ff

GSI-Preprint-97-24
April 1997

SCAN-9705077

CERN LIBRARIES, GENEVA

**ACUTE RESPONSE OF PIG SKIN TO IRRADIATION WITH
¹²C-IONS OR 200 kV X-RAYS**

509721

T. ZACHARIAS, W. DÖRR, W. ENGHARDT, TH. HABERER, M. KRÄMER, R. KUMPF,
H. RÖTHIG, M. SCHOLZ, U. WEBER, G. KRAFT, TH. HERRMANN

Gesellschaft für Schwerionenforschung mbH
Planckstraße 1 • D-64291 Darmstadt • Germany
Postfach 11 05 52 • D-64220 Darmstadt • Germany

Acute response of pig skin to irradiation with ¹²C-ions or 200 kV X-rays

T. Zacharias¹, W. Dörr¹, W. Enghardt¹, Th. Haberer³, M. Krämer³, R. Kumpf²,
H. Röthig¹, M. Scholz³, U. Weber³, G. Kraft³, Th. Herrmann¹

¹ Klinik und Poliklinik für Strahlentherapie der Medizinischen Fakultät Carl Gustav Carus der Technischen Universität, Fetscherstr. 74, D-01307 Dresden, Germany

² Experimentelles Zentrum der Medizinischen Fakultät Carl Gustav Carus der Technischen Universität, Fetscherstr. 74, D-01307 Dresden, Germany

³ Gesellschaft für Schwerionenforschung, Biophysik, Planckstr. 1, D-64291 Darmstadt, Germany

Address for correspondence: Dr. Wolfgang Dörr
Klinik und Poliklinik für Strahlentherapie
Fetscherstr. 74
D-01307 Dresden
Germany

++int 49 351 458-3390
Fax ++int 49 351 458-4339 or -4347
Email DOERR@RCS.URZ.TU-DRESDEN.DE

Running title: Acute pig skin response to ¹²C-ion irradiation

Abstract

The acute response of pig skin to treatment with high energy carbon ions (plateau region) at the Gesellschaft für Schwerionenforschung (GSI, Darmstadt, Germany) was compared to changes after 200 kV X-irradiation. Carbon doses isoeffective to the X-ray doses were computed with a recently established model for calculation of the biological effect of heavy ions (1, 2). Clinical changes and physiological symptoms (blood flow, erythema, trans-epidermal water loss, skin hydration) were scored. The parameters analyzed were maximum and mean values of each symptom during days 24 to 70 post irradiation, and the quantal endpoints for the establishment of dose-effect curves were the median values of these. With exception of the maximum change in the red blood cell concentration ($p < 0.02$) no significant differences could be found in the response to X-rays and RBE-corrected heavy ions. These results indicate that the model is valid for the calculation of biological effects of ^{12}C -ions (plateau region) and may at least for epidermis be applied to treatment planning.

Introduction

An attracting approach to increase tumour cure rates without affecting normal tissue toxicity is the modulation of physical dose distribution, aiming at maximum dose within the target volume with a steep fall-off at the margins.

In the case of conventional radiotherapy with photons or electrons, three-dimensional treatment planning and sophisticated treatment techniques allow substantial normal tissue sparing which in consequence may result in decreased normal tissue toxicity with similar local control rates, or increased cure rates without aggravated normal tissue damage. This has been demonstrated e.g. for tumours of the prostate (3, 4).

Alternatively, the physical properties of heavy charged particles like protons or heavier ions (^{12}C , ^{20}Ne) may be exploited for these purposes. The particular advantage of such particle beams is an inverse depth-dose distribution along the track of the beam: While only minor energy deposition is observed in the entrance channel, indicating complete lack of build-up processes in the skin, a marked dose maximum is achieved at the end of the particle trajectory - the Bragg peak - and a steep fall-off beyond the peak position. This physical depth-dose distribution is accompanied by systematical changes of the relative biological effectiveness (RBE) with the depth in biological material. The RBE, however, depends on and can hence be modulated by the choice of ions and energy applied.

