Skin Surface, Dermis, and Wound Healing

Roy H. Decker, Eric A. Strom, and Lynn D. Wilson

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Abstract

- More commonly, the skin is exposed to therapeutic radiation incidentally, during treatment of relatively superficial but noncutaneous malignancies such as breast cancer, or head and neck cancer.
- The skin is a multifunctional organ composed of three layers: the epidermis, dermis, and underlying hypodermis.
- There are five cell layers in the epidermis: from deep to superficial these are the strata basale, spinosum, granulosum, lucidum, and corneum.
- The microvasculature in the dermal layer regulates body temperature by dilation and constriction.
- Acute radiation dermatitis progresses through stages of severity based on accumulation of radiation-induced changes to dermal vascular and appendageal structures, epidermal stem cells, and activation of inflammatory pathways.
- TGF-β is expressed in irradiated tissue within hours of exposure (Rodemann and Bamberg 1995; Rubin et al. 1992; Rodemann et al. 1991), and has been correlated with late fibrotic changes in several tissue types (Anscher et al. 1998; Anscher et al. 2003), including skin (Kumar et al. 2008).
- The clinical hallmarks of late radiation dermatitis are fibrosis, atrophy, and telangiectasia.
- The risk of late necrosis correlated with increasing field size and appeared to be increased when the dose was delivered to greater depth.
- Retrospective review of concurrent chemoradiotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) compared to breast radiotherapy alone, the addition of concurrent therapy doubled the incidence of grade 2 or greater dermatitis.
- Radiation Recall: Radiation recall is a phenomenon first described several decades ago (D'Angio et al. 1959), describing a cutaneous reaction in the area of previous radiation exposure, in response to specific systemic agents.

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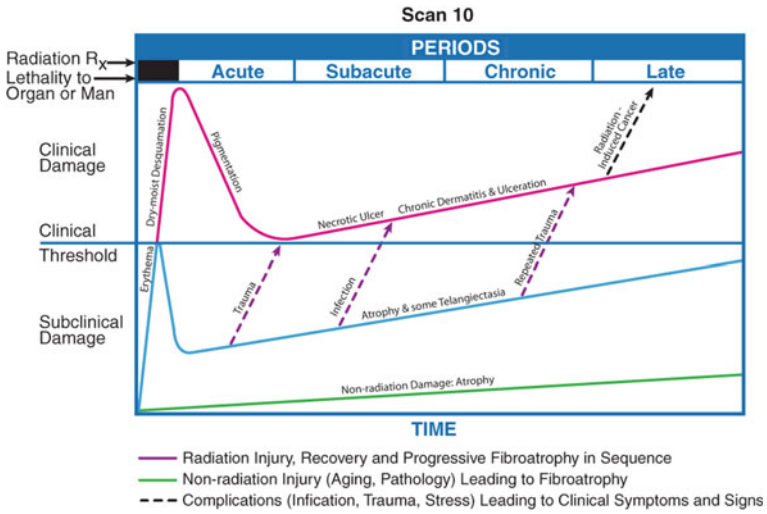

Fig. 1 Biocontinuum of adverse and late effects of the skin surface (with permission from Rubin and Casarett 1968)

- SMT: The role of therapeutic radiation in the induction of nonmelanoma skin cancer has been established in several large retrospective studies.
- Genetic Syndromes: Patients with AT are prone to severe cutaneous side effects.
- Comorbid Condition: The presence of active collagen vascular disease (CVD) is often cited as a relative contraindication to radiation treatment, due to concern for severe late fibrosis.
- Wound Healing and Grafts: Grafts are more prone to breakdown, and tissue flaps more likely to fail, especially when the site of origin also lies within the radiation field.
- Pharmaceutical treatment of fibrosis has been successful with pentoxifylline and vitamin E.

1 Introduction

Change in the appearance, texture, or protective capabilities of the skin due to radiation exposure are a commonly noted side effect both during and following therapeutic radiation treatment (Fig. 1). Exposure can occur either by design, for targets at or near the skin surface, or incidentally due to entrance or exit dose for targets deep to the skin surface. Superficial malignancies, typical primary skin cancer, have been long treated with radiation therapy either definitely or as adjuvant therapy. While radiation is reserved for advanced or high-risk lesions, the high absolute incidence of skin cancer makes this a reasonably common indication for treatment. In such cases, radiation treatment plans are specifically designed to deliver full dose to the skin, and treatment is therefore associated with robust acute and late skin changes.

