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Validity of bioeffect dose response models for normal tissue early and late complications of the skin

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Summary

Background The bioeffect of a physical dose depends on the nature of the tissue, fractionation scheme, dose rate and treatment time. Certainly, experienced radiotherapists are convinced of the existence of patient-to-patient variability in normal tissue response to radiotherapy for malignant tumours. The absorbed dose needs to be translated into a bioeffect dose, which takes into account treatment variables and the radiobiological characteristics of the relevant tissue. Various bioeffect models such as NSD, CRE, TDF and BED have been proposed to predict the biological effect of radiotherapy treatments.

Aim This study was aimed at deriving tolerance bioeffect dose values for normal tissue complication rate.

Materials/Methods Compiled clinical data of time dose fractionation schedules and incidence of erythema, desquamation and telangiectasia were used for the present analysis.

Results For erythema and desquamation the radiation dose varied from 23.9 to 55.1Gy in 04 to 50 fractions (dose per fraction 1.1 to 7.3Gy) in 11 to 40 days. For telangiectasia (score ≥1 at 3 years) the radiation dose varied from 25.8 to 55.1Gy in 04 to 50 fractions (dose per fraction 1.1 to 7.3Gy) in 11 to 40 days. For telangiectasia (score ≥2 at 5 years) the radiation dose varied from 25.8 to 63.0Gy in 04 to 50 fractions (dose per fraction 1.1 to 7.3Gy) in 11 to 68 days. For telangiectasia (score ≥1, ≥2, ≥3, ≥4 at 10 years) the radiation dose varied from 25.8 to 63.0Gy in 04 to 35 fractions (dose per fraction 1.7 to 7.3Gy) in 22 to 68 days. TDF and LQF values for erythema, desquamation and telangiectasia were evaluated with α/β values of 7.5Gy, 11.2Gy and 2.8Gy respectively. TDF and LQF had a statistically significant correlation with probability of erythema, desquamation and telangiectasia ($p<0.001$).

Conclusions TDF and LQF values should be limited to 60 and 86Gy in order to limit the probability of telangiectasia.

Key words radiotherapy • normal tissue • early and late complications

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Background

The aim of the radiation oncologist is uncomplicated loco-regional control of cancer by radiation therapy. To achieve this goal, precise knowledge of tumoricidal dose and tolerance doses of various normal tissues is most helpful. The monumental work of Rubin and Cassarett [1] was a major step in this direction. From nearly a century of clinical experience, a number of empirical rules have been obtained to aid radiotherapists in achieving higher therapeutic gain. The bioeffect of a physical dose depends on the nature of the tissue, fractionation scheme, dose rate and treatment time. The absorbed dose needs to be translated into a bioeffect dose, which takes into account treatment variables and the radiobiological characteristics of the relevant tissue. Various bioeffect models have been proposed to predict the biological effect of radiotherapy treatments.

From time to time, various concepts such as the nominal standard dose (NSD) [2], cumulative radiation effect (CRE) [3,4] and time dose fractionation (TDF) factors [5,6] have been put forward to test the equivalence of treatment schedules. The NSD formula, despite its limitations, provided radiotherapists with an important initial step in understanding the effects of fractionation on the tolerance of skin and connective tissue. The TDF formula allowed addition of the TDF values for different portions of a course of radiation treatment. These concepts were widely accepted in spite of their empirical nature. However, doubts have been raised periodically as to the accuracy of prediction of early and late effects of normal tissues. Now the linear quadratic (LQ) model is being used increasingly to predict the biological effect of fractionated radiotherapy using different parameters for a particular tissue, such as α/β, μ, K and Td [7–13]. Dale [8] proposed extrapolated response dose (ERD) equations for external beam therapy, intracavitary brachytherapy and interstitial brachytherapy. Within the context of the LQ model the parameter which quantifies the overall biological effect on a given tissue is the biologically effective dose (BED), which is obtained by applying repopulation correction to ERD [12].

Certainly, experienced radiotherapists are convinced of the existence of patient-to-patient variability in normal tissue response to radiotherapy for malignant tumours. However, there are pitfalls in the clinical impressions of the individual differences, even if the prescribed dose regimens are exactly the same. The inter-individual variation in response is most easily seen for acute effects in skin and mucosa as the patients are frequently investigated during and shortly after the treatment course. There is now evidence that dose-response relationships for normal tissue and organ effects are steep; in general, they are steeper for late effects than for early effects.