Pilot clinical studies of heavy ion radiotherapy at the Lawrence Berkeley Laboratory (5, 6) and at the HIMAC facility in Chiba, Japan (7) showed

encouraging results despite disadvantageous patient selection. An experimental heavy ion radiotherapy unit at the Gesellschaft für Schwerionenforschung, Darmstadt, Germany (GSI) using the beams of the heavy ion synchrotron SIS is now under construction (8). The maximum ranges in tissue as well as the intensities of ion beams delivered by SIS exceed the requirements of patient treatments, since the accelerator was originally designed for fundamental research in heavy ion physics.

A major prerequisite for the treatment of human cancer with heavy ions, however, is a reliable method for the estimation of the biological effect, both in the target volume and in surrounding structures. A mathematical model for the estimation of RBE and dose with biological (cell nucleus size), radiobiological (cellular radiosensitivity, fractionation effect) and physical components (track structure) has been established by Scholz and Kraft (1, 2). However, mainly in vitro data (9, 10) and only limited information from animal experiments on tumours (Jüling-Pohlitz, pers. comm.) and normal tissues (11) have been available for testing of the model. The present study, therefore, was initiated to validate the formalism for in vivo endpoints of radiation damage. Skin fields of minipigs were treated with doses of ^{12}C -ions or 200 kV X-rays which were regarded isoeffective, and the response of these organs after irradiation was quantified. The present manuscript reports the results for the acute epidermal response in these investigations.

Materials and methods

Animals and housing

Six pigs of the Mini-Lewe strain at an age of about 12 months, weighting 50-60 kg, were used in the present experiments. They were kept under conventional conditions in the animal house of the University Hospital Dresden. All six animals were housed in one box of 10.5 m². Two weeks of acclimatization were allowed before transportation to GSI Darmstadt, where the pigs were housed during the time of treatment under conditions similar to those in Dresden.

Irradiation

Before the start of the experiments, circular treatment fields (diameter 5 cm) were defined at the back of the animals and marked by tattooing after skin shaving. Three fields were positioned at the right and left part of the back, respectively, at about 9.5 cm (left side) and 11.5 cm (right side) distance of the margins from the median line. The distance between the margins of adjacent fields on either side was about 5 cm.

Carbon ion beams accelerated by the heavy ion synchrotron SIS at GSI were applied for charged particle treatments. The specific energy of the beam was varied between 90.0 and 185.0 MeV/amu, yielding a maximum range of 8 cm with a width of the extended out Bragg-peak of 6 cm, which was localized in the subcutaneous fatty tissue and beyond. Accordingly, the epidermis was in the entrance plateau region of the heavy ion beam. The heavy ion dose was delivered by a raster scanning device (12), which sweeps a pencil-like beam

of about 5 mm full width at half maximum over the treatment field by means of magnetic deflection. This gives rise to a typical dose rate within the beam spot of about 1 Gy/ms, whereas the time for delivering a surface dose of 2.35 Gy to the complete field was about 6 min. The desired depth dose distribution was produced by applying ions of 185.0 and 142.5 MeV/amu which were slowed down by means of a digital range shifter.

For X-irradiation, an ISOVOLT 320/13 device (Seifert Röntgenwerke, Ahrensburg, Germany) was operated at 200 kV with a tube current of 20 mA. A 1.0 mm Cu filter was introduced into the beam. The resulting dose rate at the focus-skin distance of 20 cm was 4.1 Gy/min.

X-ray dosimetry was performed with an ionization chamber M31003 (PTW Freiburg, Germany) connected to a dosimeter UNIDOS (PTW). The X-ray depth dose was measured in a tissue-like phantom and the surface dose was determined by regression and subsequent extrapolation. The dose and the penumbra of the X-ray beam was measured by means of densitometry of a radiograph exposed at the skin surface.

