response within each treatment series. A significant positive influence of absorbed dose on acute reaction score was detected using the proportional-odds model for only two of the treatment series (series 7 and 8). Nonetheless, an additional analysis was done to confirm the conclusion that the correlations observed in this study between the acute reaction scores from opposing fields in the same patient could not be explained by dose effects alone. In this additional analysis, the proportional-odds model was modified by adding a parameter to represent the variability in radiation sensitivity among individual patients. Details of the model are given in the Appendix. For nine of the 10 treatment groups, the variation parameter was found to be significantly different from zero ($P \leq 0.033$), again indicating significant patient-to-patient differences in response beyond any that could be explained by differences in absorbed dose. The exception was the treatment group consisting of series 3 and 4; this group had only 11 patients and, as noted earlier, all but two of these patients had the same acute reaction score in the right field, so the lack of significance of the variation parameter was not surprising.

Late skin reactions

In each of the treatment series in this study, there were wide variations from patient to patient in the observed telangiectasia scores and in the rates of progression of late injury. For example, 1 patient reached a telangiectasia score of 1 at 1.5 years and progressed to score 5 by 7.5 years, while another patient in the same treatment series did not reach score 1 until 5.5 years and has not progressed further after nearly 11.5 years. A graphical illustration of the variation in individual progression patterns for telangiectasia has been presented elsewhere [22].

To investigate the possible correlations between late skin damage in the right and left fields of individual patients, the average telangiectasia rank of each patient in a treatment series was used as a summary measure of the severity of late response, relative to that of other patients in the series. The technique

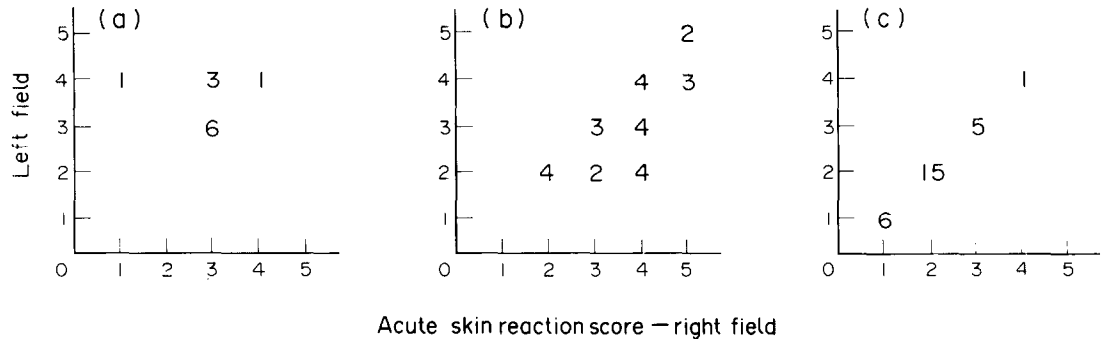

Fig. 2. Distribution of peak acute reaction scores from the right and left fields of patients in treatment series 3 and 4 (panel A), series 15 and 16 (panel B) and series 9 and 10 (panel C). Numerals indicate the number of patients with each pair of peak acute reaction scores. Spearman correlation coefficients are 0.000, 0.714 and 1.000 ($P = 0.500$, $P < 0.001$ and $P < 0.001$) for panels A–C, respectively (cf. Table 3).

used to calculate the average telangiectasia ranks is described in the Patients and Methods and is illustrated in Table 4 for series 3, which included 11 patients.

Table 4 lists the 14 distinct time points, ranging from 8 to 137 months, at which 1 or more patients in series 3 reached an increased telangiectasia score, compared with the score observed at the previous clinic visit. At each of the 14 time points, the approximate telangiectasia score of each patient is shown. For example, patient 1 was first seen to have a telangiectasia score of 1 at 8 months post-treatment, and had a score of 2 at the next clinic visit 3 months later, at which time no other patient had yet been observed to have a non-zero telangiectasia score. Patient 9 reached a score of 1 during the 3-month interval up to and including 17 months, and by 23 months, patient 1 was observed to have progressed to score 3. The numbers in parentheses in Table 4 are extrapolated scores calculated as described in Patients and Methods. The presence of an extrapolated score indicates that the telangiectasia score for that patient was not available due to censoring (from patient death or insufficient follow-up) prior to the specified time point.