This study was undertaken to apply TDF and LQF to clinical data of skin erythema, desquamation and telangiectasia in order to arrive at tolerance values for an acceptable level of probability of complication rate.

Materials and Methods

Clinical data of time dose fractionation schedules and incidence of erythema, desquamation and telangiectasia was used for the present analysis [21,22]. For erythema data radiation dose varied from 23.9 to 55.1Gy and the maximum number of patients (43.3%) was in the dose range of 40.1 to 50.0Gy. The number of fractions varied from 04 to 50 and the maximum number of patients (35.4%) was in the range of 04 to 10 fractions. The dose per fraction varied from 1.1 to 7.3Gy and the maximum number of patients (38.5%) was in the dose per fraction range of 1.1 to 2.0Gy. Treatment time varied from 11 to 40 days and the maximum number of patients (50.3%) was in the treatment days range of 21 to 30 days. For desquamation data radiation dose varied from 23.9 to 55.1Gy and the maximum number of patients (41.9%) was in the dose range of 40.1

to 50.0Gy. The number of fractions varied from 04 to 50 and the maximum number of patients (35.6%) was in the range of 04 to 10 fractions. The dose per fraction varied from 1.1 to 7.3Gy and the maximum number of patients (39.1%) was in the dose per fraction range of 1.1 to 2.0Gy. Treatment time varied from 11 to 40 days and the maximum number of patients (50.4%) was in the treatment days range of 21 to 30 days.

For telangiectasia data (score ≥1 at 3 years) radiation dose varied from 25.8 to 55.1Gy and the maximum number of patients (47.9%) was in the dose range of 40.1 to 50.0Gy. The number of fractions varied from 04 to 50 and the maximum number of patients (36.2%) was in the range of 21 to 30 fractions. The dose per fraction varied from 1.1 to 7.3Gy and the maximum number of patients (38.2%) was in the dose per fraction range of 1.1 to 2.0Gy. Treatment time varied from 11 to 40 days and the maximum number of patients (41.6%) was in the treatment days range of 21 to 30 days. For telangiectasia data (score ≥2 at 5 years) radiation dose varied from 25.8 to 63Gy and the maximum number of patients (36.3%) was in the dose range of 40.1 to 50.0Gy. The number of fractions varied from 04 to 50 and the maximum number of patients (33.2%) was in the range of 04 to 10 fractions. The dose per fraction varied from 1.1 to 7.3Gy and the maximum number of patients (33.8%) was in the dose per fraction range of 1.1 to 2.0Gy. Treatment time varied from 11 to 68 days and the maximum number of patients (40.9%) was in the treatment days range of 21 to 30 days.

For telangiectasia data (score ≥1 at 10 years) radiation dose varied from 25.8 to 63Gy and the maximum number of patients (31.3%) was in the dose range of 25.8 to 30Gy. The number of fractions varied from 04 to 35 and the maximum number of patients (40.2%) was in the range of 04 to 10 fractions. The dose per fraction varied from 1.7 to 7.3Gy and the maximum number of patients (37.5%) was in the dose per fraction range of 3.1 to 4.0Gy. Treatment time varied from 22 to 68 days and the maximum number of patients (43.2%) was in the treatment days range of 31 to 40 days. For telangiectasia data (score ≥2 at 10 years) radiation dose varied from 25.8 to 63Gy and the maximum number of patients (31.9%) was in the dose range of 25.8 to 30.0Gy. The number of fractions varied from 04 to 35 and the maximum number of patients (40.7%) was in the range of 04 to 10 fractions. The dose per fraction varied from 1.7 to 7.3Gy and the maximum number of patients (37.9%) was in the dose per fraction range of 3.1 to 4.0Gy. Treatment time varied from 22 to 68 days and the maximum number of patients (43.6%) was in the treatment days range of 31 to 40 days.