Dosimetry of the carbon beam was performed by means of ionization chambers, which were calibrated using nuclear track detectors. In these detectors the tracks of individual ions can be counted and the particle fluence can be correlated to the corresponding ionization chamber current. For particles of a given energy and thus fixed LET and a fluence Φ the dose in material of density ρ is obtained by

$$D = \Phi \cdot LET / \rho$$

and the total dose is obtained by summing up the contributions of all particle energies.

Treatment of all skin fields irrespective of radiation quality was carried out under one anaesthesia session. Sedation of the animals was achieved by Azaperone injected intramuscular at a dose of 3 mg/kg. Before anaesthesia a premedication by combined intramuscular application of Atropine (0.02 mg/kg) and Diazepam (0.5 mg/kg) was given. Anaesthesia was initiated by intramuscular injection of Ketamine (50 mg/kg) and Xylazine (2 mg/kg) and maintained for about 100 min. at maximum by subcutaneous injection of Ketamine 10-15 mg/kg after 30-45 min. Vacuum pillows were used for reproducible lateral positioning of the pigs. All skin fields were irradiated with 5 equal fractions in 5 days. The ^{12}C -ions were delivered to the fields at the right side of the back, with doses per fraction at the surface of 2.35 Gy, 4.7 Gy, and 7.05 Gy. Using the model established by Scholz and Kraft (1, 2) these doses were estimated to be isoeffective to X-ray doses of 3.8 Gy, 6.7 Gy, and 9.3 Gy, respectively, and are hence denoted as 3.8 Gye (Gray equivalent), 6.7 Gye, and 9.3 Gye. The carbon doses at a skin depth of 10 mm were between 102 and 104% of the surface doses. The "Gye"-nomenclature will be used in the subsequent text for the description of ^{12}C -doses.

X-irradiation was performed of the fields at the left side of the back of the animals, the doses at the skin surface were 3.8, 6.7 and 9.3 Gy/F. The X-ray doses at a skin depth of 5 mm and 10 mm - the range were epidermal-dermal

border is located - were estimated to be about 95% and 91% of the surface doses, respectively.

While the distribution of both radiation qualities between right and left skin fields was impracticable for technical reasons, the doses of each beam were randomly distributed between the fields at the respective side of the back.

Clinical examination

Macroscopic changes after treatment were recorded according to the scoring system depicted in table I. Skin fields were examined with a cold light source by 3-5 independent investigators twice weekly for 10 weeks post irradiation.

Physiological measurements

The investigation of changes in skin physiological parameters included characteristics of the skin blood flow (flux and concentration of blood cells), transepidermal water loss (TEWL), erythema, and skin hydration. All values were defined at similar time points once weekly from day 7 p. irr., and for each series of measurements. Sedation of the animals was achieved by intramuscular injection of Azaperone at a dose of about 2.5 mg/kg. For each parameter, the results of the in-field measurements were compared to data collected at the same time at defined unirradiated skin areas at least 2 cm apart from the respective treatment field, in order to correct for the influence of environmental factors. The latter appeared necessary as all measurements were performed in the animal house.

Measurements of *skin blood flow* parameters were carried out with a Laser Blood Flow Monitor DRT 4 (Moore Instruments). Four control measurements at each side of the back were used to establish control values. Three measurements within each treatment field were performed. For *TEWL* measurements, a Tewameter TM210 (Courage & Khazaka) was used. Four control measurements were carried out per side, and the mean values were compared to one in-field measurement. *Erythema* scores were achieved by reflectometry using a Mexameter MX16 (Courage & Khazaka). Results from 6 in-field measurements were compared to a total of 12 control measurements per side of the back. *Skin hydration* was assessed with a Corneometer CM820 (Courage & Khazaka) at 6 positions within each treatment field and 12 control measurements per side.

Statistical analysis

For each day of clinical examination, the median value of the individual scores was calculated for each skin field. The endpoints used for the quantitative description of the clinical radiation response were (i) the maximum score for each field between days 24 and 70, and (ii) the mean score during this time period. To establish dose-response relationships, the threshold response for quantalization was a maximum score of 3.5 or a mean score of 2.0, i.e. fields with higher values were regarded to show a positive radiation response.

