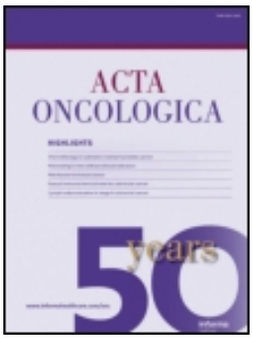

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M. Overgaard

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FROM THE DEPARTMENT OF ONCOLOGY AND RADIOTHERAPY, AND THE DANISH CANCER SOCIETY, DEPARTMENT OF EXPERIMENTAL CLINICAL ONCOLOGY, RADIUMSTATIONEN, DK-8000 AARHUS, DENMARK.

SPONTANEOUS RADIATION-INDUCED RIB FRACTURES IN BREAST CANCER PATIENTS TREATED WITH POSTMASTECTOMY IRRADIATION

A clinical radiobiological analysis of the influence of fraction size and dose-response relationships on late bone damage

M. OVERGAARD

Abstract

The influence of fraction size on normal tissue damage was analysed in 231 patients treated with postmastectomy irradiation given either with a 12-fraction regimen (1978–1980) or with a 22-fraction regimen (1981). Chest radiographs taken 1–6 years after treatment were reviewed for spontaneous, radiation-induced rib fracture within the treated area. Patients treated with a large dose per fraction had significantly higher incidence of late bone damage (19%) than patients treated with a standard dose per fraction (6%) even though they had been treated with the aim to obtain equivalent biologic response according to the NSD formula. Furthermore, there was a clear dose–response relationship, especially in the 12-fraction regimen, where the total dose at the reference point varied over a wide range. Isoeffect doses could be estimated for the two different fractionation schedules. Using the linear quadratic model, alpha/beta ratios for late bone damage were estimated to be within the range of 1.8–2.8 Gy, i.e. similar to those reported for other late responding normal tissues.

Key words: Radiations, injurious effect; postoperative irradiation of breast cancer, late radiation effect in bone, dose per fraction, dose–response relation, NSD-model, α/β-model.

Postmastectomy irradiation is encumbered with the risk of early and late complications such as skin changes, lung damage, arm oedema, frozen shoulder, atrophic changes, and spontaneous fractures in ribs and shoulder girdle (2, 4, 5, 7, 9, 11). Various factors have been shown to determine the nature and the rate of these complications, e.g. target volume, total dose, radiation quality, fractionation schedule (3, 10, 11, 12), the surgical procedure preceding irradiation, and adjuvant simultaneous or sequential chemotherapy. Radiotherapy is still being widely used as an effective loco-regional treatment modality in conjunction with conservative surgery. Therefore, it is of importance to define precisely the tolerance of each normal tissue to be included in the target volume.

The Nominal Standard Dose (NSD) concept has been widely used in equation of different fractionation schedules, but several clinical and experimental studies have revealed that only acute skin reactions may be sufficiently predicted by this formula, whereas late skin damage and damage to other tissues, lung, and bone cannot be predicted well enough (8, 13, 14, 15). The aim of the present analysis of a clinical material is to estimate and predict isoeffect doses for radiation damage in bone tissue based on dose–response relationships for spontaneous rib fractures in patients treated with two different fractionation schedules.

Material and Methods

Patients. All high-risk breast cancer patients admitted to our department from 1978 to 1981 received postmastectomy irradiation (1). In the first 3 years of this period, patients received 2 fractions per week to a total of 12 fractions; in the last year patients received 5 fractions per week to a total of 22 fractions.

The surgery and radiation treatment technique remained unchanged, which enabled us to compare the two fractionation schedules with regard to radiation complications. None of the patients included here received adjuvant chemotherapy.