For telangiectasia data (score ≥3 at 10 years) radiation dose varied from 25.8 to 63Gy and the maximum number of patients (30.5%) was in the dose range of 25.8 to 30.0Gy. The number of fractions varied from 04 to 35 and the maximum number of patients (39.5%) was in the range of 04 to 10 fractions. The dose per fraction varied from 1.7 to 7.3Gy and the maximum number of patients (38.2%) was in the dose per fraction range of 3.1 to 4.0Gy. Treatment time varied from 22 to 68 days and the maximum number of patients (45.5%) was in the treatment days range of 37 to 40 days. For telangiectasia data (score ≥4 at 10 years) radiation dose varied from 25.8 to 63Gy and the maximum number of patients (30.2%) was in the dose range of 25.8 to 30.0Gy. The number of fractions varied from 04 to 35 and the maximum number of patients (39.6%) was in the range of 04 to 10 fractions. The dose per fraction varied from 1.7 to 7.3Gy and the maximum number of patients (37.3%) was in the dose per fraction range of 3.1 to 4.0Gy. Treatment time varied from 22 to 68 days and the maximum number of patients (45.3%) was in the treatment days range of 31 to 40 days. TDF and LQF values for erythema, desquamation and telangiectasia were evaluated with the following equations with α/β values of 7.5Gy, 11.2Gy and 2.8Gy respectively [11,21,22].

Erythema

$TDF = 1.19\ d^{1.54}\ n\ x^{-0.17}$

$LQF = 1.34\ Nd\ [1+(d/7.5)]\ x^{-0.17}$

Desquamation

$TDF = 1.19\ d^{1.54}\ n\ x^{-0.17}$

$LQF = 1.34\ Nd\ [1+(d/11.2)]\ x^{-0.17}$

Telangiectasia

$TDF = 0.90\ d^{1.79}\ n\ x^{-0.16}$

$LQF = 1.23\ Nd\ [1+(d/2.8)]\ x^{-0.16}$

Results

Data regarding classification of patients as per TDF and LQF for erythema are given in Table 1. TDF values ranged from 44 to 85 and the maximum number of patients (47.7%) had TDF varying from 71 to 80. LQF values ranged from 41 to 97Gy and the maximum number of patients (34.8%) had LQF varying from 61 to 70Gy.

Table 1. Classification of patients as TDF and ERD (Erythema data).

Criteria	Range	Number	Percentage
TDF	44–50	41	5.4
	51–60	120	15.9
	61–70	129	17.1
	71–80	360	47.7
	81–85	105	13.9
ERD (Gy)	41–50	130	17.2
	51–60	155	20.5
	61–70	263	34.8
	71–80	147	19.5
	81–90	49	6.5
	91–97	11	1.5

Table 2. Correlation of TDF and LQF with probability of erythema.

Criteria	Range	No/Total	Percentage	p value
TDF	44–63	37/196	18.9	<0.001
	64–76	204/394	51.8	
	77–85	130/165	78.8	
LQF (Gy)	41–48	26/130	20.0	<0.001
	49–78	264/529	49.9	
	79–97	81/96	84.4	

Table 3. Classification of patients as per TDF and ERD (Desquamation data).

Criteria	Range	Number	Percentage
TDF	44–50	43	5.6
	51–60	131	17.2
	61–70	174	22.8
	71–80	364	47.6
	81–85	95	12.4
ERD (Gy)	38–40	14	1.8
	41–50	188	24.6
	51–60	207	27.1
	61–70	179	23.4
	71–80	165	21.6
	81–90	0	0.0
	91–93	11	1.4

Table 4. Correlation of TDF and LQF with probability of desquamation.

Criteria	Range	No/Total	Percentage	p value
TDF	44–68	6/237	2.5	<0.001
	69–78	79/400	19.8	
	79–85	50/127	39.4	
LQF (Gy)	38–59	16/369	4.3	<0.001
	60–63	28/136	20.6	
	64–93	91/259	35.1	

Correlation of TDF and LQF with probability of erythema is indicated in Table 2. Both TDF and LQF had statistically significant correlation with probability of erythema. Probability of erythema increased significantly beyond a TDF of 63 and LQF of 48Gy.

Data regarding classification of patients as per TDF and LQF for desquamation are given in Table 3. TDF values ranged from 44 to 85 and the maximum number of patients (47.6%) had TDF ranging from 71 to 80. LQF values ranged from 38 to 93Gy and the maximum number of patients (24.6%) had LQF values ranging from 41 to 50Gy. Correlation of TDF and LQF with probability of desquamation is given in Table 4. Both TDF and LQF indicated a statistically significant correlation with probability of desquamation ($p<0.001$). Probability of desquamation increased significantly beyond a TDF value of 68 and LQF value of 59Gy.