The observed and extrapolated telangiectasia scores were ranked from 1 to 11 for each of the time points listed in Table 4, and the average rank over all time points is shown for each patient. As an illustration of the ranking procedure, the ranked scores corresponding to the 43-month time point were as follows: each of the 6 patients with score 0 was assigned rank 3.5 (average of ranks 1, 2, 3, 4, 5, 6), the 3 patients with score 1 were assigned rank 8 (average of ranks 7, 8, 9), and the patients with scores 2 and 4 were assigned ranks 10 and 11, respectively. Table 4 shows that the average ranks provide a measure of the severity of telangiectasia in the sense that the patient with the lowest average rank (patient 5) had the least reaction (no telangiectasia), while the patient with the highest average rank (patient 1) had the most rapidly progressing telangiectasia.

Table 5 shows the correlation coefficients calculated using the average telangiectasia ranks from the right and left fields of

Table 4. Observed and extrapolated telangiectasia scores in treatment series 3 as a function of observation time

Observation time (months)	Patient										
	1	2	3	4	5	6	7	8	9	10	11
8	1	0	0	0	0	0	0	0	0	0	0
11	2	0	0	0	0	0	0	0	0	0	0
17	2	0	0	(0)	0	0	0	0	1	0	0
23	3	0	0	(0)	0	0	0	0	1	0	0
29	3	0	0	(0)	0	0	0	0	1	1	0
35	4	0	0	(0)	0	0	0	0	1	1	1
40	4	1	0	(0)	0	0	0	0	1	1	1
43	4	1	0	(0)	0	0	0	0	2	1	1
59	4	1	0	(1)	0	0	1	0	2	1	2
71	4	1	0	(1)	0	0	1	0	2	2	2
80	(4)	2	0	(1)	0	0	1	0	2	2	2
89	(4)	2	0	(2)	0	0	2	0	2	2	2
96	(4)	2	(2)	(2)	0	1	2	0	2	2	2
137	(4)	(2)	(2)	(2)	0	(2)	2	(2)	3	(2)	(2)
Average rank	11.0	6.2	4.2	5.3	3.5	3.9	5.3	3.8	8.5	7.1	7.0

Numbers in parentheses are extrapolated scores; see text.

Table 5. Correlations between late skin reactions in the right and left fields of individual patients

Treatment series	Spearman correlation coefficient (P value*)
1,2	0.857 (< 0.001)
3,4	0.907 (< 0.001)
5,6	0.649 (< 0.001)
7,8	0.881 (< 0.001)
9,10	0.776 (< 0.001)
11,12	0.556 (< 0.001)
13,14	0.751 (< 0.001)
15,16	0.781 (< 0.001)
17,18	0.923 (< 0.001)
19,20	0.954 (< 0.001)

* One-tailed test.

patients in each treatment group; in each case, there was a highly significant positive correlation between the late reactions in the two fields. Figure 3 illustrates the correlations between late response in the right and left fields for the treatment groups in which the correlation coefficients were lowest (series 11 and 12), intermediate (series 9 and 10) and highest (series 19 and 20).

The possible influence of dose differences in producing variation in late response from patient to patient was investigated by calculating the Spearman correlation coefficients between absorbed dose and average telangiectasia rank for patients in each of the 20 treatment series. The correlation coefficients were fairly low (median 0.250, range −0.028–0.451), but there was a statistically significant positive correlation between dose and average telangiectasia rank in six of the 20 treatment series. Therefore, a further analysis was done to factor out any influence of absorbed dose in producing differences in the late skin reactions within each group of patients. In this analysis, the times of the clinic visits at which telangiectasia score 1 was reached were fitted with the Cox proportional-hazards model [25], using TL dose as a covariate. The failure times for any other telangiectasia score could have been used instead, but the number of censored event times would then have been greater.

