

# Fluoroscopically Guided Interventional Procedures: A Review of Radiation Effects on Patients' Skin and Hair<sup>1</sup>

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Most advice currently available with regard to fluoroscopic skin reactions is based on a table published in 1994. Many caveats in that report were not included in later reproductions, and subsequent research has yielded additional insights. This review is a consensus report of current scientific data. Expected skin reactions for an average patient are presented in tabular form as a function of peak skin dose and time after irradiation. The text and table indicate the variability of reactions in different patients. Images of injuries to skin and underlying tissues in patients and animals are provided and are categorized according to the National Cancer Institute skin toxicity scale, offering a basis for describing cutaneous radiation reactions in interventional fluoroscopy and quantifying their clinical severity. For a single procedure performed in most individuals, noticeable skin changes are observed approximately 1 month after a peak skin dose exceeding several grays. The degree of injury to skin and subcutaneous tissue increases with dose. Specialized wound care may be needed when irradiation exceeds 10 Gy. Residual effects from radiation therapy and from previous procedures influence the response of skin and subcutaneous tissues to subsequent procedures. Skin irradiated to a dose higher than 3–5 Gy often looks normal but reacts abnormally when irradiation is repeated. If the same area of skin is likely to be exposed to levels higher than a few grays, the effects of previous irradiation should be included when estimating the expected tissue reaction from the additional procedure.

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**A**fter an interval of more than a half century, reports of fluoroscopically induced skin injuries reappeared in the literature in the early 1990s. These reports coincided with the introduction of fluoroscopically guided interventional procedures into the clinical armamentarium. The American College of Radiology and the Food and Drug Administration (FDA) convened a workshop on “fluoroscopic” skin injury in 1992. FDA advisory notices on fluoroscopically induced skin injury were published in 1994 (1,2). Since then, numerous reports, workshops, and advisory reports have been devoted to managing the risk of fluoroscopically induced skin injuries. In 2007, the National Council on Radiation Protection and Measurements assembled a report committee on radiation risk associated with fluoroscopically guided interventional procedures. The committee is currently preparing a report on radiation management for fluoroscopically guided procedures, and has critically reviewed the available literature on fluoroscopically induced skin injuries. This review revealed that most of the guidance developed in the past decade was based on a table in a paper by Wagner and colleagues (3). While this table has been cited and reproduced

in many publications, many of the accompanying caveats in the original paper were ignored or inadequately emphasized (4–6). Some of the guidance appearing in later reports also appears to have been confounded by mixing the effects of fractionated radiation therapy treatments with single dose accidental or interventional exposures.

The present review represents a consensus reached by the authors of the current understanding of radiation-induced skin injury resulting from single interventional procedures. Limited numbers of published case reports are available. This article is based on a review of the literature and on individual unpublished case reports that were made available to the authors. Permission to anonymously publish information and images from these unpublished case reports included in this review was provided by each patient.

### Background

Radiation-induced skin damage is a well-known complication of radiation therapy. In the past 2 decades it has been recognized as a rare complication of fluoroscopically guided interventional procedures (3,5,7–14). Skin damage can occasionally be caused by the cumulative dose from multiple diagnostic procedures, each of which is individually insufficient to cause injury (15).

Fluoroscopy-related radiation-induced skin reactions are almost always unanticipated. Mild reactions that heal on their own occur occasionally and can be an acceptable side effect when the benefits of the procedure improve the patient’s quality of life. On rare occasions, severe injuries can be an unavoidable life-saving necessity. To be able to minimize the likelihood of severe outcomes, to anticipate such outcomes when necessary, and to make informed benefit-risk decisions about radiation injury, the physician should know how to manage radiation so as to properly conserve dose, should be able to monitor radiation dose, and should know how to use the dose data to effectively anticipate and manage the outcome. Methods to conserve and monitor

dose are discussed in detail elsewhere (14,16–20).

Radiation reactions can be severe and clinically devastating. Although commonly referred to as skin injuries, severe radiation injuries can extend into the subcutaneous fat and muscle (21). Patients may face years of associated pain, multiple surgical procedures, and permanent disfigurement (5,11,22). Injuries are typically located on the patient’s back (14,23). Injuries to scalp hair and the skin of the arm or breast may also occur (11,14).

The treatment of major radiation-induced injuries can be very complex and require the combined skills of an experienced team consisting of wound care specialists, dermatologists, plastic surgeons, and others. The best guidance that can be given in this review is to refer patients with these injuries to experienced providers for appropriate treatment. All available information on the radiogenic origin of the injury must be supplied to the treating team.

Dermatologists are sometimes the first physicians to see patients with these injuries. They are typically faced with a diagnostic dilemma when a patient presents with a skin lesion but provides no history of radiation exposure (12,22,24). This can occur because patients who undergo fluoroscopically guided interventional procedures may not realize that fluoroscopy involves the use of radiation and because the interventionalist did not advise them of the need for follow-up (22). Without such information, diagnosis is often delayed by months, even though the phenomenon of radiation-induced skin reactions is well known to dermatologists owing to their experience with radiation oncology patients (9,10).

Interventionalists have mistakenly attributed the occurrence of prompt

### Essentials

- The minimum radiation dose causing a specific type of reaction in the skin or hair is best expressed in terms of a range of doses, rather than a single threshold dose.
- The times of onset and resolution of specific radiation injuries are best expressed as a range of times since exposure.
- For most patients, clinically important skin and hair reactions occur only when the skin dose is higher than 5 Gy.
- Residual effects from radiation therapy and from previous procedures influence the response of skin and subcutaneous tissues to subsequent procedures.

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#### Abbreviation:

NCI = National Cancer Institute

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radiation-induced skin reactions (a sign of a very high radiation dose) to an allergic response to defibrillator pads or to injury from grounding electrodes used for electrocautery. This can lead to unnecessary dermatologic diagnostic procedures (eg, punch biopsy), secondary complications, and a delay in diagnosis. A radiation origin should be the primary consideration for all anatomically appropriate skin lesions occurring within a few months of a fluoroscopically guided interventional procedure unless an alternative cause can be unambiguously established.

Appropriate follow-up is essential when the patient has received a dose of radiation where there is a reasonable possibility that skin effects may occur. Medical professionals need answers to specific questions: (a) What skin effects can be expected from the radiation dose the patient received? (b) What general advice should be given to the patient? (c) How should the patient be followed up? Current answers to these questions are based on estimates of threshold radiation doses from the published literature. Many published guidelines use fixed threshold doses as the basis for their recommendations, leading the casual reader to believe that threshold doses can be determined with precision and are universally applicable (4–6).

Skin dose–effect tables, such as those recently presented by the International Commission on Radiological Protection and the Centers for Disease Control and Prevention, are based on a mixture of data obtained from accidental irradiations, clinical radiation therapy, and a range of radiobiologic experiments (4–6). These tables are of limited value because they combine data from different kinds of irradiations in a hierarchy of threshold doses without correcting for differences in the type and time course of the irradiation. Additionally, their focus is on highly radiosensitive individuals. The tables also neglect the variability of responses of the skin located in different parts of the body. The influence of each of these factors is discussed later.

Many of the reproductions of the original table also included an extra

column indicating the fluoroscopy time needed to cause each effect. This practice is misleading and can be dangerous. Fluoroscopy time is an extremely poor indicator of the risk of skin injury because it does not account for either fluoroscopic dose rates or the use of fluorographic acquisition modes (eg, digital subtraction angiography, cine radiography) during a procedure. In a study of radiation dose in interventional radiology procedures (25), the variation in the relationship between peak skin dose and fluoroscopy time was two orders of magnitude for most of the procedures evaluated. Fluoroscopy time should not be relied on as the sole dose metric for complex interventional procedures.