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Table 1

Patient and treatment characteristics

	Group 1a	Group 1b	Group 2
No. of patients	82	81	68
Age (years)*	60 (31–80)	62 (19–81)	66 (41–79)
No. of patients			
with fracture	40 (48%)	15 (19%)	4 (6%)
with multiple fractures	33 (40%)	4 (5%)	1 (1%)
Obs. time (days)*	1186 (589–1994)	1079 (401–2138)	739 (482–1575)
No. of fractions	12	12	22
Treatment time (days)*	39 (37–49)	39 (37–59)	29 (29–40)
Total dose, photon field (min. IC 2 value)**	50.8 Gy (49.0–52.0)	46.4 Gy (41.6–51.1)	51.3 Gy (48.0–54.3)
Total dose, electron field (min. IC 2 value)**	50.9 Gy (38.2–53.1)	46.7 Gy (38.1–51.0)	48.8 Gy (30.2–51.4)
NSD photon field (min. IC 2 value)**	1877 ret (1810–1920)	1701 ret (1520–1867)	1674 ret (1540–1773)

*Median (range).
**Mean (range).

The present analysis included 231 patients, who were available for follow-up and review of chest x-ray taken 1–6 years after completion of radiation therapy (Table 1).

A subgroup of these (120 patients treated with same NSD-dose and evaluable for both early and late lung damage) were included in a previous iso-dose analysis (15).

Radiation treatment technique. The surgery and radiation treatment technique has been described in detail elsewhere (15). All patients were treated with an anterior photon field (8 MV) against the supraclavicular and axillary regions. The lung distal to the level of the second rib was protected by individually shaped blocks, and the chest wall covering this part of the lung was treated through an anterior electron field shaped to fit the lung block in the photon field. The electron field included the chest wall to sulcus inframammaria or at least 3 cm below the surgical scar.

The aim of the radiation therapy was to deliver a tumour dose sufficient for eradication of sub-clinical disease in peripheral lymph nodes and the chest wall. Dose recommendations for the Danish Breast Cancer Cooperative Group (1) were followed in most patients (group 1b and 2), whereas the remaining patients (group 1a) received standard maximum doses to the supraclavicular/axillary photon field and chest wall electron field respectively (Table 1).

Dose distribution. In patients treated according to the protocol recommendations, the aim was to obtain a fixed dose at of mid-plane of the axilla. This resulted in a range of different maximum doses within the volume treated from the photon field due to different A-P-diameters in the patients. Patients treated to standard maximum doses in the photon field, however, showed a similar dose variation at the mid-plane of the axilla.

The electron energy was adjusted according to individual ultrasound measurements of chest wall thickness in order to get 85% of the maximum dose at the pleural surface. Two types of lung blocks were used: a 5 cm lead block during the first 3 years and an 8 cm wood metal block during the last year. The photon transmission doses in the electron field including the photon beam have been measured for both block types at depths from 0.5 mm to 70.0 mm. The total doses in the skin, subcutaneous tissue, rib cage, and lung included in the electron field were higher than the planned dose, and consequently the actual depth doses were calculated and used for the present analyses. As described above all patients were treated with specific electron energies on the basis of measurements of the individual chest wall thickness. In patients with chest wall dimensions kept in the record (157 patients) the minimum thickness at second intercostal level (IC2) laterally to the edge of the sternum, was used for calculation of maximum dose at the pleural surface, i.e. the back of the rib cage. In patients where these dimensions were not recorded (74 patients), the chest wall thickness was estimated from the average chest wall thickness of patients treated with similar electron energy, a measure which was known in all patients. Thus, realistic dose ranges could be calculated for all patients at this depth both in the electron and in the photon field (Table 1).

Evaluation of the end-point. Late bone damage was recorded as spontaneous rib fractures within the irradiated area as illustrated in Fig. 1. Fractures were evaluated from normal chest radiograms only, which are not optimal for the detection of bone changes. The chest radiograms were taken routinely every year in protocol patients (group 1b and 2) but more infrequently in non-protocol patients (group 1a). For all patients the most