Classification of patients as per TDF and LQF for telangiectasia (score ≥1 at 3 years) is shown in Table 5. TDF values ranged from 46 to 98 and the maximum number of patients (34.2%) had TDF values ranged from 58 to 107Gy and the maximum number of patients (44.3%) had LQF values ranging from 91 to 100 Gy. Correlation of TDF and LQF with probability of telangiectasia (score ≥1 at 3 years) is given in Table 6. TDF and LQF had a statistically significant relationship with probability of telangiectasia ($p<0.001$). Probability of telangiectasia increased significantly beyond a TDF value of 60 and LQF value of 87Gy.

Table 5. Classification of patients as per TDF and ERD (Telangiectasia score 1 at 3 year data).

Criteria	Range	Number	Percentage
TDF	46–50	35	6.3
	51–60	26	4.7
	61–70	190	34.2
	71–80	179	32.3
	81–90	32	5.8
	91–98	93	16.8
ERD (Gy)	58–60	24	4.3
	61–70	11	20.0
	71–80	35	6.3
	81–90	159	28.7
	91–100	246	44.3
	101–107	80	14.4

Table 6. Correlation of TDF and LQF with probability of telangiectasia score 1 at 3 year.

Criteria	Range	No/Total	Percentage	p value
TDF	46–60	14/61	23.0	<0.001
	61–85	169/393	43.0	
	86–96	76/101	75.2	
LQF (Gy)	58–87	50/179	27.9	<0.001
	88–91	60/114	52.6	
	92–107	149/262	56.9	

Table 7. Classification of patients as per TDF and ERD (Telangiectasia score 2 at 5 year data).

Criteria	Range	Number	Percentage
TDF	46–50	31	5.9
	51–60	22	4.2
	61–70	134	25.3
	71–80	172	32.5
	81–90	58	10.9
	91–98	113	21.3
ERD (Gy)	58–60	21	4.0
	61–70	10	1.9
	71–80	34	6.4
	81–90	149	28.1
	91–100	183	34.5
	101–110	78	14.7
	111–114	53	10.4

Table 8. Correlation of TDF and LQF with probability of telangiectasia score 2 at 5 year.

Criteria	Range	No/Total	Percentage	p value
TDF	46–60	9/53	17.0	<0.001
	61–73	68/193	35.2	
	74–98	183/284	64.4	
LQF (Gy)	58–87	39/166	23.5	<0.001
	88–94	69/131	52.7	
	95–114	152/233	65.2	

Classification of patients as per TDF and LQF for relangiectasia (score ≥2 at 5 years) is given in Table 7. TDF values ranged from 46 to 98 and the maximum number of patients (32.5%) had TDF values ranging from 71 to 80. LQF values ranged from 58 to 114 and the maximum number of patients (34.5%) had LQF ranging from 91 to 100Gy. Correlation of TDF and LQF with probability of telangiectasia (score ≥2 at 5 years) is shown in Table 8. TDF and LQF indicated a statistically significant relationship with probability of telangiectasia ($p<0.001$). Probability of telangiectasia increased significantly beyond TDF value of 60 and LQF value of 87Gy.

Classification of patients as per TDF and LQF for telangiectasia (score ≥1 at 10 years) is shown in Table 9. TDF values varied from 47 to 97 and the maximum number of patients (29.7%) had TDF values ranging from 81 to 90. LQF values ranged from 67 to 114Gy and the maximum number of patients (37.5%) had LQF values ranging from 91 to 100Gy. Correlation of TDF and LQF with probability of telangiectasia (score ≥1 at 10 years) is shown in Table 10. TDF and LQF indicated a statistically significant relationship with probability of telangiectasia ($p<0.001$). Probability of telangiectasia increased significantly beyond TDF value of 71 and LQF value of 89Gy.

Classification of patients as per TDF and LQF for telangiectasia (score ≥2 at 10 years) is given in Table 11. TDF values ranged from 47 to 97 and the maximum number of patients (29.8%) had TDF val-

Table 9. Classification of patients as per TDF and ERD (Telangiectasia score 1 at 10 year data).

Criteria	Range	Number	Percentage
TDF	47–50	8	3.1
	51–60	21	8.1
	61–70	23	8.9
	71–80	75	29.0
	81–90	77	29.7
	91–97	55	21.2
ERD (Gy)	67–70	8	3.1
	71–80	31	12.0
	81–90	65	25.1
	91–100	97	37.5
	101–110	0	0.0
	111–114	58	22.4

Table 10. Correlation of TDF and LQF with probability of telangiectasia score 1 at 10 year.