### Clinical Use of Radiation

Fluoroscopically-guided interventional procedures are performed by using x-ray beams with peak voltages ranging from 50 to 125 kVp and with filtrations ranging from the minimum permitted up to 1 mm of copper. Dose rates at the skin surface range from less than 1 mGy/min (very-low-dose-rate fluoroscopy) to several grays per minute (digital subtraction angiography or cine angiography in a large patient). These values vary from machine to machine and, in most cases, with the exact clinical mode selected to perform a particular procedure. Single procedure peak skin doses on the order of several tens of grays have occurred (14). The same region of a patient's skin may be irradiated during a subsequent procedure, occurring hours to years after the preceding procedure. These irradiation patterns differ from those associated with most therapeutic and accidental exposures.

Radiation therapy with 250-kVp x-ray beams (orthovoltage radiation therapy) provides a great deal of insight into the effects of radiation on skin (26–29). The physical dose distribution near the skin surface produced by 250-kVp x-ray beams is not too dissimilar from modern fluoroscopic beams. Dose rates to skin were usually in the range of several hundred milligrays per minute. Orthovoltage radiation therapy was, for the

most part, replaced by therapy with higher energy x-ray beams by the late 1970s. The maximum dose delivered by beams in the million-volt range occurs at a depth of millimeters to centimeters below the skin. The build-up of dose below the surface can minimize injury of skin. This is often called *skin sparing*.

Because orthovoltage radiation therapy does not exhibit skin sparing, clinical radiation therapy with orthovoltage equipment was prescribed in a manner that minimized skin injury by allowing repair of sublethal radiation damage and some tissue regeneration between treatment fractions (30,31). A typical orthovoltage prescription was 2–3 Gy per fraction to the skin, usually given in five fractions per week, for a treatment course of approximately 6 weeks. Single-field skin doses were always higher than the tumor doses. Because of this, multiple-field treatment plans were used as a means of delivering a higher dose to the tumor than to the skin. The transfer of experience from orthovoltage radiation therapy to fluoroscopy is relevant. However, some individual interventional procedures result in skin doses of a few tens of grays; these high single-fraction doses are outside of most radiation therapy experience.

Skin dose is influenced by x-ray field size. Backscatter from the patient increases with increasing field size. Appendix A in ICRU report 74 presents detailed information (32). For typical interventional fluoroscopic beams, the backscatter factor is in the range of 25%–40%. Skin dose is higher than air kerma at the skin by a field-size-independent factor of 1.06. An additional physical factor related to field size is the increased likelihood of overlap between two or more larger fields in comparison to smaller fields.

The clinical concept that field size influences the radiation response of the skin first came from the publication in the 1940s of tables of skin tolerance doses for different areas of human skin exposed to orthovoltage radiation (30,31,33). The same dose delivered

to different-sized fields will produce the same initial reaction. For a small field, the dose prescribed as tolerance resulted in moist desquamation because the small area did heal quickly, largely by means of cell migration from the field edges. The same reaction from the same dose to a large field would not heal quickly and was thus clinically unacceptable; therefore, doses were reduced to prevent the development of moist desquamation, hence the term *tolerance doses*, or “doses that are tolerated,” which were not isoeffective. The tables of skin tolerance dose were based on experience with orthovoltage x-ray beams and radium. These data were then inappropriately used to establish mathematic relationships between dose and treatment area, with the premise that the quoted tolerance doses represented biologically isoeffective doses.

In subsequent studies in human skin, no influence of field size on the development of moist desquamation was found for fields  $40 \times 40$  mm or larger (34). Comparable results have been obtained for pig skin: For fields 22.5 mm in diameter or larger, field size had no influence on the development of moist desquamation (35). The difference between tolerance and isoeffect was first recognized by von Essen (36,37) and has subsequently been discussed in greater depth. Since most interventional fields are larger than  $40 \times 40$  mm at the patient's skin, the effect of field size can be ignored.

Experimental radiation protocols on pig skin have been reported (35,38–40). These experiments used orthovoltage x-rays, with single doses of up to a few tens of grays, as well as a wide variety of dose fractionation schedules. Because of the similarities between pig and human skin, these data are valuable if the experimental protocol matches, or can be adjusted radiobiologically to match, the fluoroscopic situation.

Sigmoidal dose-response and dose-complication curves are well established in clinical radiation therapy. Similar curves are observed after experimental irradiation of pig skin by orthovoltage x-rays. The general shape of

the dose-response curves is likely to be similar for diagnostic x-rays. However, well-defined single-dose clinical dose-response curves are not available for interventional fluoroscopy irradiations. Reports in the literature have proposed threshold doses for various specific tissue responses. Because of biologic variability, the threshold dose can be quite low for the most sensitive patient relative to that for an average patient.

#### Biologic Factors That Influence Skin Reactions

The pathophysiology of radiation-induced skin injury has been reviewed in detail (9). Tissues at risk include the skin, hair, subcutaneous fat, and muscle. The expression of this injury varies, and is dependent on a number of factors that affect the dose-response relationship and the kinetics of healing (9,41). Total dose, the interval between radiation exposures (dose fractionation), and the size of the irradiated area can affect the expression and severity of radiation injury. Physical and patient-related factors that affect the expression of the injury include smoking, poor nutritional status, compromised skin integrity, obesity, overlapping skin folds, and the location of the irradiated skin (9). The anterior aspect of the neck is the most sensitive site. The flexor surfaces of the extremities, the trunk, the back, the extensor surfaces of the extremities, the nape of the neck, the scalp, and the palms of the hands and soles of the feet are less sensitive, in that order. The scalp is relatively resistant to the development of skin damage, but scalp hair epilation occurs at lower doses in comparison to hair elsewhere on the body (41). Hair loss is illustrated in Figure 1, as well as the differential sensitivity of the skin of the neck and scalp. Ethnic differences in skin coloration are also associated with differences in radiation sensitivity; individuals with light-colored hair and skin are most sensitive.

Defects in DNA repair genes predispose individuals to increased radiation sensitivity. The predisposed population is relatively small making the difference

Figure 1



**Figure 1:** Radiation injury in a 60-year-old woman subsequent to successful neurointerventional procedure for the treatment of acute stroke. Estimated fluoroscopy time was more than 70 minutes; 43 imaging series were performed during course of the procedure. The head was not shaved. Note focal epilation on scalp and skin injury on neck but not on scalp. No dose estimates were available for this case.

relative to normal difficult to quantify. This includes individuals with the *ATM* gene, an autosomal recessive gene that is responsible for ataxia telangiectasia. It has been suggested that many patients with serious and unanticipated radiation injuries may be heterozygous for the *ATM* gene, or harbor some other *ATM* abnormality (9). Heterozygosity for *ATM* occurs in approximately 1% of the population. Irradiation of patients with hereditary nevoid basal cell carcinoma (Gorlin syndrome) may result in widespread cutaneous tumors. Other disorders with a genetic component that affects DNA breakage or repair have been found to increase radiation sensitivity. These include Fanconi anemia, Bloom syndrome and xeroderma pigmentosum. Familial polyposis, Gardner syndrome, hereditary malignant melanoma and dysplastic nevus syndrome also increase radiation sensitivity (9).



