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Single dose irradiation response of pig skin: a comparison of brachytherapy using a single, high dose rate iridium-192 stepping source with 200 kV X-rays

P C J HAMM, MSc, E J BAKKER, BSc, A P VAN DEN BERG, PhD, G J M J VAN DEN AARDWEG, PhD, A G VISSER, PhD and P C LEVENDAG, MD, PhD

Department of Radiation Oncology, University Hospital Rotterdam-Daniel den Hoed Cancer Centre, Groene Hilledijk 301, Rotterdam, The Netherlands

Abstract. An experimental brachytherapy model has been developed to study acute and late normal tissue reactions as a tool to examine the effects of clinically relevant multifractionation schedules. Pig skin was used as a model since its morphology, structure, cell kinetics and radiation-induced responses are similar to human skin. Brachytherapy was performed using a microSelectron high dose rate (HDR) afterloading machine with a single stepping source and a custom-made template. In this study the acute epidermal reactions of erythema and moist desquamation and the late dermal reactions of dusky mauve erythema and necrosis were evaluated after single doses of irradiation over a follow-up period of 16 weeks. The major aims of this work were: (a) to compare the effects of iridium-192 (^{192}Ir) irradiation with effects after X-irradiation; (b) to compare the skin reactions in Yorkshire and Large White pigs; and (c) to standardize the methodology. For ^{192}Ir irradiation with 100% isodose at the skin surface, the 95% isodose was estimated at the basal membrane, while the 80% isodose covered the dermal fat layers. After HDR ^{192}Ir irradiation of Yorkshire pig skin the ED_{50} values (95% isodose) for moderate/severe erythema and moist desquamation were 24.8 Gy and 31.9 Gy, respectively. The associated mean latent period ($\pm$SD) was 39 ± 7 days for both skin reactions. Late skin responses of dusky mauve erythema and dermal necrosis were characterized by ED_{50} values (80% isodose) of 16.3 Gy and 19.5 Gy, with latent periods of 58 ± 7 days and 76 ± 12 days, respectively. After X-irradiation, the incidence of the various skin reactions and their latent periods were similar. Acute and late reactions were well separated in time. The occurrence of skin reactions and the incidence of effects were comparable in Yorkshire and Large White pigs for both X-irradiation and HDR ^{192}Ir brachytherapy. This pig skin model is feasible for future studies on clinically relevant multifractionation schedules in a brachytherapy setting.

Good results, with low radiotoxicity, have been obtained for tumours in the head and neck, breast, bladder, cervix and uterus using external beam radiotherapy combined with brachytherapy. In brachytherapy, low dose rate (LDR) sources have traditionally been used. However, over the past decade substantial technical progress has been made, resulting in the clinical use of afterloading machines with a high dose rate (HDR) stepping source. These afterloading machines undoubtedly have technical and logistic advantages over LDR line sources, including dose optimization, mobility of the patient between HDR fractions, treatment on an outpatient basis and a reduction in radiation exposure to personnel [1–3].

Mathematical models have already been proposed for a comparison of clinical LDR data with those from fractionated HDR schedules [2, 4–7]. The first clinical HDR studies indicated good results in terms of tumour cure and normal tissue sparing [8–11]. However, doubts have been raised about the validity of these mathematical models in relation to the therapeutic ratio and in particular to the duration of interfraction intervals and dose distribution [11–16]. To overcome these problems, so-called pulsed dose rate (PDR) brachytherapy was proposed for exploiting radiobiological advantages obtained with LDR irradiation together with the logistic advantages of fractionated HDR brachytherapy. For PDR brachytherapy, mathematical models have also been proposed, and PDR schedules equivalent to LDR treatment have been calculated [2, 7, 17].

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Address correspondence to Dr G J M J van den Aardweg.

Present address for Dr A G Visser: Radian, Joint Center for Radiation Oncology Arnhem–Nijmegen, University Hospital Nijmegen, The Netherlands.

The first clinical and experimental PDR data have been published, suggesting equivalence between LDR and PDR schedules [17, 18]. Nevertheless, concerns still remain owing to a limited knowledge of the half times for repair of sublethal damage in various (normal) tissues and of the effects of very short intervals between multiple daily fractions [19]. Therefore, experimental studies are required to improve knowledge of radiation-induced responses in normal tissues. Recently, new research has been initiated in our radiobiology laboratory to investigate the effects of brachytherapy on normal tissues to provide further critical testing of new clinical fractionation strategies. Within the framework of this research, acute epidermal and late dermal skin responses have been studied in pig skin. Pig skin has been used as a model because its structure, morphology and cell kinetic properties are very similar to human skin [20–35]. Although skin is not normally a dose-limiting tissue in brachytherapy, adverse reactions have occasionally been seen in patients after implantations for breast-conserving treatment [36].