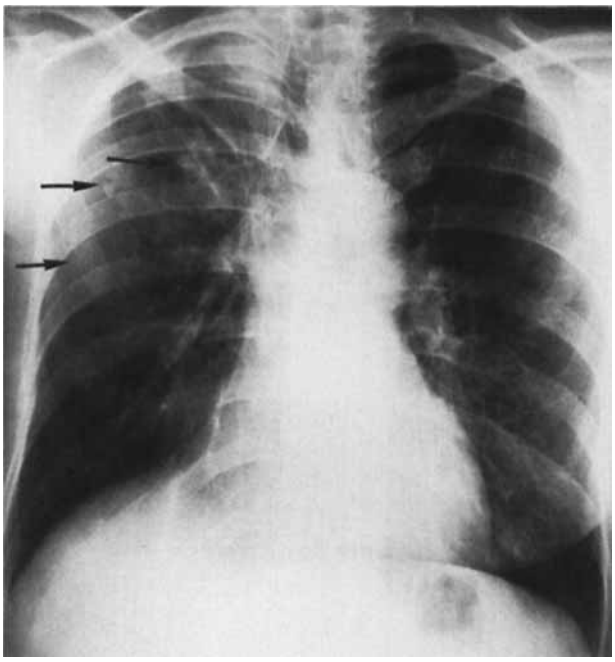

Fig. 1. 55-year-old woman treated with postmastectomy on the right side with 51.36 Gy to the photon field and 47.52 Gy to the electron field in 12 fractions. Increased density of bone structure in 3 upper ribs anteriorly with spontaneous fractures marked with arrows.

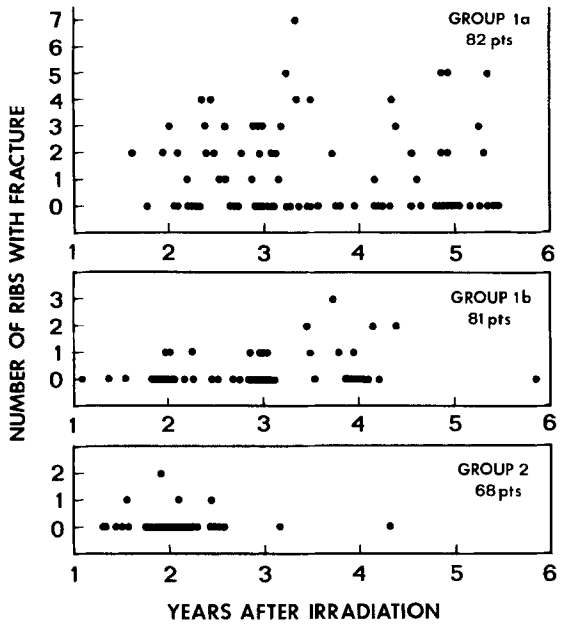

Fig. 2. Relationship between length of observation time (time from treatment start to chest x-ray) and individual number of spontaneous rib fractures in group 1a, 1b and 2.

recent radiogram (i.e. the longest follow-up) was used in the present analysis. As described elsewhere (14, 15), the chest radiograms were all reviewed in cooperation with a diagnostic radiologist, mainly for scoring of radiation damage in the lung. However, at the same time visible rib fractures with and without healing were recorded. Only fractures occurring after 1 year of follow-up were included. This was assured by comparing with chest radiograms taken prior to radiation treatment and within 6 months after start of treatment. The quality of the radiograms prevented evaluation and grading of the radiation-induced changes in bone density, bone sclerosis, and necrosis as proposed by the RTOG/EORTC late radiation morbidity scheme.

Special roentgenologic examinations were rarely performed as most fractures were asymptomatic. However, in the case of suspected malignant rib destruction, the diagnostic procedures included both special radiography, bone scans, and biopsy.

Several patients had multiple fractures within both the photon and the electron field. It was impossible to separate fractures occurring in either one or both of the fields since the chest radiograms were not made in the treatment position. Therefore, any spontaneous non-malignant rib fracture within the target area was recorded as the rough end-point, irrespective of location and total number of fractures. Moreover, by scoring all patients from chest radiograms, the diagnostic sensitivity was equal for all patients.

Statistical analysis. Comparison between the complication rate in the 2 fractionation schemes was performed by a simple chi-square independence test. A Student's t-test was used to compare NSD-values in the 3 groups. Linear regression analysis was used to evaluate the influence of observation time on the distribution of the actual complications (18).