Criteria	Range	No/Total	Percentage	p value
TDF	47–71	42/75	56.0	<0.001
	72–97	169/184	91.8	
LQF (Gy)	67–89	67/104	64.4	<0.001
	90–114	144/155	92.9	

Table 11. Classification of patients as per TDF and ERD (Telangiectasia score 2 at 10 year data).

Criteria	Range	Number	Percentage
TDF	47–50	8	3.2
	51–60	20	8.1
	61–70	30	12.1
	71–80	74	29.8
	81–90	71	28.6
	91–97	53	21.4
ERD (Gy)	67–70	8	3.2
	71–80	31	12.6
	81–90	63	25.5
	91–100	93	37.5
	101–110	0	0.0
	111–114	53	21.4

Table 12. Correlation of TDF and LQF with probability of telangiectasia score 2 at 10 year.

Criteria	Range	No/Total	Percentage	p value
TDF	47–71	24/72	33.3	<0.001
	72–97	143/176	81.3	
LQF (Gy)	67–86	36/81	44.4	<0.001
	87–114	131/167	78.4	

Table 13. Classification of patients as per TDF and ERD (Telangiectasia score 3 at 10 year data).

Criteria	Range	Number	Percentage
TDF	47–50	8	3.4
	51–60	21	9.0
	61–70	22	9.4
	71–80	70	30.0
	81–90	64	27.5
	91–97	48	20.6
ERD (Gy)	67–70	8	3.4
	71–80	29	12.5
	81–90	62	26.6
	91–100	86	36.9
	101–110	0	0.0
	111–114	48	20.6

ues ranging from 71 to 80. LQF values ranged from 67 to 114 and the maximum number of patients (37.5%) had LQF values ranging from 91 to 100Gy. Correlation of TDF and LQF with probability of telangiectasia (score ≥2 at 10 years) is shown in Table 12. TDF and LQF had a statistically significant correlation with probability of telangiectasia ($p<0.001$). Probability of telangiectasia increased beyond TDF values of 71 and LQF value of 86Gy.

Classification of patients as per TDF and ERD for talengiectasia (score ≥3 at 10 years) is given in Table 13. TDF values ranged from 47 to 97 and the maximum number of patients (30.0%) had TDF values ranging from 71 to 80. LQF values ranged from 67 to 114 and the maximum number of patients (36.9%) had LQF values ranging from 91 to 100Gy. Correlation of TDF and LQF with probability of telangiectasia (score ≥3 at 10 years) is given in Table 14. TDF and LQF indicated a statistically significant relationship with probability

Table 14. Correlation of TDF and LQF with probability of telangiectasia score 3 at 10 year.

Criteria	Range	No/Total	Percentage	p value
TDF	47–60	0/29	0.0	<0.001
	61–78	24/92	26.1	
	79–97	80/112	71.4	
LQF (Gy)	67–86	12/79	15.1	<0.001
	87–97	29/62	46.8	
	98–114	63/92	68.5	

Table 15. Classification of patients as per TDF and ERD (Telangiectasia score 4 at 10 year data).

Criteria	Range	Number	Percentage
TDF	47–50	8	3.6
	51–60	21	9.0
	61–70	21	9.0
	71–80	78	34.7
	81–90	61	27.1
	91–97	46	20.5
ERD (Gy)	67–70	8	3.6
	71–80	27	12.1
	81–90	62	27.6
	91–100	81	36.0
	101–110	0	0.0
	111–114	47	20.9

of telangiectasia (p<0.001). Probability of telangiectasia increased significantly beyond TDF value of 60 and LQF value of 86Gy.

Classification of patients as per TDF and LQF for telangiectasia (score ≥4 at 10 years) is shown in Table 15. TDF values ranged from 47 to 97 and the maximum number of patients (34.7%) had TDF ranging from 71 to 80. LQF values ranged from 67 to 114 and the maximum number of patients (36.0%) had LQF values ranging from 91 to 100Gy. Correlation of TDF and LQF with probability of telangiectasia (score ≥4 at 10 years) is given in Table 16. TDF and LQF indicated a statistically significant relationship with probability of telangiectasia (p<0.001). Probability of telangiectasia increased significantly beyond TDF value of 60 and LQF value of 86Gy.