For all physiological measurements, each data point (d) was expressed as the relative deviation (RD) from the control value (co) in untreated skin monitored

at identical time points, i.e. $RD=(d-co)/co$. For all RD data of the individual parameters, the maximum and mean value for each skin field between day 24 and 70 were calculated as endpoints. From these 36 data for each endpoint, the respective median was defined and used for quantalization. The detailed threshold changes used are summarized in table II.

From the quantalized data, dose response curves were established by probit analysis using the SAS analytical software (13,14). The most prominent parameters to describe the results are the ED50-values, i.e. doses to achieve a positive response in 50% of the treated skin fields, and their standard deviation σ . Corresponding dose-effect curves were compared using a log likelihood ratio χ^2 -test (13). With this method, p-values were calculated on the basis of a normal distribution function and without defining a threshold response rate. In addition, an analysis of variance was performed for each data set, with radiation quality as the source parameter, and the results of the respective measurements as the dependent variables. For this, the General Linear Models Procedure of the SAS software (14) was applied.

Results

The time course of macroscopic changes for all radiation doses of both radiation qualities is illustrated in fig. 1. First responses, which were clearly different from the control level of about 0.50 were observed after day 32. This time of onset of the response appeared to be independent of both dose and radiation quality. Subsequently the scores rapidly increased to reach dose-dependent maxima after day 45. Healing of the moist response was observed in most cases by day 73.

The frequency of fields with a maximum response of >3.5 or a mean response >2.0 was used to establish dose response relationships for both radiation qualities. For the maximum clinical scores the resulting ED50-values and their standard deviations were 33.5 ± 1.9 Gy or Gye after treatment with X-rays and carbon ions, respectively, as well as for the mean scores after carbon treatment. Analysis of mean scores after X-ray irradiation yielded a slightly increased ED50 of 34.8 ± 10.3 Gy. The corresponding dose-effect curves were identical for the maximum score ($p=1.0$), and similar for the mean score ($p=0.8$). For neither endpoint a substantial difference of the curves could be observed. Similarly, the analysis of variance did not reveal any significant difference between the response to carbon ions or X-rays with $p=0.94$ and $p=0.52$ for maximum and mean scores, respectively. For the untreated skin at the back of the pigs, control values for the physiological parameters (mean $\pm$ SD) were: blood flux 23 ± 8 RU (relative units), concentration of red blood cells

124 $\pm$ 27 RU, TEWL 12 $\pm$ 1.5 g/m²/h, erythema 550 $\pm$ 11 RU, and skin hydration 10 $\pm$ 2.5 RU.

The results of the probit analysis of changes in the physiological measurements by radiation quality and dose are summarized in table III. With exception of the red blood cell concentration, none of the parameters did show a significant difference after irradiation with either X-rays or carbon ions in doses that were predicted to be isoeffective to the X-ray doses. The ED50 values for an increase in maximum red blood cell concentration by 58% were 42.5 $\pm$ 8.8 Gy after X-irradiation and 27.6 $\pm$ 13.0 Gye after heavy ion treatment, with a significant difference at $p < 0.02$. However, the mean concentration over days 24-73 did not show a significant difference ($p = 0.70$). In addition, the analysis of variance for the maximum concentration, similarly to all other parameters tested for, did not reveal a significant difference ($p = 0.7456$). In face of the similarity in almost all parameters tested for, the apparent difference for the maximum change in red blood cell concentration must be regarded an outlier.

Discussion

The use of heavy ions, especially of carbon, from the GSI heavy ion synchrotron is intended for the treatment of human cancer, particularly for advanced malignancies of brain, trunk, pelvis and extremities, in the forthcoming years. The estimation of the biologically effective ion dose, in a target volume covered by primary and secondary particles of different energies, requires complex mathematical models that take into account the substantial variations of the RBE within the irradiated volume. This is caused by the change of LET along the particle tracks and by the conversion of the treatment primary particles to those with a lower atomic number via nuclear fragmentation reactions. Validation of these models both by cell culture studies and in-vivo investigations in experimental animals and with a variety of clinically relevant biological endpoints is necessary. Irradiation of the skin with significant doses is inevitably associated with radiotherapy of deep seated tumours, and hence in the present study the epidermal response to carbon ions and X-rays was compared. For this, the carbon doses were adjusted to be isoeffective to the X-ray doses on the basis of a recently developed mathematical model (1, 2).