The results obtained from experimental brachytherapy, as performed with a microSelectron HDR afterloading machine (Nucletron, Veenendaal, The Netherlands), were compared with data from an existing type of irradiation, *i.e.* single doses of X-rays, because X-rays are widely used as standard treatment in radiobiological research and because the Oxford group has published skin data for Large White pigs using X-rays. This offers the possibility to compare simultaneously pig strains and types of irradiation.

Part of the present study was the establishment of the experimental model. This required verification of our choice of pig strain and brachytherapy method using available knowledge. The design of the template and dose distribution specification are presented. The purebred Yorkshire pig was chosen because this strain is readily available in The Netherlands. Time-related changes in the skin responses of Yorkshire pigs have been described in great detail [20, 21]. Archambeau et al [22, 23] also demonstrated that the skin of Yorkshire pigs had sufficient similarities with human skin to support our choice of pig strain. In Oxford (UK), extensive radiobiological research has been carried out using the skin of Large White pigs as a model for human skin [28, 32, 34, 35, 37–42]. Therefore, our data on the incidence and latencies of the skin reactions for the Yorkshire pig are compared with those for the Large White pig. In addition, three Dutch Large White pigs were irradiated with HDR iridium-192 (^{192}Ir).

A further aim of this study was the standardization of logistics. Special attention was paid to the method of marking skin fields on the flanks of the pigs, assessment of the skin reactions, transport, feeding and housing of the animals, and anaesthetic procedures.

Materials and methods

In this single dose study, 16 immature female purebred Yorkshire pigs were used, 10 for teletherapy and 6 for brachytherapy irradiations. All pigs were obtained from a registered breeder. During the study the animals were kept in the animal facilities at the Erasmus University, Rotterdam (EUR). Ten pigs were housed individually, the other six as two per pen.

On arrival, the pigs were allowed an acclimatization period of 11 days. At the start of treatment the pigs had an average weight of 25 kg. 6 or 7 days prior to irradiation, the hair on the flanks was clipped and fields were marked with India ink [28]. For the X-irradiations a total of eight fields, 4 cm × 4 cm, was tattooed on the left flank, four on the dorsal area and four on the ventral area. All fields were separated by 4 cm (Figure 1). For brachytherapy irradiation, 30 fields, 3 cm × 3 cm, 15 fields on each flank, were used. The fields were positioned in three rows of five fields, one each on the dorsal, lateral and ventral area of the flank. All fields were separated by 3 cm (Figure 1). In addition, three female Large White pigs were tattooed in a similar way.

Tattooing was performed using a sharp, 2 mm long needle to pierce the skin. India ink was drawn through the needle by capillary action into the skin. These marks persisted throughout the follow-up period.

For 24 h prior to anaesthesia and irradiation the pigs had no access to solid food, but had access to water *ad libidum.* On the day of irradiation the pigs were transported in a custom-designed container from the EUR to the Daniel den Hoed Cancer Center (DDHCC), a journey time of approximately 20 min. Before transport the animals were sedated by a combined injection of ketamine (10 mg kg^{-1} im; Ketalin^{R} pi, Apharmo, The Netherlands) and atropine (0.05 mg kg^{-1} im; Atropini sulfas, Pharmachemie B.V., The Netherlands). After sedation of the first 10 pigs this pre-medication was changed to reduce saliva production. About 30 min before transport the pigs were injected with a combination of Stresnil^{R} (0.2 mg kg^{-1} im; ACF Chemiefarma nv, The Netherlands) and ketamine (10 mg kg^{-1} im).