The dose–response curves were calculated by use of a logit method (16) by grouping the patients with 1 Gy intervals for the total dose at the reference point.

Results

Spontaneous radiation-induced rib fractures was recorded in 59 of 231 patients, and in 38 patients 2–7 ribs were fractured. The frequency of spontaneous rib fractures was much higher after the 12-fraction regimen (48% and 19%) than after the 22-fraction regimen (6%) (Table 1).

Influence of observation time. The relationship between observation time and both severity and incidence of spontaneous rib fractures is shown in Fig. 2.

The time from treatment to chest radiography (observation time) varied between 401–2139 days (Table 1). We assessed the occurrence and number of rib fractures during the observation period as it is known that late bone damage may progress with time. However, in none of the 3 groups linear regression analysis showed statistically significant relationship between observation time and incidence or severity (number of fractures).

Implication of the NSD formula. In patients treated

Table 2

Isoeffect values and alpha-beta ratios for radiation-induced rib fractures

Reference point	Isoeffect level	Isoeffect dose (Gy)		Alpha/beta ratio***
		12 fx (Group 1)	22 fx (Group 2)	
Photon field (min. IC 2)	6%	41.4 (36.3–47.1)*	52.0 (49.5–54.5)*	1.8 Gy
Photon field (min. IC 2)	6%	41.4 (36.3–47.1)*	51.3 (48.1–54.5)**	2.2 Gy
Electron field (min. IC value)	6%	40.1 (34.3–47.8)*	48.8 (43.0–54.6)**	2.8 Gy

* Value estimated by logit analysis. 95% confidence limits in brackets.
** Mean value. 95% confidence limits in brackets.
*** Estimated according to formula (1).

according to protocol recommendations (group 1b and 2) —the Nominal Standard Dose (NSD) formalism, without computation of partial tolerances—the formula was used for the conversion from 2 to 5 fractions per week, attempting to obtain isoeffects for the two regimens. However, in spite of equal ret values at the reference point (mean 1701 and 1674 ret at IC2) (Table 1) there was a significant difference in the number of spontaneous fractures between the two groups ($p<0.05$). Thus, the NSD formalism could not predict isoeffects with respect to late bone damage after the two fractionation schedules.

Dose–response relationship. There was a clear dose–response relationship in the two groups treated with the 12-fraction regimen. Spontaneous rib fractures occurred more frequently and the severity of damage (number of fractures) was more pronounced in group 1a, which had received a higher total dose (Table 1). The variation in total doses at the IC2 reference point behind the rib cage allowed construction of well-defined dose–response curves for both the photon field and the electron field of the 12-fraction regimen (Fig. 3).

In the 22-fraction regimen, proper dose–response curves could not be constructed as spontaneous rib fractures were few and only occurred within a narrow dose range.

Isoeffect and α/β ratio. The well-defined 6% incidence of fractures in the 22-fraction schedules could be used for calculation of isoeffect doses for the two regimens (Table 2). These isoeffect doses allowed estimation of the α/β ratio from the formula (8):

$$\alpha/\beta = \frac{(D_1 \times d_1 - D_2 \times d_2)}{D_2 - D_1}$$

where D and d are total dose and dose per fraction in the two schedules.

The values for α/β ratios ranged between 1.8–2.8 Gy depending on the chosen isoeffect dose and field (Table 2).

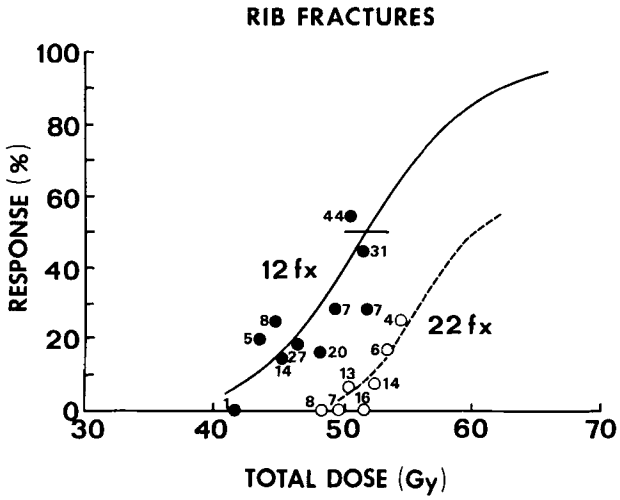

Fig. 3. Dose–response relationship for spontaneous rib fractures in photon irradiated fields treated with a total of 12 or 22 fractions. Horizontal bar indicates 95% confidence limit of the 50% level. The upper part of the curve for the 22-fraction scheme has been fitted by eye.