Table 16. Correlation of TDF and LQF with probability of telangiectasia score 4 at 10 year.

Criteria	Range	No/Total	Percentage	p value
TDF	47–60	0/29	0.0	<0.001
	61–78	5/89	5.6	
	79–97	55/107	51.4	
LQF (Gy)	67–86	4/97	4.1	<0.001
	87–97	10/38	26.3	
	98–114	46/90	51.1	

Discussion

Bioeffect dose takes into account treatment variables and the radiobiological characteristics of the relevant tissue. Certainly, experienced radiotherapists are convinced of the existence of patient-to-patient variability in normal tissue response to radiotherapy for malignant tumours. To establish the influence on normal tissues of various prognostic factors requires that a sufficient number of patients be treated with a wide range of fractionation regimens and that sufficient numbers develop complications. The pooling of clinical data from a large multi-institutional experience characterized by a wide diversity of dose fractionation patterns, extending over decades, yields a sufficient number of patients and a wide enough range of variables for correlation of the probability of severe late sequelae. Despite the limitations of retrospective analyses they provide useful radiobiological parameters of normal tissue responses.

Hamilton et al. [14] studied the underprediction of human skin erythema at low doses per fraction by the linear quadratic model. The linear quadratic model significantly underpredicted peak erythema values at doses less than 1.5Gy per fraction. This suggests that either the conventional linear quadratic model does not apply for low doses per fraction in human skin or that erythema is not exclusively initiated by radiation damage to the basal layer. The data are potentially explained by an induced repair model.

Simonen et al. [15] studied the contribution of inflammatory processes in erythema observed in the skin of humans in two prospective trials that evaluated potential effects of topical indomethacin (1%) and hydrocortisone (1%) applied before and during radiotherapy. Drugs were compared

for erythema induced by 20Gy in four fractions (n=26, 6MV) in trial I and effects of topical hydrocortisone (1%) applied before and during radiotherapy and no medication were compared for erythema induced by 1, 3, 5 and 7Gy in five fractions (n=21, 120kV) in trial II, respectively. The authors concluded that inflammatory responses may play a role in the mediation of the erythematous response to radiation in human skin.

Denham et al. [16] determined the influence of changes in dose rate over the range 0.8–240Gy/h on acute oropharyngeal mucosal reactions in human subjects, and estimated the values of the important parameters that influence these reactions. Sixty-one patients requiring radiotherapy to palliate incurable head and neck cancer were treated on a telecaesium unit, using opposing lateral portals to total midline doses, varying between 30 and 42Gy in 10 daily fractions over 2 weeks, at dose rates of 0.8, 1.8, 3.0 and 240Gy/h according to a central composite study design. The severity and time course of reactions were charted at least twice weekly for each patient, using the EORTC/RTOG acute mucosal reaction grading system. Duration of reaction at each grade was observed to provide a more sensitive reflection of effect than the proportion of patients reaching any particular reaction grade. Analysis of duration by direct and indirect methods suggest α/β ratios in the range 7–10Gy and half-time ($t_{1/2}$) values in the range 0.27–0.5h, if mono-exponential repair kinetics are assumed. The $t_{1/2}$ values are short and raise the question as to whether the repair kinetics of this tissue are well described by a mono-exponential function. Further prospective studies involving multiple daily fraction treatment regimes delivered at high dose rate, in which interfraction interval is deliberately varied, are needed to find out whether the parameters derived from this project are applicable to fractionated treatment courses at high dose rate.

Denham et al. [17] studied mucosal regeneration during radiotherapy. Mucosal reactions were observed in 100 patients undergoing conventionally fractionated treatment at 2Gy/day over 7 weeks and 88 receiving accelerated treatment at 1.8Gy twice daily over 31/2 weeks in the Trans-Tasman Radiation Oncology Group head and neck cancer trials. Similar observations in 61 patients treated palliatively using ten 3.0–4.2Gy fractions over 2 weeks are compared. The study suggests that the timing and magnitude of the regenerative response vary between sites and individuals but are linked to the amount of epithelial cellular depletion occurring during treatment.