Preexisting autoimmune and connective tissue disorders predispose patients to the development of severe radiation effects in an unpredictable fashion. The cause is not known. These disorders may include scleroderma, systemic lupus erythematosus, and possibly rheumatoid arthritis, although there is controversy regarding whether systemic lupus erythematosus predisposes patients to these effects (9,42–46). It has been suggested that concomitant administration of some medications may be a factor in sensitizing these patients (47). Hyperthyroidism and diabetes mellitus are also associated with increased radiation sensitivity (48–50).

A number of drugs are known to increase radiosensitivity. These include actinomycin D, doxorubicin, bleomycin, 5-fluorouracil, and methotrexate (11). When given in conjunction with radiation therapy, mitoxantrone, 5-fluorouracil, cyclophosphamide, paclitaxel, docetaxel, and possibly tamoxifen can result in cutaneous toxicity (9,51).

A separate form of radiation-related drug toxicity is termed *radiation recall*. This is an inflammatory skin reaction of unknown origin that occurs in a previously irradiated body part after drug administration (52,53). Radiation recall may occur minutes to days after drug exposure and weeks to years after radiation exposure (9). It occurs with chemotherapeutic agents (eg, doxorubicin, etoposide, paclitaxel, bleomycin, epirubicin, and gemcitabine), antibiotics (cefotetan), statins (simvastatin), and herbal preparations (hypericin, otherwise known as St John's wort) (52,54,55).

### Radiobiology of Radiation Injuries

Avoidance of critical damage to healthy tissues is one of the basic principles of radiation therapy. Clinical time-dose fractionation prescriptions (classically, 30 fractions spread over 6 weeks) are largely based on this consideration. The response of normal tissues and structures to the effects of radiation therapy depends, to a large extent, on the radiation dose, the fraction size, and the integrity of the tissue (related to prior

surgery, chemotherapy, or radiation therapy), among other factors. Until relatively recently, conventional fractionation regimens were routinely used. Hypofractionation treatment schedules (a smaller number of fractions and a larger dose per fraction) were more often reserved for a palliative treatment setting. With image-guided radiation therapy techniques, more precise targeting can be achieved with enhanced accuracy. As a result, there has been increasing interest in the use of treatment regimens that use several large dose fractions of 6–12 Gy. Stereotactic radiosurgery and image-guided radiation therapy schedules have also delivered single doses of 20–30 Gy to finite tumor volumes, with excellent tumor control rates. Clinicians need to be aware that, depending upon the location of the treatment, skin reactions are possible with the administration of very-high-dose fractions that result in relatively high doses to the skin surface.

Interventional procedures are typically performed in one to a few sessions over a period ranging from days to months. The number of sessions and their timing depend on the underlying disease process and on procedural factors such as contrast material use. Different interventional sessions may or may not irradiate the same portion of the patient's skin.

The interval between sessions is important because of cellular DNA repair and repopulation. The effects of radiation on tissue are mitigated by the repair of sublethal damage in the DNA of viable cells and the replacement of killed cells by means of repopulation. Repair processes are essentially complete within 1 day of exposure. Repopulation, on the other hand, can take up to several months to complete.

Experimental models can demonstrate these effects. In the pig, moist desquamation occurs 50% of the time after a single dose of 28 Gy (56). When the irradiation is delivered in two equal fractions separated by 24 hours, it takes a higher total dose of 36 Gy (two times 18 Gy) to achieve the same effect. Further extension of the time interval, up to 14 days, does not permit a larger

total dose to be delivered for the same skin effect. This indicates that repair of sublethal damage to DNA is completed within 24 hours. The DNA repair kinetics for other clinical endpoints (eg, late dermal necrosis) are similar.

The timing of repopulation in irradiated skin depends on the type of skin effect. For the early response of moist desquamation, repopulation is not seen in the first two weeks because a certain level of cell depletion is required before repopulation by surviving cells is initiated. In the epidermis, this is a 50% reduction of the density of cells in the basal layer (38). After skin doses of less than 15 Gy, repopulation of depleted cells in the basal layer is essentially complete within 2 months. Repopulation occurs more slowly as the dose increases because of the dose-related decrease in the number of surviving cells in the basal layer. Repopulation of depleted cells occurs over a much longer time in dermal tissue.

Interventional sessions are typically separated by days to months. Skin recovery between sessions is therefore governed by both the kinetics of repair of sublethal damage to DNA and the repopulation of skin from surviving reproductively viable cells.

### Initiating Dose and Time Course of Radiation Injury

Damage may be expressed in the epidermis, dermis, and subcutaneous tissues. When this damage becomes evident depends on the radiation dose and biologic factors. Lesions can be loosely classified as prompt, early, midterm, or late in terms of their time of expression. A summary of skin and hair effects as a function of dose and time is given in Table 1. Due to dosimetric uncertainty and biologic variability, the dose and time boundaries between the rows and columns in the table are not rigid. There is overlap between events in any one time-dose zone and all adjacent zones.

The characteristics and timing of the signs and symptoms of radiation-induced injuries are also influenced by a variety of aggravating and mitigating

Table 1

## Tissue Reactions from Single-Delivery Radiation Dose to Skin of the Neck, Torso, Pelvis, Buttocks, or Arms

Band	Single-Site Acute Skin-Dose Range (Gy)*	NCI Skin Reaction Grade†	Approximate Time of Onset of Effects			
			Prompt	Early	Midterm	Long Term
A1	0–2	NA	No observable effects expected	No observable effects expected	No observable effects expected	No observable effects expected
A2	2–5	1	Transient erythema	Epilation	Recovery from hair loss	No observable results expected
B	5–10	1–2	Transient erythema	Erythema, epilation	Recovery; at higher doses, prolonged erythema, permanent partial epilation	Recovery; at higher doses, dermal atrophy or induration
C	10–15	2–3	Transient erythema	Erythema, epilation; possible dry or moist desquamation; recovery from desquamation	Prolonged erythema; permanent epilation	Telangiectasia‡; dermal atrophy or induration; skin likely to be weak
D	>15	3–4	Transient erythema; after very high doses, edema and acute ulceration; long-term surgical intervention likely to be required	Erythema, epilation; moist desquamation	Dermal atrophy; secondary ulceration due to failure of moist desquamation to heal; surgical intervention likely to be required; at higher doses, dermal necrosis, surgical intervention likely to be required	Telangiectasia‡; dermal atrophy or induration; possible late skin breakdown; wound might be persistent and progress into a deeper lesion; surgical intervention likely to be required

Note.—Applicable to normal range of patient radiosensitivities in absence of mitigating or aggravating physical or clinical factors. Data do not apply to the skin of the scalp. Dose and time bands are not rigid boundaries. Signs and symptoms are expected to appear earlier as skin dose increases. Prompt is <2 weeks; early, 2–8 weeks; midterm, 6–52 weeks; long term, >40 weeks.

\* Skin dose refers to actual skin dose (including backscatter). This quantity is not the reference point air kerma described by Food and Drug Administration (21 CFR § 1020.32 [2008]) or International Electrotechnical Commission (57). Skin dosimetry is unlikely to be more accurate than  $\pm 50\%$ . NA = not applicable.

† NCI = National Cancer Institute

‡ Refers to radiation-induced telangiectasia. Telangiectasia associated with area of initial moist desquamation or healing of ulceration may be present earlier.

factors. Specifically, anything that damages irradiated skin (sunburn, abrasion, biopsy) is likely to aggravate the tissue response and may increase the probability of infection. Areas of skin that are thin and lack redundant dermal tissue, such as the anterior tibia and the sole of the foot, may be more prone to radiation injury. Caution must be exercised when exposing such areas to radiation (58).

Because of clinical variability, it is appropriate to assume that any skin changes observed following an interventional procedure are radiogenic in origin unless a definitive alternative diagnosis is established.