In the proportional-hazards model analysis, it was assumed that among patients receiving absorbed dose D, the proportion who would reach telangiectasia score 1 by time t is given by

$$F(t) = 1 - \exp\left[- \exp(\beta \cdot D) \cdot \int_0^t \lambda_0(s)ds \right],$$

where β is a dose coefficient and where $\lambda_0(t)$ is a baseline hazard function common to all patients. A fit of the model to score 1 failure-time data from a treatment series yields an estimate of β and $\lambda_0(t)$ for that series.

To correct for the effects of absorbed dose and of differences in the fractionation schedules from right to left, thereby allowing a comparison of the score 1 failure times in the opposing treatment fields of individual patients, the failure times were converted to percentiles of failure time distributions. That is, quantities $100 \cdot F(t)$ were calculated from the times, t, at which telangiectasia score 1 was reached. For each treatment field, the calculation was based on the absorbed dose, D, to the field in question and on the dose coefficient, β, and the baseline hazard function, λ_0, from the corresponding series.

Figure 4 shows the normalised failure times calculated using this procedure for the patients treated to the right and left fields with series 9 and 10, respectively. These two series were among those in which there was evidence of a possible correlation between absorbed dose and late response, as measured by the telangiectasia rank sums ($P = 0.038$ and $P = 0.034$, respectively). However, Fig. 4 shows that after correcting for the effect of differences in TL dose, there is still a significant correlation between the times to reach telangiectasia score 1 in the right and left fields of individual patients. Patients who reached score 1 earlier than average in the right field also tended to reach score 1 earlier than average on the left, whereas patients who responded later than average on one side tended to do so on both sides. The actual correlation coefficient was not calculated because of incomplete data (censored failure times for 3 patients), but it is clear that the points in Fig. 4 are not distributed uniformly throughout the unit square as they would be if the failure times on the two treatment fields per patient were unrelated. Instead, the points are clustered around the diagonal, indicating consistent patient-to-patient differences in skin sensi-

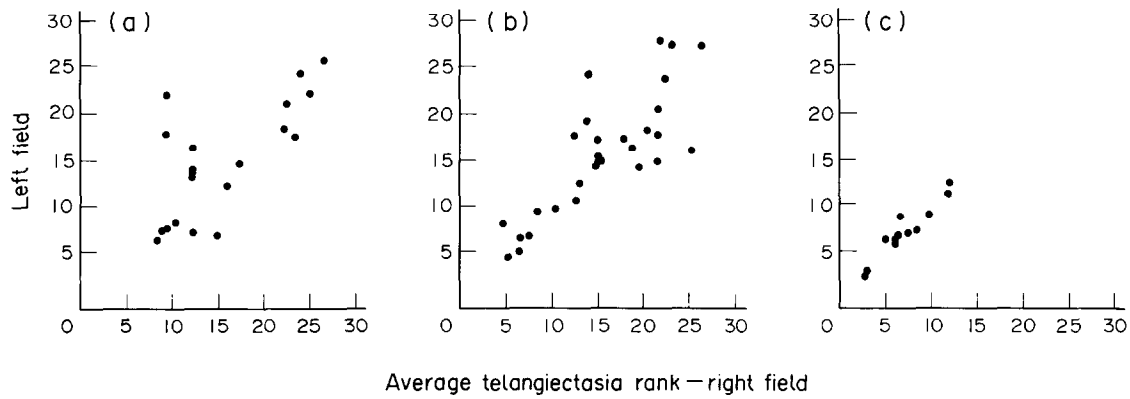

Fig. 3. (Late reactions) Paired average telangiectasia ranks from the right and left fields of patients in treatment series 11 and 12 (panel A), series 9 and 10 (panel B) and series 19 and 20 (panel C). Spearman correlation coefficients are 0.556, 0.776 and 0.954 for panels A–C, respectively ($P < 0.001$ in each case; cf. Table 5).