The model used for the calculation of RBE values is based on the knowledge of the spatial microscopical dose distribution inside the charged particle tracks. In contrast to X-rays, where the energy is deposited quite homogeneously, the energy distribution of heavy ions is concentrated around the trajectories of the particles and is thus more inhomogeneous on a μm scale. The high local doses in the center of the track lead to the increased biological efficiency of the

particles. The biological effective dose is determined by folding the spatial local dose distribution with the X-ray dose response curve. It could be shown that according to this model RBE values are largely determined by the shape of the shoulder of the X-ray dose response curve, i.e. by the α_x/β_x -ratio. Thus the model can be applied to complex biological endpoints like normal tissue complications, for which the α_x/β_x -ratio is known (2).

In radiobiological studies pig skin should be used rather than rodent skin, since the latter shows substantial anatomical differences to human skin. However, the consequence of using large animals is that only few animals can be incorporated in the individual experiments. Therefore, although several skin fields may be treated per animal, the amount of data is considerably less than in rodent experiments. Therefore, the statistical value of such experiments has to be regarded with caution.

In the present study, six animals were used. In each minipig, 3 skin fields were given either carbon ions or X-rays, respectively, and 3 doses of each radiation quality were applied. Hence, a total of 3 fields were available for dose response analysis, and the possible response frequencies therefore were limited to 0%, 33%, 67%, or 100%.

A number of parameters of the radiation response were tested. Most important macroscopic epidermal changes have been quantified according to a scoring system adopted from clinical practice (15) and, with minor modifications, extensively used in radiobiological pig skin studies (16, 17, 18). In addition, a number of physiological changes associated with the acute skin response, like

increased blood flow, erythema, or loss of the skin barrier function, have been assessed.

For none of the parameters assessed with exceptions of the red blood cell concentration, a significant difference could be established between the dose-effect of X-rays and carbon ions, when the carbon doses are modified according to the RBE values predicted by the model of refs. (1, 2). It can therefore be concluded that the model is valid for these calculations at least for acutely responding surface epithelia like skin or mucosa. However, further information on the predictive capacity of the model for late radiation sequelae and for the effect in the Bragg peak region is required to test for a general applicability of the model in future heavy charged particle radiotherapy in patients.

Acknowledgements

The authors kindly acknowledge the support of Dr. H. Alheit, P. Geyer, P. Henzel, C. Geipel, J. Kulig and M. Reimann (Medizinische Fakultät der TU Dresden), of W. Becher and G. Lenz (GSI Darmstadt) as well as of R. Hinz and M. Sobiella (Research Center Rossendorf Inc). We are indebted to the accelerator and radioprotection staffs of the GSI Darmstadt for their cooperation. Furthermore, we thank K. Reimers of the Richard Seifert GmbH, Röntgenwerk, Ahrensburg, Germany for providing an X-ray device and installing it temporarily at GSI Darmstadt.

The present experiments were supported by the Deutsche Forschungsgemeinschaft grant number He1985/2-1 and were carried out with permission of the Regierungspräsidium Dresden according to the valid animal welfare legislation (number 75-9185.81-1.4/94).