At the DDHCC the larynx was locally anaesthetized using a lidocaine spray (Xylocaine^{R} 10% spray; Astra Pharmaceutica BV, The Netherlands) to facilitate endotracheal intubation. This was followed by full inhalation anaesthesia with a gas mixture of approximately 70% oxygen, 30%

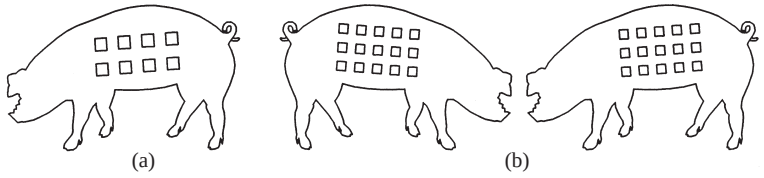

Figure 1. Distribution of skin fields over the flank of the pigs. a, orthovolt X-irradiation; b, high dose rate ^{192}Ir irradiation.

nitrous oxide and 1–2% halothane (Fluothane, ICI Pharmaceuticals, UK) [27].

Single doses of X–rays were given using a Philips Orthovolt RT250 machine (Eindhoven, The Netherlands) operating at 200 kV and 20 mA with a 1 mm copper filter and a 10 cm × 8 cm applicator. The source-to-skin distance (SSD) was 30 cm. The surrounding skin was shielded against radiation with a 3 mm thick lead mould of 13 cm × 13 cm with a central aperture of 4 cm × 4 cm.

A total of 76 fields was irradiated with single doses ranging from 13.3–35.2 Gy, randomly distributed over the 10 pigs. Only 6 out of 10 pigs received a dose of 35.2 Gy because during the follow-up of the first pigs this dose seemed to cause internal complications. After irradiation the pigs were returned to the EUR.

During X–irradiation, extensive dosimetry was carried out to establish the dose rate. On 62 fields, three thermoluminescent dosemeters (TLDs) were used per field. The maximum difference between the TLD measurements was ±5% per field. TLD dosimetry was calibrated by means of ionization chamber measurements in a water phantom at different depths. The mean dose rate (±SD) was 1.87 ± 0.03 Gy min^{-1}.

Brachytherapy irradiations were performed using a microSelectron HDR afterloading device with a single ^{192}Ir stepping source. During irradiation, four parallel afterloading catheters were placed in a flexible silicone template [43–45] that was applied to the marked skin field. The distance between two neighbouring catheters was 1 cm in a single plane geometry. In each catheter, seven dwell positions separated by a distance of 0.5 cm were defined, covering a total length of 3 cm. The SSD distance was 0.5 cm.

Dose distributions were calculated using the Nucletron Planning System (NPS version 11.2; Veenendaal, The Netherlands) applying so-called dwell time optimization on a set of dose points at the skin surface. By using variable dwell times a uniform dose distribution can be obtained over the 3 cm × 3 cm field. The relative dwell weights per dwell position are presented in Table 1. The dose distribution was specified at the skin surface in the centre of the field. The delivered dose at a certain depth of irradiated tissue is described by the isodose (Figure 2). In this pig skin model the epidermal thickness is approximately 90 μm, which is mainly covered by the 95% isodose. The dermis, which is around 1500 μm in depth, is covered by the 80% isodose. A total of 180 skin fields was irradiated with doses ranging from 18–43 Gy (100% isodose level) in 10 dose steps. The doses were equally distributed over the dorsal, lateral and ventral area of six Yorkshire pigs. The dose rate at the skin surface varied from about 1.6 Gy min^{-1} to 0.8 Gy min^{-1}, as a consequence of radioactive decay over a 3-month period using an ^{192}Ir source.

Twice a week, three observers assessed the irradiated skin fields using a scoring system that describes separately the acute epidermal reactions of erythema, and dry and moist desquamation, and the late dermal reactions of dusky mauve erythema and dermal necrosis. This scoring system was developed to study radiation reactions in the skin of Large White pigs [35]. Erythema was assessed at several levels: absent, mild, moderate and severe, with intermediate variants. Moist desquamation, dusky mauve erythema and dermal necrosis were assessed for their absence or presence in each field.

Radiation studies in the Large White pig [35, 38], where the skin responses were assessed at weekly intervals, demonstrated that a follow-up period of 16 weeks was sufficient to investigate both acute and late skin reactions. Archambeau et al [20–22] studied acute epidermal and late dermal responses in the Yorkshire pig with a follow-up period of about 17 weeks. On this basis it was decided that a follow-up period of 16 weeks would be adequate.

To characterize the development of skin reactions, both the time of occurrence (latent period) and the incidence were used as parameters. The latent period for a particular skin reaction is calculated as the number of days between irradiation and occurrence of the reaction. The possible influence of dose on this parameter and the degree of interanimal and intraanimal variations were analysed using correlation and analysis of variance for the 10 pigs receiving X-irradiation.