The National Cancer Institute (NCI) has defined five grades of skin toxicity for radiation dermatitis (59). This grading scale and the appearance of the skin reaction resulting from experimental

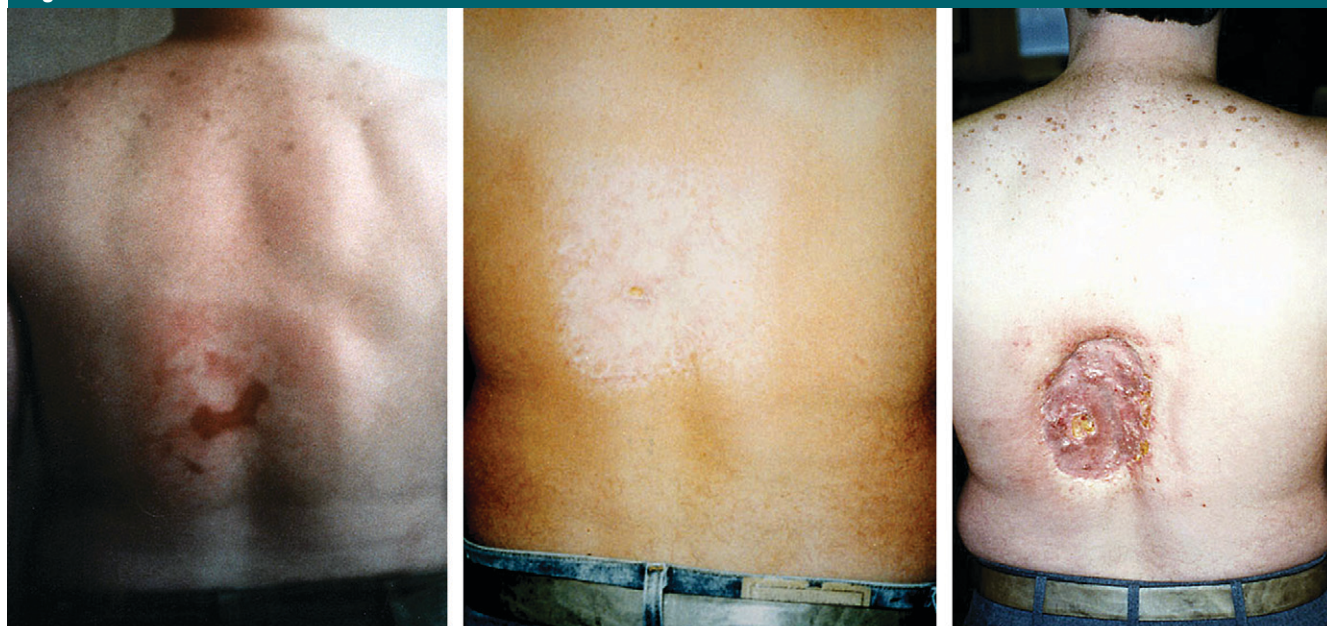
(animal) or interventional (human) irradiation for the first four grades are shown in the Appendix. It is proposed that the same scale be used to define the skin toxicity associated with interventional fluoroscopy.

### Prompt Reactions

Prompt reactions are those that occur less than 2 weeks after irradiation. The most frequently reported prompt reaction is the so-called early or 24-hour erythematous reaction. This can occur from a few hours up to 24 hours after a radiation dose of more than 2 Gy. Once this reaction has resolved, there is no conclusive evidence to suggest that it has any influence on subsequent responses. It is believed to represent an acute inflammatory reaction with an associated increase in vascular permeability. In animal studies, this increase

in permeability is dose related, but only up to approximately 8 Gy (60).

There are very few reports of promptly developing symptoms following fluoroscopically guided interventional procedures. Two cases are reported here. One patient, shown in Figure 2, had undergone a percutaneous transluminal coronary angioplasty (PTCA) of the right coronary artery 6 months before a subsequent procedure that involved two PTCAs, performed an hour apart, in a branch of the left anterior descending coronary artery. The latter two procedures entailed nearly 1½ hours of fluoroscopy, with concomitant cine radiography. The physician noted in the procedure report that some prompt erythema was apparent on the back of the patient at the time the patient was removed from the table (no image available). Several weeks later, the patient

**Figure 2**

**Figure 2:** Radiation injury in a 40-year-old man who underwent multiple coronary angiography and angioplasty procedures. Images show time sequence of a major radiation injury (7). These images often provide the first hint to individual patients that injury is related to a previous fluoroscopic procedure. **(a)** At 6–8 weeks after exposure, prolonged erythema with mauve central area appears, suggestive of ischemia. **(b)** At 16–21 weeks, depigmented skin with central area of necrosis is seen. **(c)** At 18–21 months, deep necrosis with atrophic borders is seen. (This sequence is available on the Food and Drug Administration Web site and is in the public domain ([61].)

noticed erythema that progressed over time into a large area of necrosis. The necrosis possibly represents a severe midterm reaction, as discussed later.

In a different case, a patient reported stabbing pain in the right thorax 24 hours after unsuccessful PTCA of the right coronary artery. Three days after this prompt event, erythema developed that then progressed into what appeared to be a superficial acute ulceration as a result of exposure to a very high radiation dose (see next paragraph). However, the timing of events was not clearly recorded in this case.

Very serious prompt reactions occur at very high doses (>80 Gy) (62–64). Lesions, varyingly described as ulceration or total necrosis, develop between 14 and 25 days after exposure. The appearance of this pattern of response after an interventional procedure should be viewed with extreme concern. Accidental exposure to such high doses in an interventional setting should be

carefully investigated to prevent the likelihood of reoccurrence. The patient must also be followed up for possible late effects in other irradiated organs.

### Early Reactions

Early reactions occur 2–8 weeks after exposure. These effects take place in the basal cells of the epidermis and the germinal region of the hair follicles (collectively called *stem cells*). These are the more rapidly proliferating cells in the skin. The underlying mechanism is comparable in both systems: Cell differentiation and cell loss continue at the normal rate, but radiation inhibits cell proliferation and new cell production. Thus, the timing of the responses depends on the turnover time of the system and is independent of the radiation dose. While the timing is independent of the radiation dose, the severity of the radiation response in the epidermis and the hair is dose dependent, since the reproductive survival of stem cells is dose related.

The main erythematous reaction is a secondary inflammatory reaction to effects occurring in the epidermis (65). Animal studies, including pig studies with exposure to a single dose of orthovoltage irradiation of 15 Gy or higher or daily fractionated doses of approximately 2 Gy, demonstrate a marked decrease in the number of cells synthesizing DNA in preparation for cell division and in the number of cells seen in mitosis. This represents a marked reduction in cell production (66,67). Cells in the basal layer of the epidermis that are not reproductively viable continue to differentiate and migrate into the upper layers of the epidermis. This causes a steady decline in both the density of cells in the basal layer and in the number of viable cell layers in the epidermis. The rate of decline in basal cell density depends on the rate of epidermal turnover at the site of irradiation (usually 4–6 weeks). It is independent of the radiation dose and



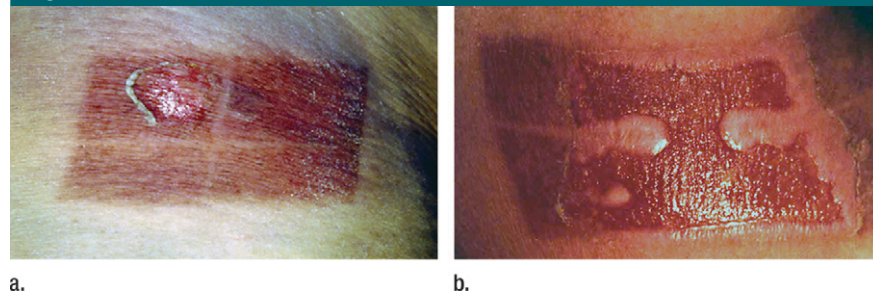
the dose-fractionation schedule used to administer that dose (38,68). A decline in the basal cell density to approximately 50% of its normal value appears to provide a stimulus to the remaining viable clonogenic stem cells in the basal layer to proliferate rapidly; the number of such cells will depend on the radiation dose (38). These proliferating cells form colonies of viable cells within the otherwise degenerating epidermis.