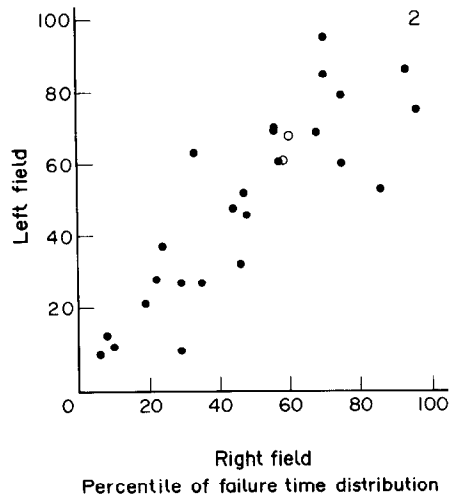

Fig. 4. Times to reach telangiectasia score 1 in the right and left fields of individual patients treated in series 9 and 10, expressed as percentiles of the relevant failure time distributions; see text for further description of the normalisation procedure. Closed circles: failure times observed in both treatment fields; open circles: failure times censored in both treatment fields; symbol 2: failure time censored in the right field and observed in the left field.

tivity. This analysis was also performed for each of the other treatment groups in this study, and in every case, the resulting points were clustered about the diagonal, as in Fig. 4.

Relationship between acute and late response

Within each treatment series, the relationship between the acute and late skin reactions in individual patients was investigated. In only one of the series was there a statistically significant positive correlation between the reflectance measure of erythema and average telangiectasia rank, although the Spearman correlation coefficient in that case was low (0.374), indicating considerable scatter in the data. For the remaining 19 treatment series the correlations were not significant, and in five of them, the correlation coefficients were actually negative, indicating a trend toward *less* severe late reactions among patients experiencing the more severe early responses.

A similar result was found concerning the relationship between the acute skin reaction scores and the average telangiectasia ranks. No statistically significant correlation was found in any of the treatment series. In fact, the Spearman correlation coefficients were negative for a substantial proportion (7/20) of the treatment series.

DISCUSSION

Possible factors contributing to the response of normal tissues to radiotherapy can be grouped into two general categories: those related to the treatment (fractionation schedule, volume of the treatment field, radiation quality, etc.) and those inherent to the patient (intrinsic cell radiosensitivity, patient age, physiological characteristics, etc.).

Until rather recently, the study of normal tissue responses to radiotherapy has focused primarily on the influence of treatment-related factors. This situation can be contrasted with the investigation of tumour responses to radiotherapy, where the prognostic significance of various patient characteristics has been studied extensively for years. Lately, however, attention has been increasingly aimed at determining the extent to which differences in normal tissue injury might be due to intrinsic patient factors, as opposed to being simply random expressions of radiation damage. Knowledge of patient factors contributing to normal tissue response would have important implications with regard to radiotherapy [26]. If it is the case, for example, that the most serious radiation sequelae occur in patients who are inherently most sensitive to radiation, and if those patients could be identified prior to treatment, then the dose to the remaining patients could potentially be increased without significantly increasing the incidence of unacceptable normal tissue injury, and with the possibility of achieving an improved rate of local tumour control.

It has been known for some time that patients with ataxia telangiectasia are unusually sensitive to radiation [10], and data indicate that this is due to a greater than average intrinsic cell radiosensitivity, e.g. [27]. However, evidence for heterogeneity in radiation sensitivity among apparently normal individuals is more sketchy. Perhaps the best evidence is provided by a study of Loeffler *et al.* [28], in which it was shown that fibroblast cell lines established from five women exhibiting unusually severe clinical responses to radiotherapy for the treatment of breast cancer were significantly more radiosensitive *in vitro* than those established from 6 patients chosen at random from among the patients exhibiting a normal clinical response. The correlations between *in vitro* and clinical response suggest it is unlikely that the patients who experienced unusually severe skin reactions did so merely by chance.