For the skin reactions of moist desquamation, dusky mauve erythema and dermal necrosis, the endpoint was the incidence of any degree of reaction. For erythema, the endpoint included the incidence of moderate and severe responses only. The incidence of the skin reactions was evaluated using logit analysis to derive dose response curves and to estimate the associated ED_{50} values (±SE and 95% CI), that is the dose required to obtain a

Table 1. Relative dwell times of the high dose rate ^{192}Ir source for each source position in a single plane geometry

Position (0.5 cm spacing)	Parallel afterloading catheters at 1 cm spacing			
	Catheter 1	Catheter 2	Catheter 3	Catheter 4
1	1.00	0.76	0.76	1.00
2	0.50	0.31	0.31	0.50
3	0.50	0.31	0.31	0.50
4	0.55	0.36	0.36	0.55
5	0.50	0.31	0.31	0.50
6	0.50	0.31	0.31	0.50
7	1.00	0.76	0.76	1.00

reaction in 50% of skin fields. Significant differences between ED_{50} values were evaluated by Student's *t*-test.

Results

The latent periods for all skin reactions both in Yorkshire and Dutch Large White pigs after X-irradiation and HDR ^{192}Ir irradiation are presented in Table 2. Data obtained from the literature [39, 41] for the English Large White pig have been added for comparison. Ten of the pigs receiving X-irradiation were kept under observation for up to 7 months after irradiation. The appearance of a significant skin reaction for the first time occurred no later than 14.5 weeks after irradiation for all doses used.

Moist desquamation after X–irradiation was confounded by skin damage not related to irradiation. From the point of view of animal welfare, it was attempted to house two pigs together. Playful fights between those pigs resulted in skin damage to some of the irradiated fields prior to the onset of moist desquamation. Consequently, 6 of the 76 irradiated fields had to be excluded from the analysis.