The number of developing colonies, which is dose related, dictates the subsequent outcome. If large numbers of colonies develop (lower dose), they will coalesce. Moist desquamation will be avoided, and the main erythematous reaction will resolve. The epidermis may display hyperplasia prior to full recovery. This is evident clinically as dry desquamation. If a limited number of colonies develop (higher doses), the areas between them will continue to lose cells from the basal layer at the same rate. All cells and viable cell layers will be lost from the areas between colonies at a time associated with the normal turnover time of the epidermis—typically 4–6 weeks. This represents the development of moist desquamation. Colonies of viable cells may be seen within areas of moist desquamation (69). Regeneration of the epidermis takes place due to the continued proliferation of cells in these cell colonies and cell proliferation from around the field edges. In this situation, a bright red erythema persists until repopulation nears completion.

With high radiation doses, few or no viable cells remain in the irradiated area. Repopulation progresses slowly, primarily from the edges of the field. Regeneration after a high dose of radiation to the lateral aspect of the hip during radiographic localization of a brachytherapy applicator is illustrated in Figure 3 (70). Regeneration is seen both from the edges of the irradiated area and from surviving cells that were partially shielded by the lead cross wires.

In areas where moist desquamation is developing, infection and dehydration of subepithelial tissues after high radiation doses can lead to the development

**Figure 3**



**Figure 3:** (a) Early erythema and developing moist desquamation in a diabetic woman caused by a localization radiographic exposure. Notice well-demarcated x-ray field and protection of the region of the skin shielded by the lead cross hairs in the field. (Reprinted, with permission from reference 70.) (b) Healing of moist desquamation by means of epithelial regeneration, both from epithelial stem cells extending inward from margin of irradiated area and from shadow of the lead cross hairs in the field. (Image courtesy of B. R. Thomadsen, PhD, University of Wisconsin, Madison.)

of secondary ulceration and the loss of dermal tissue over a midterm time frame. These skin lesions are likely to require surgical intervention to remove irradiated dermal and subcutaneous tissue. Extensive scar tissue formation will result if these lesions are left to heal slowly.

When hair is irradiated, the cells at the base of the hair follicle are affected. The degree of radiation response depends on the number of cells that remain reproductively viable. The timing of the appearance of these radiation effects depends on the normal growth rate of the hair. After low doses (1–8 Gy in pigs; 5–14 Gy in humans), only a relatively small transient loss of stem cells occurs. This is associated with a transient reduction in the diameter of the hairs. Subsequent recovery to a normal diameter will occur (71,72). The maximum reduction in hair diameter in both species appears to be 30%. Beyond this limit, the terminal part of the hair distal to the thinned region tends to snap off, giving the appearance of temporary (and usually partial) epilation prior to regrowth of the remaining hair to a normal diameter. In the pig, the probabilities of both detectable hair loss and hair loss of more than 50% after 6 weeks were clearly dose related. The dose to produce these effects in 50% of irradiated sites was  $9.8 \text{ Gy} \pm 0.6$  and  $13.8 \text{ Gy} \pm 0.9$ , respectively. Total permanent epilation occurs at the radiation dose where all stem cells in

the follicle are reproductively sterilized and the hair follicle is lost.

### Midterm Reactions

Midterm reactions occur 6–52 weeks after irradiation. These are associated with the development of delayed lesions in the walls of blood vessels in the dermis and subcutaneous fat (73). Skin with a “dusky” or “mauve” appearance provides evidence for the presence of ischemia (Fig 2a), with a measurable reduction in blood flow and a reduction in vascular density 12 weeks after irradiation (74,75). The probability of developing either dusky-mauve erythema or full- or partial-thickness dermal necrosis depends on the radiation dose (38). Slices of skin taken during this time period demonstrate that necrosis may affect only part of the thickness of the dermis, while at the same time there is evidence of vascular changes in the subcutaneous fat (Fig 4a). In some instances these vascular changes, with associated necrosis, may involve the fat and not the dermis (Fig 4b). As areas of partial-thickness necrosis heal, the epidermis migrates under the dead tissue to form a new covering. Small areas of full thickness necrosis may heal or may require surgical intervention to remove necrotic dermal and subcutaneous tissue.

For irradiated sites that do not develop dermal necrosis, the blood flow per unit volume of dermis returns to normal concomitant with the development of dermal thinning and contraction in size of



**Figure 4****a.****b.**

**Figure 4:** Slices through a region of pig skin obtained 16 weeks after irradiation with a single dose of 20.7 Gy (250-kVp x-rays). **(a)** Necrosis of a partial-thickness (dark gray area) of dermis and evident vascular changes are present in underlying subcutaneous fatty layer. **(b)** Region of necrosis in the subcutaneous fatty layer. Overlying dermis shows no evidence of necrosis. (These photographs were obtained circa 1960 and have been cleaned and enhanced for this publication.)

the originally irradiated area over a period from 12 to 16 weeks after exposure (75). This has been clearly demonstrated in pig skin by means of serial measurements of relative dermal thickness after irradiation with single doses of strontium 90 ( $^{90}\text{Sr}$ )/yttrium 90 ( $^{90}\text{Y}$ ) beta rays (38).

### Long-term Reactions

Primary long-term reactions occur more than 40 weeks after irradiation and include the further development of dermal thinning, also measured as a reduction in the size of the original irradiated field or as clinically detectable induration due to the atrophy of both dermal and subcutaneous fat (38,76). Serial measurements of relative dermal thickness after irradiation with single doses of  $^{90}\text{Sr}/^{90}\text{Y}$  beta rays show that this phase of dermal thinning develops between 52 and 78 weeks after irradiation. For single doses in the 10–33-Gy range, this timing is independent of the radiation dose, although the severity of the reaction is dose-related. The severity of dermal thinning, as assessed according to a

measured reduction in field size, may be influenced by the initial development of transient moist desquamation.

Radiation-induced telangiectasia is different from the clinical telangiectasia that results from wound healing. It is a well-recognized long-term reaction of human skin, representing the dilation of capillaries in the superficial papillary dermis. These vessels are often visible though the epidermis. They are rarely seen before 52 weeks after the completion of radiation therapy, but they then increase in both incidence and severity for at least 10 years. The rate of progression is dose related (77). The origin of this type of lesion is unclear. It has been suggested that the development of telangiectasia is secondary to smooth muscle degeneration in end arterioles in the dermis. In pig skin, there is histologic evidence for the presence of telangiectasia after more than 52 weeks, with associated hyaline change in the walls of end arterioles, petechial hemorrhages, and focal dermal necrosis. In humans, areas of skin that show transient moist desquamation tend to show more pronounced telangiectasia in the long term (78).

In addition to these late deterministic changes, late stochastic effects are possible. Experience from radiation therapy demonstrates that there is a small but real increased risk for the development of malignancies such as carcinoma, melanoma, and sarcoma, with latency periods that can extend beyond 20 years (58,79).