Turesson et al. [18] studied the predictive value of skin telangiectasia for late radiation effects in different normal tissues. Comprehensive radiopathological studies have shown that vasculoconnective tissue is an important common target for late effects in various organs. Scoring of skin telangiectasia was used as a clinical assay of late tissue effects after different dose schedules. All studies were done prospectively with standardized skin area, field size and radiation quality. The patients were scored regularly up to 10 years. The analysis shows that: 1) ED_{10}/5yr and ED_{50}/5yr for 5×4.0Gy/wk is 50Gy and 65Gy, respectively, for distinct telangiectasia; 2) The latent period, concerning both a certain frequency and degree of reaction, varies exponentially with dose level; 3) The latent period for 50% of patients to obtain a certain score, LP_{50}, is correlated to that for 10%, LP_{10}, with LP_{50}/LP_{10}=2.2±0.2 (S.D.). This correlation is independent of score, total dose, and fractionation; 4) Isoeffective doses for 5×2.0Gy/wk and 2×4.0Gy/wk, determined from the dose-response curves, resulted in repair factors exp N between 0.31 and 0.32 and α/β ratios between 2.9 and 3.1Gy and determined from the dose-latency curves in exp N between 0.30 and 0.32 and α/β ratio between 3.4 and 2.9Gy. In conclusion, frequent and careful follow-up with registration of normal tissue reactions, until at least 10% of the patients have obtained that prescribed effect, is predictive for the further progression of the late effects. The fractionation characteristics for telangiectasia agree well with those for animal experimental morphological and functional endpoints for late effects in different organs and support the relevance of telangiectasia as a model for predicting late effects.

Bentzen et al. [19] analysed the methodological problems in estimating radiobiological parameters from clinical data. A number of biological, dosimetric and statistical problems encountered in the determination of α/β ratios and the relative biological efficiency (RBE) of high energy electrons are discussed. As a practical example, the dose-response relationships for severe erythema and subcutaneous fibrosis are discussed in two series of patients treated with post-mastectomy irradiation with electrons and photons in two fractionation schedules. Because of a different dose per fraction in the electron and photon fields, determination of RBE requires a fraction size correction. This is performed using that α/β

formalism. This analysis suggests a high energy electron RBE for severe erythema of 0.93 (95% confidence limits 0.89 and 0.96) and for subcutaneous fibrosis of 0.84 (95% confidence limits 0.77 and 0.92).

Baltas et al. [20] analyzed the late effects data using dose-response models for human skin telangiectasia. The clinical data for skin telangiectasia from previous prospective studies at the Radiotherapy Department in Gothenborg are reanalyzed using two dose response models – the general formulation of the well known linear-quadratic (LQ) and NSD isoeffect models. The results show that within the interval of the number of fractions used, 10–35 fractions, the NSD model gives predictions comparable to those of the LQ model. For number of fractions smaller than 5, a high discrepancy occurs between the two models, the NSD model predicting higher values of the isoeffective total dose. Based on the estimated dose response curves, considering the telangiectasia as the decisive late tissue effect, the requirement for the combined uncertainty in the dose delivery is estimated at between 3 and 4.5%.

Turesson et al. [21] studied repair capacity and kinetics of human skin during fractionated radiotherapy after 3 and 5 years of follow-up. The clinical assay consisted of breast cancer patients irradiated postoperatively to the internal mammary nodes from unilateral or bilateral fields exposed to various dose schedules. Unexpectedly, there was no significant time factor during radiotherapy courses up to 6 weeks for erythema and desquamation, but the repair capacity was changed after 4 weeks for both endpoints, and α/β increased to between 18.3 and 34.5Gy. The repair capacity for late telangiectasia differed significantly from that for erythema and desquamation, with α/β values as 2.8 and 4.3Gy. There was a significant time factor for talangiectasia with characteristic doubling time of about 16 days, when an exponential function for time was used. The time factor and the relatively long half-time for repair for late effects have important implications for multiple-fraction-per-day treatment, and imply that interfraction intervals of 4h or less, as commonly used, will be insufficient. Instead, intervals of 6h or longer are recommended. Using accelerated fractionation with a significant reduction in overall treatment time, a dose reduction is still necessary to take into account the time factor for late effects. Further data are necessary for more reliable estimates of the time factor and the repair kinetics for both acute and late effects.