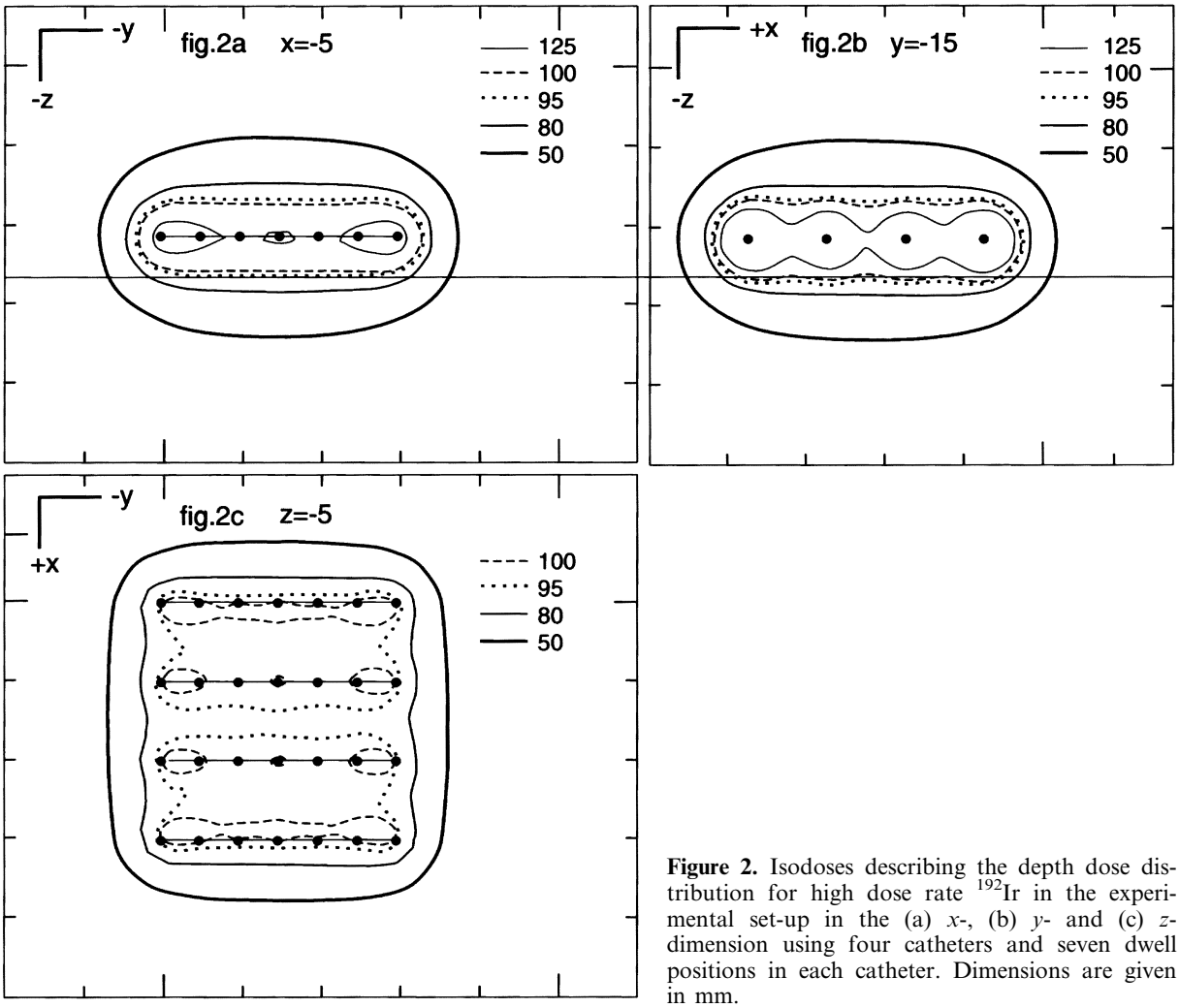

Figure 2. Isodoses describing the depth dose distribution for high dose rate ^{192}Ir in the experimental set-up in the (a) *x*-, (b) *y*- and (c) *z*-dimension using four catheters and seven dwell positions in each catheter. Dimensions are given in mm.

Table 2. Latent periods (days ± SD) for acute and late skin reactions in Yorkshire and Large White pigs. Pig skin was irradiated with either X–rays or high dose rate (HDR) ^{192}Ir. (n=number of skin fields developing radiation damage)

Skin reaction	Yorkshire pigs		Large White pigs	
	X-rays	HDR ^{192}Ir	HDR ^{192}Ir	HDR ^{90}Sr/Y (Oxford data)[a]
Erythema	43 ± 8 (n=44)	39 ± 7 (n=98)	39 ± 9 (n=61)	—
Moist desquamation	48 ± 8 (n=21)	39 ± 7 (n=57)	35 ± 9 (n=28)	36 ± 3
	X–rays	HDR Ir-192	HDR Ir-192	X–rays (Oxford data)[b]
Dusky mauve erythema	63 ± 6 (n=53)	58 ± 7 (n=139)	56 ± 9 (n=74)	—
Necrosis	80 ± 13 (n=44)	76 ± 12 (n=93)	82 ± 8 (n=40)	76 ± 3

[a]High dose rate strontium/yttrium-90 [41]. [b]Reference [39].

Moist desquamation developed between 5 and 8 weeks after irradiation, while dermal necrosis developed between 9.5 and 14.5 weeks after irradiation. After teletherapy, the acute and late skin reactions were well separated in time. There was always a period of healing between recovery from moist desquamation and onset of dermal necrosis, indicating that these two skin reactions were indeed independent events. In 23 out of the 72 skin fields irradiated with HDR ^{192}Ir, the occurrence of moist desquamation and dermal necrosis overlapped for doses of 33 Gy and higher (100% isodose). Since dermal necrosis had already reached an incidence of 100% for these higher doses, these 23 skin fields were excluded from analysis.

Several factors, which may have influenced the latent period of a particular skin reaction, were investigated. The latent period, defined as the number of days between irradiation and the first appearance of the skin reaction, was analysed for the 10 animals that received X-irradiation. The influence of dose was investigated first, since higher doses might result in a shorter latent period. The correlation coefficients for the four different skin reactions were not significant; r varied between -0.06 and -0.20, from which it was concluded that the latent period did not depend significantly on the size of the radiation dose over the dose range studied. Therefore, all latent period data from the different dose groups were pooled together for further analysis.

All fields from these 10 pigs were used in an analysis of variance to investigate possible differences in latency between animals in relation to field positions. The latent periods for moist desquamation, dusky mauve erythema and dermal necrosis were significantly different between the 10 individual pigs ($p<0.02$ for each endpoint), but were independent of the flank position of the field. Skin reactions of the four dorsal fields had a similar latent period to those of the four ventral fields ($p>0.2$).