The present study provides further evidence for the existence of patient-to-patient differences in factors influencing the radiation sensitivity of normal tissues. The clinical data analysed in this study are unique in that observations from two different treatment fields treated with different radiotherapy schedules were available for each patient. Since all patients in each of the 10 distinct treatment groups in this study received the same pair of prescribed fractionation schedules to the two fields, treatment-related factors could be largely ruled out *a priori* as explanations for the observed correlations in response between the right and left fields in individual patients. The exception was absorbed dose, which did vary somewhat from patient to patient within treatment series, and for which there were correlations from right to left in individual patients. This was mainly due to individual differences in dose contributions from adjacent fields in the loco-regional radiotherapy following mastectomy. However, a number of different statistical analyses were performed to correct for differences in absorbed dose within series, and after these corrections, significant patient-to-patient differences in skin sensitivity were still observed.

One might ask if the failure of dose to account fully for the individual differences in skin response observed in this study could be due to uncertainty in the measured doses. That is, if the absorbed doses could be measured with perfect precision, would we still find significant patient-to-patient differences in response after correcting for individual differences in dose? The following calculations were done to test this possibility. Assuming that the standard deviation in replicate dose estimates obtained using TL dosimetry is about 9% of the mean, an approximate 95% confidence interval for the reported total dose (D) is given by $D \pm D \cdot 18\%/\sqrt{n}$, where n is the number of dose fractions. A 9% coefficient of variation in replicate TL dose measurements is a conservative estimate derived from data from the earliest group of patients to be treated, when the TL system was still under development [11]. The accuracy of TL dose estimates in later series is judged to be somewhat better, with a

coefficient of variation of about 7%. A simulation study was done in which the dose-corrected correlation analyses between the reflectance measures of erythema in the right and left treatment fields (cf. Table 2, last column) were repeated after replacing each reported total dose with a dose chosen randomly from the approximate 95% confidence interval for the reported dose; these correlation analyses done on data with randomly selected doses were repeated 10^4 times per treatment group. For the smallest treatment group in this study (series 3 and 4), there were 266 cases from among the 10^4 analyses, or 2.66%, in which the right–left correlations in the dose-corrected reflectance measures failed to reach statistical significance ($P \leq 0.05$). For two additional treatment groups, the significant right–left correlations were removed less than 0.5% of the time, and for the remaining seven series, no random 'wiggling' of the reported doses within their estimated 95% confidence intervals was able to eliminate the statistical significance of the observed patient-to-patient differences in the reflectance measures. Thus, the results of these calculations strongly suggest that the consistent differences in skin response observed among these patients were due primarily to inherent differences among the patients rather than to any undetected dose–response relationships.

The reasons for the individual differences in radiation sensitivity of human skin are not yet known. One likely contributing factor is patient-to-patient heterogeneity in intrinsic cell radiosensitivity. This possibility is supported by the study of Loeffler *et al.* [28] and also by the study of Little and Nove [27], who found differences in *in vitro* fibroblast radiosensitivity among 31 normal individuals and 83 other patients with a variety of genetic disorders. Studies are currently underway to determine the *in vitro* fibroblast radiosensitivity of a subset of the patients described in this study and to determine whether those sensitivities correlate with skin response. Studies are also underway to obtain a quantitative measure of the amount of variability among patients from the *in vivo* data; such analyses require the use of mathematical models to correct for the large differences between the treatment series with respect to prescribed dose, dose per fraction, fractionation interval, and overall treatment time.

Other factors may also contribute to the observed differences in skin sensitivity, however. Patient characteristics such as age and smoking habits may influence the physiological response to radiation exposure. Further work is currently in progress to assess the influence of factors such as these on the skin responses of patients in this study.