References

1. Scholz, M., Kraft, G. Calculation of heavy ion inactivation probabilities based on track structure, X-ray sensitivity and target size. *Radiat. Prot. Dosim.* 1994; 52: 29 - 33.
2. Scholz, M. Calculation of RBE for normal tissue complications based on charged particle track structure. *Bull. Cancer* 1996; submitted.
3. Leibel, S.A., Heimann, R., Kutcher, G.J., Zelefsky, M.J., Burman, C.M., Melian, E., Orazem, J.P., Mohan, R., LoSasso, T.J., Lo, Y.-C., Wiseberg, J.A., Chapman, D.S., Ling, C.C., Fuks, Z. Three-dimensional conformal radiation therapy in locally advanced carcinoma of the prostate: preliminary results of a phase I dose-escalation study. *Int. J. Radiat. Oncol. Biol. Phys.* 1993; 28: 55-65.
4. Soffen, E.M., Hanks, G.E., Hunt, M.A., Epstein, B.E. Conformal static field radiation therapy treatment of early prostate cancer versus non-conformal techniques: a reduction in acute morbidity. *Int. J. Radiat. Oncol. Biol. Phys.* 1992; 24: 485-488.
5. Castro, J.R., Reimers, M.M. Charged particle radiotherapy of selected tumours in the head and the neck. *Int. J. Radiat. Oncol. Biol. Phys.* 1988; 14: 711 - 720.

6. Castro, J.R., Saunders, W.M., Austin-Seymour, M.M., Woodruff, K.H., Gaucher, G., Chen, G.T.Y., Collier, J.M., Phillips, T.L., Zink, S.R. A phase I-II trial of heavy charged particle irradiation of malignant glioma of the brain: a Northern California Oncology Group study. *Int. J. Radiat. Oncol. Biol. Phys.* 1985; 11: 1795 - 1800.
7. Tsujii, H., Morita, S., Hiyamoto, T., Mizoe, J., Mukai, M., Nakano, T., Morita, K. Clinical experiences of HIMAC carbon-ion therapy at NIRS. 5th Workshop on Heavy Charged Particles in Biology and Medicine, Darmstadt, Germany, Aug. 1995, *GSI Report* 1995; 9: 167 - 170.
8. Gademann, G., Hartmann, G.H., Kraft, G., Lorenz, W.-J., Wannenmacher, M. The medical heavy ion therapy project at the Gesellschaft für Schwerionenforschung facility in Darmstadt. *Strahlenther. Onkol.* 1990; 166: 34 - 39.
9. Wulf, H., Kraft-Weyrather, W., Miltenburger, H.G., Blakely, E.A., Tobias, C.A., Kraft, G. Heavy-ion effects on mammalian cells: Inactivation measurements with different cell lines. *Radiat. Res.* 1985; 104: 122-134.
10. Kraft, G. Radiobiological effects of very heavy ions: Inactivation, induction of chromosome aberrations and strand breaks. *Nucl. Sci. Appl.* 1987, 3: 1-18.

11. Leith, J.T., McDonald, M., Powers-Risius, P., Bliven, S.F., Howard, J.
Response of rat spinal cord to single and fractionated doses of accelerated heavy ions. *Radiat. Res.* 1982; 89: 176-193.
12. Haberer, Th., Becher, W., Schardt, D., Kraft, G. Magnetic scanning system for heavy ion therapy. *Nucl. Instr. Meth. Phys. Res. A* 1993; 330: 296-305.
13. SAS Institute Inc., *SAS/STAT User's Guide Version 6*. 4th edn., Cary, NY. U.S.A., 1990; 1633-1640.
14. SAS Institute Inc., *SAS/STAT User's Guide, Version 6*. 4th edn., Cary, NY. U.S.A., 1990; 1324-1350.
15. Hopewell, J.W., Foster, J.L., Gunn, Y., Moustafa, H.F., Patterson, T.J.S., Wiernik, G., Young, C.M.A. Role of vascular damages in the development of late radiation effects in pig skin. In: *Late Effects of Ionising Radiation*. Vol. I., IAEA, Vienna, 1978; 483-492.
16. Hopewell, J.W., Van den Aardweg, G.J.M.J. Current concepts of dose fractionation in radiotherapy. Normal tissue tolerance. *Br. J. Radiol.* 1988; Suppl. 22: 88-94.