The mean latent periods after HDR ^{192}Ir irradiation were consistent for both Yorkshire and Large White pigs. In Yorkshire pigs, the mean latent period observed after X-irradiation was slightly longer than that seen after HDR ^{192}Ir brachytherapy. For erythema, the mean latent period (± SD) was 43 ± 8 days after X-irradiation and 39 ± 7 days after HDR ^{192}Ir irradiation. Moist desquamation started at 48 ± 8 days after X-irradiation and at 39 ± 7 days after brachytherapy. Late responses occurred a few weeks later; dusky mauve erythema at 63 ± 6 days and 58 ± 7 days after X-irradiation and HDR ^{192}Ir irradiation, respectively. Dermal necrosis was observed at 80 ± 13 days and 76 ± 12 days after X-irradiation and HDR ^{192}Ir, respectively.

In the Dutch Large White pig irradiated with HDR ^{192}Ir, moderate/severe erythema occurred after 39 ± 9 days, while moist desquamation was seen after 35 ± 9 days, dusky mauve erythema after 56 ± 9 days and dermal necrosis after 82 ± 8 days. These data were not significantly different from those obtained for the English Large White pig [39, 41] with a latent period of 36 ± 3 days for moist desquamation and of 76 ± 3 days for dermal necrosis.

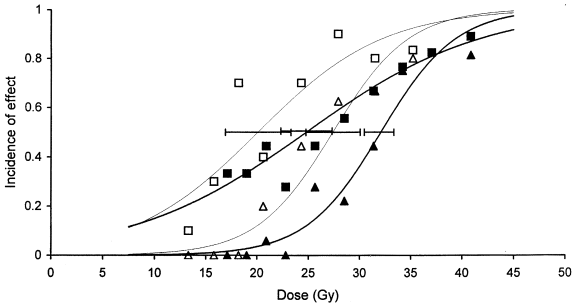

Figure 3. Dose–response curves for the incidence of acute epidermal reactions of erythema (□, ■) and moist desquamation (△, ▲) after X-irradiation (thin lines) and high dose rate ^{192}Ir (bold lines). Error bars indicate 95% confidence intervals. (Error bars on individual data points omitted for convenience.)

Table 3. ED_{50} values in Gy (95% confidence interval) for acute and late skin reactions in Yorkshire and Large White pigs. Pig skin was irradiated with X-rays or with high dose rate (HDR) ^{192}Ir

Skin reaction	Yorkshire pigs		Large White pigs	
	X-rays	HDR ^{192}Ir (95% isodose)	HDR ^{192}Ir (95% isodose)	HDR $^{90}Sr/Y$ (Oxford data)[a]
Erythema	20.1 (16.9–23.3)	24.8 (22.3–27.3)	14.8 (8.0–21.7)	20.4 (17.8–23.0)
Moist desquamation	27.4 (24.7–30.0)	31.9 (30.4–33.3)	29.2 (26.9–31.6)	27.8 (26.0–29.6)
	X–rays	HDR ^{192}Ir (80% isodose)	HDR ^{192}Ir (80% isodose)	X-rays (Oxford data)[a]
Dusky mauve erythema	17.8 (17.0–18.5)	16.3 (15.5–17.1)	14.0 (13.2–14.8)	18.6 (17.6–19.6)
Necrosis	20.0 (19.2–20.7)	19.5 (18.8–20.1)	17.1 (15.8–18.4)	20.5 (19.7–21.3)

HDR $^{90}Sr/Y$, high dose rate strontium/yttrium-90.
[a] References [28, 34, 39, 41].

Dose–response curves for the acute skin reactions after single doses of X-rays and HDR ^{192}Ir are presented in Figure 3. The slopes of the curves for the incidence of erythema and moist desquamation are not significantly different. The curves show a shallow slope, characteristic of acutely responding tissues. The ED_{50} values and the 95% confidence interval (CI) for all skin reactions in the Yorkshire and Dutch Large White pig are summarized in Table 3. The ED_{50} values for the various skin reactions in the English Large White pig have been added for comparison [28, 34, 39, 41]. The ED_{50} values for erythema (moderate and severe reactions) are reasonably consistent, with the exception of 14.8 Gy (8.0–21.7 Gy) found after ^{192}Ir irradiation in Large White pigs. The ED_{50} value (95% CI) of 31.9 Gy (30.4–33.3 Gy) for moist desquamation after HDR ^{192}Ir in Yorkshire pigs is significantly higher than that of 27.4 Gy (24.8–30.0 Gy) obtained after single doses of X-rays. The Dutch Large White pig irradiated with HDR ^{192}Ir gave an ED_{50} value for moist desquamation of 29.2 Gy (26.9–31.6 Gy), which was not significantly different from that obtained for the Yorkshire pig.