Turesson et al. [22] analysed skin telangiectasia and head and neck morbidity and studied the characteristics of dose-response relationships for late radiation effects. One, 2 and 5 fractions per week and 3 to 4 dose levels per schedule were used for this study. The following parameters were determined for each schedule and the equivalent single dose-response curves for each endpoint using probit analysis: ED_{50}, the absolute steepness, measured as the probit width, K; the relative steepness, K/ED_{50}; and the normalized effect gradient, γ_{50}. The α/β value was found to be independent of the degree of telangiectasia used as endpoint. The absolute steepness of the dose-incidence curve increased with increasing dose per fraction and was correlated to the degree of damage. The relative steepness was independent of the dose per fraction when the dose-response curve was generated by a fixed dose per fraction, and was less than if generated by a fixed number of fractionations. The relative steepness increased with higher degree of damage. The highest steepness determined for relangiectasia score ≥4 (partially confluent or more) at 10 years corresponded to K=0.8Gy, K/ED_{50}=5%, γ_{50}=7 and D_0=0.7Gy. The dose response characteristics found for late skin telangiectasia score ≥2 to ≥4 were consistent with those determined for necrosis and fatal complications 5 years after radiotherapy for head and neck tumours.

Maciejewski et al. [23] studied the acute and late effects on normal tissue responses with dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx. The severity of acute responses correlated with dose intensity. The incidence of severe late responses increased with increase in dose per fraction and was characterized by a low α/β ratio. Severe late responses were significantly associated with severe acute responses independently of dose per fraction and total dose, and were also ameliorated slightly by protraction of treatment time, suggesting that some late effects were, at least partly, a consequence of acute injury. Probability of local tumour control correlated with severity of acute response, suggesting that excessive protraction of overall treatment time to minimize acute toxicity may compromise local control of the tumour. There was no demonstrable correlation between the volume of tissue irradiated and the severity of acute or late responses.

Hopewell et al. [24] studied reappraisal of the importance of the overall treatment and its effects on radiosensitization and incomplete repair

with dose fractionation on early and late responses in pig skin. A simple approach to a time factor could not be used to calculate iso-effect doses for acute reactions in pig skin when treatment time was increased from ≤16 days to 28–39 days. This was due to the opposing effects of radiosensitization and repopulation when the cell cycle time of epidermal basal cells was shortened. For late dermal necrosis in pig skin, repair of sublethal damage was not completed in 24 hours. This finding has a significant effect on the interpretation of the results of fractionation studies using this late endpoint. Many of the fractionation effects reported for acute and late damage to pig skin would appear to be in excellent agreement with those for human skin.

Bentzen et al. [25] studied the relationship between early and late normal tissue injury after postmastectomy radiotherapy. Patients who developed moist desquamation had a statistically significantly increased risk of developing telangiectasia after a specific course of radiotherapy. As an example the estimated incidence of severe telangiectasia after 44Gy in 22 fractions increases from 27% to 49% in patients who developed grade ≥2 moist desquamation as an early radiation reaction. A reanalysis of the Aarhus data with telangiectasia as the endpoint gave an α/β ratio at 2.8Gy and a relative biological effectiveness (RBE) of high energy electrons relative to 8MV photons at 0.89. Patients' age or the occurrence of severe erythema did not predispose to telangiectasia. A similar predisposition after moist desquamation was not seen for subcutaneous fibrosis.

Turesson et al. [26] analysed the prognostic factors for acute and late skin reactions in 402 breast cancer patients. Multivariate analyses were performed with peak reflectance erythema and peak acute reaction score as endpoints for the acute reactions, and with progression rate of telangiectasia as well as telangiectasia score as endpoints for the late reactions. Twenty patient- and treatment-related factors were tested, such as age, menopausal status, haemoglobin level, serum calcium, smoking habits, hypothyroidism, diabetes, hypertension, blood pressure, cardiovascular and autoimmune disease, the influence of hormone therapy and chemotherapy, pretreatment reflectance value, acute skin reactions, radiation quality, individual dose, bilateral fields, and the total effect (TE) for the dose schedule applied. The TE was a strong prognostic factor for all endpoints. The only independent prognostic factors found for the progression of skin telangiectasia and telangiectasia score except for TE were the individual dose and acute skin reactions.

Conclusions

We analysed the clinical data of patients for erythema, desquamation and telangiectasia on the basis of bioeffect models. TDF and LQF had a statistically significant correlation with probability of erythema, desquamation and telangiectasia. TDF and LQF values should be limited to 60 and 86Gy in order to limit the probability of telangiectasia.

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