### Time Sequence

The sequence shown in Figure 2 demonstrates the pattern of injuries previously described in a patient who has undergone several procedures involving radiation. Prompt erythema was followed by mauve erythema and ischemia, evident at 6–8 weeks; necrosis, at 16–21 weeks; and persistent necrosis, at 1.5 years after the last interventional procedure.

### Interaction between Different Types of Damage

If surgical intervention is required to repair acute ulceration, secondary

ulceration, or dermal necrosis, the total thickness of irradiated skin and some subcutaneous tissue are usually involved. Provided that good healing is achieved, no subsequent radiation-induced reactions would be expected to occur. If these lesions are small and involve only a small portion of the exposed site, unassisted healing will result in the formation of extensive scar tissue. The healed wound will not have the strength of nonirradiated skin, and the atrophic dermal tissue will be at greater risk for subsequent breakdown. This can be precipitated by mild trauma, among other things. Atrophic dermal tissue is also more likely to show the effects of trauma, with delayed necrosis. All of these events tend to be random in nature, but the instructions given to radiation therapy patients should be applied equally to patients receiving substantial radiation doses from interventional procedures. The BC Cancer Agency (<http://www.bccancer.bc.ca>) provides useful information for this purpose (80). Detailed information on the management of radiation injuries is beyond the scope of this paper. Limited general information may be found in the following sections of this article.

### Risk Management of Skin Effects in Interventional Procedures

The possible effects of irradiation from a single interventional procedure are listed in Table 1, which is divided into four dose bands. Data derived from fractionated exposures have been converted to a single-fraction equivalent by using standard radiobiologic techniques. The assignment of an effect to one of these dose bands reflects a judgment of the response of most patients to this level of radiation exposure. The effects listed in any cell may occur at lower doses for radiosensitive patients or at a higher dose for radiation-resistant patients. General advice for clinicians as to the required follow-up and information to be provided to patients is given in Table 2 and by the British Columbia Cancer Agency (80). Individualized management supplied by an experienced radiation wound care team should be provided for wounds

Table 2

## General Advice to Be Provided to Patients and Treating Physicians

Band	Skin Dose Range (Gy)	Advice to Patient
A1	0–2	No need to inform patient, because there should be no visible effects; if patient reports skin changes, then treat in response to the signs and symptoms
A2	2–5	Advise patient that erythema may be observed but should fade with time; Advise patient to call you if skin changes cause physical discomfort
B	5–10	Advise patient to perform self-examination or ask a partner to examine for skin effects from about 2 to 10 weeks after the procedure; tell patient where skin effects would most likely occur; if skin erythema and itching occur, patient should call radiologist's office; skin reactions are often treated conservatively; might advise patient to be examined by dermatologist or other treating physician and to inform treating physician that injury may be due to radiation; radiologist should also provide that physician with medical details of where the radiation-related skin effects are likely to occur
C	10–15	Medical follow-up is appropriate; advice is same as that for band B but also advise dermatologist or other treating physician that skin effects may be prolonged due to radiation dose and that prophylactic treatment for infection and monitoring of wound progression may be required; pain could become a concern if doses were in the higher range of this band
D	>15	Medical follow-up is essential, nature and frequency of which depending on estimated radiation dose; advice is same as that for band C, but advise treating physician that the wound could progress to ulceration or necrosis

Note.—Applicable to normal range of patient radiosensitivities in the absence of mitigating or aggravating physical or clinical factors.

related to higher doses. For any patient exposed to a dose in band D, not only is medical follow-up essential, but a full investigation of the situation leading up to the high-dose is desirable to minimize the likelihood of such an event being repeated.

## Staged and Repeated Procedures

Interventional procedures are often divided into multiple sessions. If the same portion of the patient's skin is irradiated in different sessions, the radiobiologic consequences can be expected to be similar to those of a time-matched course of orthovoltage radiation therapy. If there is no overlap of the entrance beam ports from different exposures, then each session can be considered separately.

A mathematic model that can be used to evaluate the biologic results of staged irradiations is available in the online supplement (Appendix E1 [online]) to this article (81–83). This model provides estimates of the biologi-

cally adjusted dose for sessions that occur within a 24 hour period (including the effects of the incomplete repair of sublethal damage) and for sessions occurring at least 24 hours apart (where complete repair of sublethal damage from previous sessions has occurred). This model is sufficiently complex that each case has to be evaluated on its own merit—simple extrapolations can be dangerous.

A conservative approach to multiple radiation exposures of the same portion of the patient's skin is to assume that there is no repair of sublethal DNA damage when the sessions are performed on the same or successive days. The applicable dose is, therefore, the total accumulated dose delivered to the area of skin at risk. This resulting overestimate of the biologically effective dose provides a clinical margin of safety.

The effect of a second procedure within a few months is a function of the kinetics of skin repopulation after the index procedure. As discussed

above, a higher dose from the first irradiation slows repair because of a lesser availability of stem cells. If the second stage is likely to irradiate exposed skin, the time between stages should be increased with increasing dose from the first procedure. In such situations, it is advisable to examine the patient's skin for radiation effects before starting a subsequent procedure.

Interventional procedures may be repeated, or new ones required, after an interval of months to years. Unless the skin dose from the planned procedure is minimal or to a different skin field, it is not safe to assume that previous radiation doses can be ignored. Previously irradiated skin often looks normal, but reacts abnormally when exposed to another insult (eg, further irradiation, minor trauma or topical agents). If the x-ray beam port overlaps previously irradiated areas, residual effects from the first procedure may influence the response of the irradiated skin and subcutaneous tissues to subsequent exposures. If overlap is anticipated, skin doses above 3–5 Gy from previous procedures should be included when estimating the expected tissue reaction from an additional procedure.

Studies of recovery from moist desquamation and the associated erythematous reaction have been performed in pigs. Split-dose studies, with variable gaps between exposures, have shown that full repopulation of the epidermis is complete when there is an interval of approximately 7 weeks between exposures of about 20 Gy. Repopulation begins after 2 weeks (56). For the mid-term reaction ischemic dermal necrosis, the recovery-repopulation phase is much slower; there is no suggestion of any recovery until after 28 days. There is a suggestion of full recovery with an interval of 112 days (16 weeks) between exposures. Additional studies in the pig indicate that after an initial exposure of 18 Gy, there is residual injury in dermal tissue amounting to 5%, 7%, and 2% of the initial dose with a gap between single dose exposures of 17, 35 and 52 weeks, respectively (84).

After a radiation dose estimated to be higher than 10 Gy, cutaneous tissue

will never return to its pristine state. This is evident from the studies described above, which involved reexposure after intervals of up to 52 weeks. The observed dose-response relationships indicated almost no residual damage in terms of the subsequent risk of necrosis. However, the severity of the associated erythematous reactions was substantially reduced in previously irradiated skin, suggesting the presence of residual damage in previously irradiated vasculature. This residual damage, although not associated with obvious changes at the macroscopic level, leaves the tissues at increased risk of developing complications from the effects of external factors such as minor trauma or topical agents, in a random way (84).

### Discussion

Cutaneous radiation reactions range from mild and transient to severe and clinically devastating. Damage can be expressed in the epidermis, the dermis, and the subcutaneous tissues. Although commonly referred to as skin injuries, severe radiation injuries can also extend into the subcutaneous fat and muscle.

The radiation dose, the interval between irradiations (dose fractionation), and the size of the skin area irradiated all affect the expression and severity of the radiation injury, as do a variety of physical and patient-related factors. The timing of the appearance of various specific tissue responses depends on intrinsic biologic factors. Owing to biologic variability, the dose threshold can be quite low for the most sensitive patient relative to that for an average patient.