The dose–effect relationships of the late skin reactions are presented in Figure 4. The curves for dusky mauve erythema and dermal necrosis show a steeper slope compared with those for the acutely responding tissues. The slope of the X-ray curve for dusky mauve erythema alone could not be established since there is only one single informative data point between 0% and 100% incidence. The combined data for both late end-points are therefore used for analysis, assuming no significant differences in the slopes of the dose–effect curves.

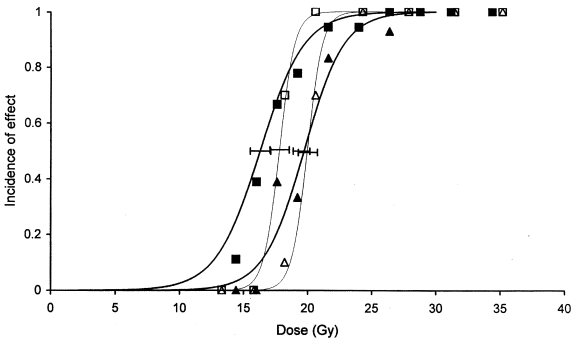

Figure 4. Dose–response curves for the incidence of late dermal reactions of dusky mauve erythema (□, ■) and necrosis (△, ▲) after X-irradiation (thin lines) and high dose rate ^{192}Ir (bold lines). Error bars indicate 95% confidence intervals. (Error bars on individual data points omitted for convenience.)

The ED_{50} values for dusky mauve erythema (Table 3) were lower for HDR ^{192}Ir treatment compared with X-irradiation, which was independent of pig strain. The ED_{50} values for dermal necrosis in Yorkshire pigs were consistent for both X-irradiation and HDR ^{192}Ir irradiation, and in agreement with those for the English Large White pig (Oxford data). The only exception was the ED_{50} value of 17.1 Gy (15.8–18.4 Gy) for the Dutch Large White pig, which is significantly lower than the other values.

Discussion

A pig model of normal tissue effects in the skin following irradiation was evaluated. Several properties of this model were investigated, which included end-point assessment, biological comparison with other (pig skin) models and the method of irradiation.

Assessment of pig skin reactions in small fields is usually done under light anaesthesia to immobilize the pig. This can be avoided by assessing the animals while they are eating, provided field sizes are large enough. The size used in this study (4 cm × 4 cm, or 3 cm × 3 cm) proved adequate to apply this more animal-friendly method.

In the clinical situation, the most commonly used methods to assess skin reactions are ones following the European Organization for Research on Treatment of Cancer (EORTC)

and The Radiation Therapy Oncology Group (RTOG) grading criteria. To study the development and recovery of radiation damage in pig skin, a similar ordinal scoring system, based on visual assessments, has been used. Four different types of reactions were seen during the follow-up period of 16 weeks. Acute epidermal-related reactions of erythema and moist desquamation developed and healed in the first 10 weeks after irradiation, while late dermal reactions of dusky mauve erythema and necrosis were seen between 10 and 16 weeks after irradiation. After irradiation with doses less than 33 Gy, moist desquamation always healed completely before the onset of dermal necrosis, indicating that these were independent skin reactions.

Erythema, reddening of the skin, is difficult to assess objectively by visual means. The reaction is caused by an increase in blood volume in the papillary dermis as a result of inflammation. Visual assessment of erythema is susceptible to observer variations and has poor reproducibility. To overcome the limitations of this visual method, skin erythema can be assessed by reflectance spectrophotometry [46–53]. A limitation in this method is the confounding influence of moist desquamation or pigmentation in the irradiated area on the outcome of these measurements. Comparative studies showed a lack of correlation between visual observation and reflectance spectrophotometry measurements [52, 53]. In the present study, doses were chosen such that there were always skin fields showing moist desquamation and erythema at the same time. Therefore, reflectance spectrophotometry was not suitable.