17. Van den Aardweg, G.J.M.J., Arnold, M., Hopewell, J.W. A comparison of the radiation response of the epidermis in two strains of pig. *Radiat. Res.* 1990; 124: 283 - 287.
18. Van den Aardweg, G.J.M.J., Hopewell, J.W., Simmonds, R.H. Repair and recovery in the epithelial and vascular connective tissues of pig skin after irradiation. *Radiother. Oncol.* 1988; 11: 73-82.

Table I: Arbitrary scoring system applied for the description of acute macroscopic skin reactions after irradiation with X-rays or ^{12}C -ions

Score	Symptoms
0	none
0.5	erythema questionable
1.0	minimum erythema
1.5	mild erythema
2.0	intermediate erythema
2.5	pronounced erythema
3.0	dry desquamation, intense erythema
3.5	dry desquamation, maximum dark-red erythema
4.0	moist desquamation, <1/2 field
4.5	moist desquamation, =1/2 field
5.0	moist desquamation, >1/2 field

Table II: Clinical and physiological parameters assessed to quantify the radiation response in pig skin.

Parameter	MED _{max}	MED _{mean}
clinical score	3.5	2.0
blood flow velocity	130	32
red blood cell concentration	58	12
erythema score	5	1.94
TEWL	100	50
hydration	67	-2.85 (0)

Summarized are the postirradiation (day 24-70) median values for maximum (MED_{max}) and mean relative deviation (MED_{mean}) of the scores of the individual skin fields from the control values taken at identical time point in untreated skin. These median values were used to establish threshold values for the quantalization of the post-irradiation data. Numbers in parenthesis indicate threshold values different from median values.

Table III: Dose-effect for X-rays and carbon ions

Parameter	beam	ED50 [Gy]	σ [Gy]	p_{probit}	p_{anova}
<i>clinical score</i>					
max	C	33.5	1.9	1.0	0.94
	X	33.5	1.9		
mean	C	33.5	1.9	0.8	0.52
	X	34.8	10.3		
<i>blood flux</i>					
max	C	33.5	1.9	0.54	0.45
	X	30.5	9.6		
mean	C	28.4	8.8	0.11	0.06
	X	38.0	14.0		
<i>red blood cell concentration</i>					
max	C	42.5	8.8	0.02	0.48
	X	27.6	13.0		
mean	C	33.1	14.2	0.7	0.11
	X	29.7	20.3		
<i>erythema score</i>					
max	C	30.5	9.6	0.4	0.14
	X	35.5	14.2		
mean	C	33.1	14.2	0.71	0.05
	X	35.5	14.2		
<i>TEWL</i>					
max	C	32.7	1.9	0.25	0.31
	X	34.3	1.8		
mean	C	33.5	1.8	1.0	0.14
	X	33.5	1.8		
<i>hydration</i>					
max	C	32.7	1.9	0.42	0.64
	X	35.5	14.2		
mean	C	33.5	1.9	0.44	0.36
	X	39.4	19.5		

ED50-values and their standard deviation σ , resulting from probit analysis of the dose-effect of carbon ions (C) and X-rays (X) for the various parameters tested. A log likelihood maximum χ^2 -test was used to compare the dose effect curves and to compute the values p_{probit} . ANOVA of all response data was applied to achieve values p_{anova} for the significance of radiation quality on the parameter studied.

Legends to figures

Figure 1

Time course and extent of clinical changes in pig skin after irradiation with graded doses of X-rays or carbon ions. Physical carbon doses of 2.35 Gy, 4.7 Gy, and 7.05 Gy corresponding to 3.8, 6.7, and 9.3 Gye, respectively were applied per fraction, which were calculated using the model of Scholz and Kraft (1, 2) to be isoeffective to X-ray doses of 3.8 Gy, 6.7 Gy, and 9.3 Gy. Scoring was performed according to the parameters described in table I. Data points represent median values from 3-5 independent investigators.

Fig. 1

Zacharias et al.

Acute responses of pig skin to irradiation with ^{12}C -heavy ions or 200 kV X-rays