Discussion

The literature offers only few reports on the influence of dose per fraction on late bone damage.

Although Ellis stated that the NSD formula could not be used for prediction of the tolerance dose to bone and brain (6), this formula has been widely used in clinical radiotherapy to equate different fractionation regimens. Therefore, the results showing a significant difference in late bone damage in the 2 groups of patients treated to the same NSD value clearly illustrate the limitations and danger of using this formula for prediction of isoeffects in different normal tissues.

The present study of a clinical material represents an exceptional opportunity to generate dose–response data for radiation induced bone damage. All patients were treated with identical technique, and an equal amount of

normal tissue was included in the target volume, i.e. amount/volume of rib cage. A dose range was established as a reference for the damage score in the rib cage (spontaneous rib fractures). This reference was calculated on the basis of the variations in dose aim and chest wall thickness, and it could be used to estimate isoeffect doses for the two fractionation regimens. However, the infrequency of this complication in the 5-fraction per week schedule only allowed proper calculation of isoeffect expressions at the 6% level, at which level an α/β ratio of about 2 Gy could also be estimated. It is of importance to underline that the calculated α/β ratio is not a fixed value. Several factors, such as chosen level of isoeffect and the confidence limits at different levels on the two dose–response curves can considerably affect the size of the α/β ratio as described for other end-points (8, 14, 17). The isoeffect level for the present α/β calculations has been chosen to obtain the most realistic value of the present clinical situation.

In addition to the adjustments which have to be made for the mathematical estimations, the clinical evaluation of the end-point is also encumbered with several problems. As described, the changes in the ribs could only be evaluated from chest radiograms since most patients were asymptomatic and therefore underwent no special roentgenologic examinations of the ribs. When bone metastasis was suspected, the patient was further examined and excluded if malignancy was confirmed. Spontaneous rib fractures could be due to simple osteoporosis, which is common in elderly and postmenopausal women (11). The median age was slightly higher in the group treated with the 5-fraction per week regimen, and the very low frequency of rib fractures in this group contradicts that age could be the cause of the rib fractures. Further analysis of the 3 groups revealed a slightly higher rate of spontaneous rib fractures in the premenopausal women than in the postmenopausal ones. The rib fractures could be caused by very high radiation doses obtained by overlap of the photon and electron fields. However, the treatment technique and control of every treatment set-up remained the same during the 4-year period, which makes this explanation of the observed difference in bone damage unlikely.

Radiation-induced bone damage may progress with time (2, 4, 9, 11). The median follow-up time was 3 years in the 2-fraction per week regimen and 2 years in the 5-fraction per week regimen. However, there was no evidence of an increased rate of rib fractures in patients with a long follow-up in group 1a and 1b. In group 2, the low frequency of complications and the overall shorter follow-up time makes this question difficult to answer, and additional follow-up of these patients is necessary.

Spontaneous radiation-induced rib fracture did not cause serious disability in any of the patients, but similar damage in other bones, i.e. mandibulae, humeri or collum femoris may cause serious functional disability. Although the risk of radiation-induced bone fractures and necrosis has been considerably reduced following the introduction of high energy radiation, this complication is still a major problem when high dose treatment includes bone. Therefore, the presented clinical data concerning impact of dose per fraction and dose–response relationship have obvious relevance, when radiation tolerance of mature bones must be considered.

Request for reprints: Dr Marie Overgaard, Dept of Oncology and Radiotherapy, Radiumstationen, DK-8000 Aarhus C, Denmark.

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