Moist desquamation occurs as a result of epidermal loss due to sterilization of a high proportion of clonogenic cells in the basal layer [35]. The skin breaks open and serum leaks to the surface causing the moist reaction. Macroscopically, moist desquamation looks like a scab or graze, a superficial damp wound. Recovery is the result of repopulation from surviving clonogenic cells. Healing of moist desquamation also progresses from the edges of the skin field [22, 40]. For a proper evaluation of radiation-induced moist desquamation it is necessary to prevent the skin from being otherwise damaged, *e.g.* by playful fights between pigs. For this reason the pigs had to be housed separately.

Visual assessment of the late dermal reactions is relatively straightforward. Dusky mauve erythema is the reaction by which the skin becomes pale rose to violet and purple as a result of vascular damage in the dermis. Necrosis of dermal tissues is a consequence of vascular insufficiency [35]. Macroscopically, dermal necrosis looks like a scab lying deeply in the skin. The crust is dark reddish brown to black because of the presence of coagulated blood cells.

One of the aims of the present study was the justification of our choice of Yorkshire pig as a skin model by verifying that many of the properties were similar to those of the Large White pig. In Oxford, UK, extensive radiobiological experiments have been carried out using the skin of Large White pigs as a model for human skin [27, 28, 32, 34, 35, 38]. Large White pigs are rarely available in The Netherlands, while Yorkshire pigs are readily available. Since the Yorkshire pig originated from the Large White pig these two strains show great resemblance. Archambeau et al [20–23] used the skin of Yorkshire pigs in their radiobiological studies. Their results were comparable with the Oxford data, which supported our choice for the Yorkshire pig in radiobiological studies on normal tissues. Nevertheless, a small additional experiment was carried out to underline this choice. The acute and late skin reactions of three Dutch Large White pigs irradiated with HDR brachytherapy were compared with the results of our Yorkshire data (HDR ^{192}Ir and X-irradiation) and with the Oxford Large White data (HDR strontium-90 and X-irradiation). The incidence of the various skin responses and their latencies were comparable.

The latent period for the development of different skin lesions appeared to be independent of the pig strain and method of irradiation. The relatively longer latent periods for erythema and dusky mauve erythema after X-irradiation were due to variations in the time of assessment. The number of days between two assessments was 3 or 4 days, while in other studies this period was 7 days, explaining a difference in latent period of 4 or 5 days. The only exception is the latent period for moist desquamation after X-irradiation, which is significantly longer than that obtained after HDR ^{192}Ir (Table 2). The latent period was independent of dose, an effect that was also seen for the development of ulcers in the mouse oral mucosa [54].

The ED_{50} values (Table 3) for acute and late skin reactions did not show significant systematic differences between the different pig strains and the methods of irradiation. Nevertheless, some of the values seemed to deviate from this pattern. This may be merely owing to statistical fluctuation, but might also point to some specific biological differences. The erythema response in Large White pigs after ^{192}Ir treatment was relatively low, but showed extreme heterogeneity, precluding the detection of any small difference. In Yorkshire pigs the ED_{50} value for moist desquamation was slightly higher for ^{192}Ir brachytherapy than for X–irradiation. In this case,

difficulties in the assessment of desquamation may have played a role. Dry desquamation appeared as white, parchment-like skin flakes without any serum at the skin surface. A very mild form of moist desquamation was seen as skin flakes similar to those for dry desquamation, but with a dark brownish heart containing coagulated blood as proof of skin breakdown and leakage. Because of these slight differences between dry and moist desquamation, which are sometimes difficult to distinguish, an underestimation of the number of skin fields developing moist desquamation could occur. For the late skin reactions observed after ^{192}Ir irradiation, small differences between Yorkshire and Large White pigs were seen. The ED_{50} values for both dusky mauve erythema and necrosis were slightly lower in Large White pigs. Since these end-points can be assessed with good accuracy, some underlying biological differences could not be fully excluded.

Conclusions

Published data already indicated that pig skin is a good model for human skin in radiobiological experiments. Overall, the present data indicate that the radiation effects are not evidently dependent on the strain of pig used. Irradiation of the skin with an HDR ^{192}Ir stepping source is feasible and radiobiological equivalent to X-irradiation. Both early and late skin responses could be studied in the same fields because of a clear separation of their occurrence in time. The method is sufficiently characterized and standardized to investigate multiple daily fractionation schedules and the kinetics for sublethal damage repair.

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