Whatever the patient factors determining normal tissue response, the results of this study suggest that they are not the same for all tissue endpoints. In this study, no significant correlations were found between the acute skin reaction scores and the average telangiectasia ranks of patients in the same treatment series. A weak correlation between average telangiectasia rank and reflectance measure of erythema was found for one of the treatment series, but for the remaining 19 series, no correlation was apparent. A similar result was presented by Bentzen and Overgaard [29], who found no correlation between erythema and telangiectasia in another series of patients receiving postmastectomy radiotherapy, although they did find a predisposition for severe telangiectasia among patients who developed moist desquamation.

If intrinsic cell radiosensitivity is a major determinant of normal tissue response, then the lack of correlation between acute and late skin responses found in this study suggests that relative radiosensitivity is not the same for all target cells in an individual, contrary to the concept that intrinsic radiosensitivity is dominated by a genetically determined component common to all cells. This conclusion is also suggested by the results of Kushiro *et al.* [30] and Geara *et al.* [31], who found no correlation between the radiosensitivities of fibroblasts and lymphocytes from the same individuals. Thus, if predictive assays are to be used to estimate the likely normal tissue response of radiotherapy patients, it appears that it will be necessary to customise the assay to the particular endpoint of concern.

APPENDIX

Proportional-odds model for the analysis of the acute skin reaction scores

The possible influence of absorbed dose in contributing to individual differences in the peak acute skin reaction core was investigated by fitting the proportional-odds model [24] to the data in each treatment series. Suppose that $S_1,\ldots,S_n$, $n \leq 6$, are the distinct values of the peak acute reaction scores, in order, observed in a particular treatment series (e.g. $S_1 = 2$, $S_2 = 3$ and $S_3 = 5$). In the proportional-odds model, it is assumed that p_i, the probability of achieving a peak score $\leq S_i$, is a sigmoid-shaped function of absorbed dose given by the logistic expression:

$$\ln\left[\frac{p_i}{1-p_i}\right] = \theta_i - \beta \cdot D\ .$$

It is further assumed that the coefficient of dose is the same for each reaction level, so the unknown parameters in the model are β and θ_i, $i = 1,\ldots,n-1$. (Since $p_n = 1 - p_{n-1}$, there is no need to consider p_n separately.) By using maximum likelihood analysis to fit two versions of the model—with and without the dose term—to the data from each treatment series, the significance of the dose term was determined using the likelihood ratio test.

Modification of the proportional-odds model

Suppose that $S_1^r,\ldots,S_n^r$, $n \leq 6$, are the distinct, ordered values of the peak acute reaction scores in the right field of patients in a particular treatment group, while $S_1^l,\ldots,S_m^l$ are the distinct, ordered scores from the left fields of the same patients. Let p_i^r, $i = 1,\ldots,n$, denote the probability of achieving a score $\leq S_i^r$ in the right field, and let p_j^l, $j = 1,\ldots,m$, denote the probability of achieving a score $\leq S_j^l$ in the left field.

In the modified version of the proportional-odds model, individual differences in skin sensitivity were modelled as consistent additive changes in the logistic constants from patient to patient. Specifically, it was assumed that for each patient there is some number, ϵ, such that

$$\ln\left[\frac{p_i^r}{1-p_i^r}\right] = \theta_i + \epsilon - \beta \cdot \Delta D_r$$

and

$$\ln\left[\frac{p_j^l}{1-p_j^l}\right] = \theta_j + \epsilon - \beta \cdot \Delta D_l\ ,$$

where ΔD_r and ΔD_l are the doses to the right and left fields, expressed as deviations from the average absorbed dose in the corresponding series. The values of epsilon were assumed to be distributed normally with mean zero and variance σ^2. When the

model was fitted to paired skin reaction data from the right and left fields of patients in the same treatment group, there were $n + m$ unknown parameters: θ_i, $i = 1,\ldots, n-1$; θ_j, $j = 1,\ldots, m-1$; β; and σ^2. Maximum likelihood analysis was used to fit two versions of the model—with and without the parameter σ^2—to each data set, and the significance of the variation parameter (σ^2) was investigated using the likelihood ratio test.

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