This review has presented a consensus, based on available information, of the radiobiology of the skin and the relationship between radiation dose and skin effects in interventional fluoroscopy. To accommodate a wide range of dose-effect relationships, these relationships have been represented in Tables 1 and 2 by a series of overlapping time and dose bands, rather than by threshold doses for individual radiation effects. This method for describing

dose-effect relationships emphasizes the wide variability in these relationships. The assignment of a radiation effect to one of these dose bands reflects a judgment of the response of most patients to this level of radiation exposure.

The radiation doses in Tables 1 and 2 are given as skin doses. Fluoroscopy time has been used as a surrogate for skin dose, but it is a poor proxy because it does not account for factors such as radiation dose from radiographic or fluoroscopic images, differences in fluoroscopic dose rate, or movement of the radiation field on the patient's skin. Better metrics are specified by the International Electrotechnical Commission (57) and the Food and Drug Administration (21 CFR§ 1020.32 [2008]). Both of these documents define the dose metric reference point air kerma and require that it be displayed to the operator during a fluoroscopically guided procedure. This dose metric is better indicator of skin dose, but it is not ideal. Tools that provide a real-time estimate of actual skin dose distribution are currently in development.

Figure 5 demonstrates the inadequacy of fluoroscopy time. The interventional procedure that produced the

more superior skin reaction required 35 minutes of fluoroscopy time and resulted in a reference point air kerma of 6.2 Gy. The midline skin reaction occurred after a subsequent procedure that required 75 minutes of fluoroscopy time and resulted in a reference point air kerma of 8.7 Gy. Enough geometric information was available to provide skin dose estimates of 10 and 8 Gy respectively for these two procedures. Despite less fluoroscopy time, there was a higher skin dose in the more superior area. This higher dose was due to a combination of factors, including a longer radiation path through the patient's body and less beam motion during the procedure. Conversely, in the second procedure, the beam path was shorter and there was more movement of the radiation field. Some of this movement of the radiation field can be seen in the midline lesion on the patient's skin, where there are two overlapping fields.

Rigid adherence to any dose-effect table is unwise. Because of clinical variability, it is appropriate to assume that any skin changes observed after a fluoroscopically guided interventional procedure are radiogenic in origin unless a definitive alternative diagnosis is established.

**Figure 5**



**Figure 5:** NCI skin toxicity grade 2 (see Appendix). Radiation injury due to overlapping radiation fields in 80-year-old woman. Shown are superior region of injury 12 weeks after approximately 10-Gy peak skin dose and midline region of injury (with overlap) 10 weeks after approximately 8-Gy peak skin dose in overlap area. Reactions had faded at 6 months (according to telephone interview) (not shown).

### Appendix

The NCI has defined five grades of skin toxicity for radiation dermatitis (57). This grading scale and the appearance of the skin reaction resulting from experimental (animal) or interventional (human) irradiation for the first four grades are shown. It is proposed that the same scale be used to define the skin toxicity associated with interventional fluoroscopy. Representative images are included for each of the grades.



**Grade 1**

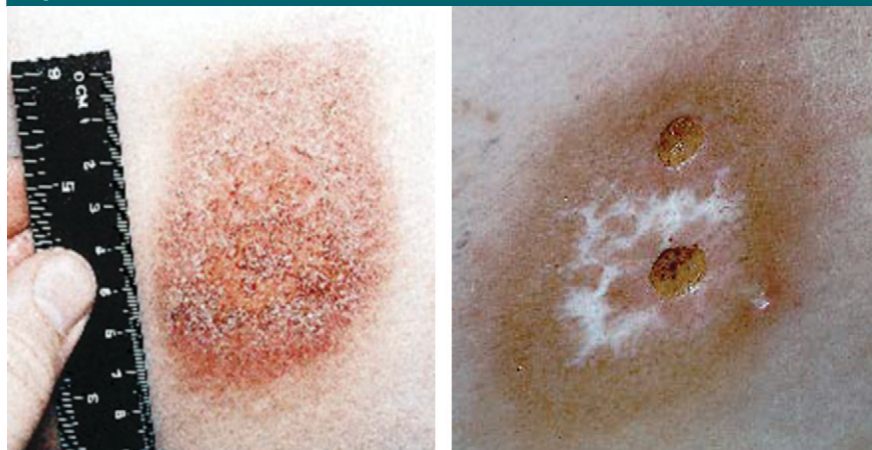
NCI skin toxicity grade 1 manifests as faint to moderate erythema (Fig A1).

**Figure A1**

**Figure A1:** NCI skin toxicity grade 1. Two fluoroscopically guided procedures were performed through overlapping skin ports in a 65-year-old man. Note enhanced reaction in the overlap zone. The first procedure was performed 6 weeks before and the second procedure, 2 weeks before this photograph was obtained.

**Grade 2**

NCI skin toxicity grade 2 manifests as moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; and moderate edema (Figs 5, A2, A3).

**Figure A2**

**Figure A2:** NCI skin toxicity grade 2. **(a)** Subacute radiation dermatitis from fluoroscopy during coronary artery stent placement. Photograph obtained 2 months after fluoroscopy. **(b)** Lesion progressed to hyperpigmentation, sclerosis, and ulceration 5 months after fluoroscopy. (Reprinted, with permission, from reference 85.)

**Figure A3**

**Figure A3:** NCI skin toxicity grade 2. **(a)** Radiation injury in 50-year-old man. Photograph was obtained 2 months after treatment with approximately 10-Gy peak skin dose. **(b)** Same patient 6 months after treatment.



**Grade 3**

NCI skin toxicity grade 3 manifests as moist desquamation in areas other than skin folds and creases (Figs A4, A5).

**Figure A4**

**Figure A4:** NCI skin toxicity grade 3. Pig model demonstrates early radiation reaction: moist desquamation with dried serum exudates on the final day of irradiation schedule involving 18 dose fractions delivered over 39 days (three per week for total dose of 72 Gy). Reaction developed in final week of irradiation. Dried exudate on surface is due to serosanguinous fluid leakage. (Image was obtained circa 1960 and has been cleaned and enhanced for this publication.)

**Figure A5**

**Figure A5:** NCI skin toxicity grade 3. Increased severity of reaction in an area of radiation field overlap is evident. (Reprinted, with permission, from reference 86.)

**Grade 4**

NCI skin toxicity grade 4 manifests as skin necrosis or ulceration of full-thickness dermis and spontaneous bleeding from involved site (Figs A6–A9).

**Figure A6**

**Figure A6:** NCI skin toxicity grade 4. Ulceration 4 months after an electrophysiology ablative procedure in which patient's arm had accidentally been positioned within the radiation field during the 10-hour procedure. Estimated peak skin dose was 15–20 Gy. After plastic surgery, patient's ulceration healed and his pain resolved. (Reprinted, with permission, from reference 87.)

**Figure A7**

**Figure A7:** NCI skin toxicity grade 4. Deep necrosis at the elbow months after a procedure. Under the cover of the sterile drapes, the patient had unknowingly rested an arm over the port of the x-ray tube during an electrophysiology and ablation procedure. (Reprinted, with permission, from reference 19.)

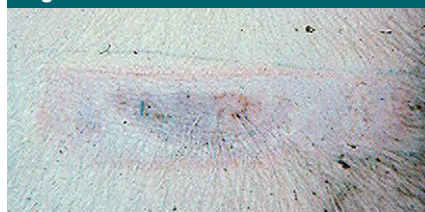
**Figure A8**

a.

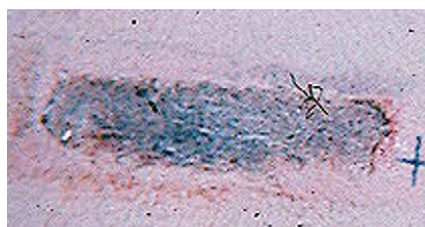
b.

**Figure A8:** NCI skin toxicity grade 4. (a) Central area of deep necrosis surrounded by indurated and depigmented skin within an area of prolonged erythema at 30 weeks after coronary angioplasty in a 60-year-old man. (b) Same patient 38 weeks after the procedure.

Figure A9



a.



b.

**Figure A9:** NCI skin toxicity grade 4. (a) Midterm radiation reaction in a pig model: Dusky mauve re-action indicates dermal ischemia 12–14 weeks after single exposure of 23 Gy. (b) Subsequent dermal necrosis in a pig model at 14–16 weeks after single exposure of 23 Gy. (Images were obtained circa 1960 image and have been cleaned and enhanced for this publication.)

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# Fluoroscopically Guided Interventional Procedures: A Review of Radiation Effects on Patients' Skin and Hair

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## Appendix E1

This approach uses models developed and tested for radiation therapy, which are used to calculate equivalent biologically effective doses when dose fractionation schedules are changed or to modify the subsequent dose if errors are found in the original dose prescription. The equations are based on the so-called linear quadratic model of cell survival, which takes account of the amount of repair of DNA damage between separate radiation exposures. For use with complex procedures consisting of multiple sessions, the full procedure should not extend over more than 1–2 months because the model has only been applied to standard radiation therapy schedules within this time scale. Initially a reference point is established for single dose procedure using the following equation:

$$\text{BED} = D \left( 1 + \frac{D}{\alpha / \beta} \right), \quad (\text{E1})$$

where BED is the biologically effective dose to which the likely effects of a more complex procedure have to be compared,  $D$  is the size of the dose from the single procedure, and  $\alpha/\beta$  is a tissue-specific constant related to the survival characteristics of the cells in the tissue at risk. For late radiation damage to the skin, a value of 3–4 Gy is frequently applied (82,83).

For a complex procedure involving multiple sessions with 24 hours or more between each session, the total dose  $D$  in the simple equation (ie, Eq [E1]) is replaced by the dose received at each stage,  $d_1$ ,  $d_2$ ,  $d_3$ , such that

$$\text{BED}_m = d_1 \left( 1 + \frac{d_1}{\alpha / \beta} \right) + d_2 \left( 1 + \frac{d_2}{\alpha / \beta} \right) + d_3 \left( 1 + \frac{d_3}{\alpha / \beta} \right) \dots \quad (\text{E2})$$

When compared with the BED value,  $\text{BED}_m$  will indicate if the biologic effectiveness of the more complex procedure is similar to or higher or lower than what is considered acceptable for a single session. If necessary, the single dose equivalent can be calculated by substituting the value of  $\text{BED}_m$  into Equation (E1) and solving this for the new value of  $D$ .

Equation (E2) assumes the complete repair of sublethal damage between sessions. However, when two or more sessions are performed in one day there will be incomplete repair of sublethal damage between successive sessions, leading to

increased biologic damage. In this situation a more complex equation has been proposed (81):

$$\text{BED} = d \cdot n \left( 1 + \frac{d(1+h)}{\alpha/\beta} \right), \quad (\text{E3})$$

where  $h$  is a factor representing the increased damage caused by incomplete repair. The function  $h$  is complex. Equation (E3) was developed for comparing radiation therapy schedules, so it has been used mainly with fixed intervals between exposures and fixed doses for each exposure. Values of  $h$  for late effects in tissues have been calculated for both monoexponential and reciprocal repair kinetic models (81).

More recently, there has been a reaffirmation of the view that the repair kinetics of sublethal damage may be best represented by a biexponential repair kinetics model. This is based on acute skin reaction data from pig skin using both fractionated and various low dose-rate protocols. Comparable suggestions have also been proposed on the basis of data for human breast skin (81,88). The equation for such a model is complex, particularly when it takes into account multiple exposures of differing doses with varying time intervals between exposures. This is akin to the use of the gamma knife in radiation therapy. The gamma knife is used to treat both benign and malignant conditions of the central nervous system while preserving normal tissue tolerance (in this case, in the normal brain) (89). The BED equation in this equivalent situation is

$$\text{BED} = D_T + \frac{1}{\alpha/\beta} \frac{[\phi(\Xi, \mu_1) + c\phi(\Xi, \mu_2)]}{1+c} D_T^2, \quad (\text{E4})$$

where  $D_T$  represents the total dose,  $\mu_1$  and  $\mu_2$  represent the two repair rates for the repair of sublethal damage,  $c$  is the partition coefficient for the slower

component,  $\Xi$  represents the protocol (dose, dose rate, time at which each exposure was given), and  $\phi(\Xi, \mu)$  is a complex function of the protocol and the different repair rates, which are beyond the scope of this article. Further information can be obtained elsewhere (90).

Values of 3–4 Gy are frequently quoted for  $\alpha/\beta$  for use in calculating equivalent total doses for late reactions in the skin, irrespective of the period over which the total dose is delivered, up to an upper limit of approximately 6–7 weeks for the acute reaction of moist desquamation. However, the value of this constant appears to change with total exposure time. For short overall exposure periods (<18 days), when inhibition of cell proliferation is likely, the  $\alpha/\beta$  ratio for the endpoint of moist desquamation is 4 Gy. When the overall exposure period is increased to approximately 3–4 weeks, so that repopulation has begun in the surviving basal cells, higher  $\alpha/\beta$  ratios of 11.2 and 13.3 Gy have been obtained for human and pig skin, respectively. With treatment times of 5–6 weeks, the effective  $\alpha/\beta$  ratio is increased to approximately 35 Gy in both human and pig skin (91).

For the patient shown in Figure 5, two doses were delivered to the same area of skin. These were estimated to be 3.5 Gy ( $d_1$ ) from the first intervention and 5.9 Gy ( $d_2$ ) from the second intervention. However, uncertainty in the physical dose reconstruction suggests that these doses may be as high as 5.25 and 8.85 Gy. The interval between the two interventional procedures was 26 days. For the cell population, damage to which is responsible for the development of late skin damage, no effects of proliferation between exposures would be expected. For late skin damage an  $\alpha/\beta$  ratio of 3.5 Gy is appropriate. Thus, in Equation (E2):

$$\text{BED}_m = 3.5 \left( 1 + \frac{3.5}{3.5} \right) + 5.9 \left( 1 + \frac{5.9}{3.5} \right),$$

which yields a  $\text{BED}_m$  of 22.85. By using this BED value, the equivalent single dose can be calculated by using Equation (E1):

$$22.85 = D \left[ 1 + \frac{D}{3.5} \right]$$

Solving this for total dose  $D$  provides an equivalent single dose of approximately 7.3 Gy, compared with the total physical dose of 9.4 Gy.

For the higher estimated physical dose, the equivalent single dose would be 10.8 Gy, compared with the total physical dose of 14.1 Gy.

For radiation therapy with a few large dose fractions, the concern is always the risk of late effects, not the risk of acute skin effects. However, for acute effects, with an  $\alpha/\beta$  ratio of 11 Gy (for an irradiation time of 26 days) the corresponding equivalent single dose would be approximately 7.9 Gy for the lower of the two estimates of the total physical dose and 11.5 Gy for the higher estimate.