More commonly, the skin is exposed to therapeutic radiation incidentally, during treatment of relatively superficial but noncutaneous malignancies such as breast cancer, or head and neck cancer. One of the most significant advances in radiation therapy technology over the past several decades is the advent of high-energy treatment units (megavoltage linear accelerators), which provide treatment that is more skin sparing than their predecessor, lower-energy, treatment machines. Depending on the specific energy used and the depth from the skin of the target lesion, the radiation dose at the skin surface might range from 5 (e.g., for a prostate treatment) to 90 % or more (e.g., for a breast or head and neck treatment).

The side effects of therapeutic radiation treatment are typically divided into acute and late effects. Acute effects are those that occur during fractionated treatment, or within a relatively arbitrary number of days of cessation of treatment (i.e., within 90 days). These symptoms are mainly the result of permeability changes in the tissue stroma (i.e., inflammation) and depletion of rapidly dividing tissue stem cells. These occur, progress, and regress in a relatively well-described series of events. Both the timing and severity are related to the volume of skin exposed, the radiation dose, and the fractionation schedule. The severity may be modified by treatment technique (e.g., the use of bolus materials), patient factors, and concomitant radiosensitizers.

Late effects are usually defined, solely for the purpose of evaluating treatment toxicity, as those which occur more than 90 days after radiation treatment. In truth there are signs and symptoms which may develop months to years later. These are often related to long-term loss of stromal microvasculature, and fibrotic replacement of normal tissue architecture. They are more loosely correlated to the dose and volume of radiation, but are more likely to be affected by clinicopathologic factors that affect local circulation and inflammatory response, as well as by genetic predisposition.

Treatment for acute radiation toxicity is generally supportive, addressing the symptoms and attempting to ameliorate the loss of normal skin barrier function. Late

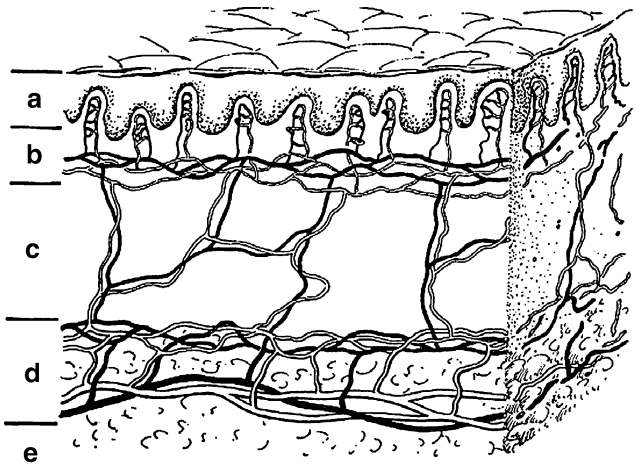

Fig. 2 Schematic drawing of skin showing the epidermal, dermal, and subcutaneous shells while emphasizing the critical microvascular components. The part labeled **a** is the epidermis (epidermal shell). **b** is the papillary dermis containing microvessel tufts arising from the papillary plexus. **c** is the rete dermis with arcuate vessels connecting the subdermal with papillary plexus. **d** is the dermal subcutaneous junction with the dermal plexus. **e** is the subcutaneous layer (From Archambeau et al. 1995, IJROBP LENT SOMA)

radiation toxicity is more effectively prevented than treated, although there is now accumulating evidence that late radiation changes can be ameliorated with appropriate medical and management. The Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The skin can be divided into its surface sectors and the lymph node region that drains a sector (Figs. 2, 3a, b).

- The head and neck includes the face and scalp. The vast majority of cancers arise on the skin of the face. Therefore, it is the face and scalp that demand careful attention clinically because of the complex functions, cosmesis, and special senses. All need to be preserved when resecting the cancer. The lymph node drainage of the integumentary surface differs from the upper aerorespiratory and digestive passages.
- Anterior chest wall from the clavicles to the navel in males tends to be hirsute. Lesions on the skin of the anterior thoracic wall drain to the anterior axillary nodes.
- Posterior chest wall to the same level tends to be less hirsute, is exposed more often to the sun, and subject to forming cancers. The regional nodes are along the posterior wall of the axilla although all axillary nodes are at risk.
- Upper extremity is an infrequent sector involved with skin cancer, but can be a site for burn and chronic inflammation. It is notorious for radiation-induced cancer in dentists who finger-held dental films during their practice. Endless resections occur with loss of fingers, then the hand, then the forearm. Involvement of epitrochlear node, then axillary nodes invariably leads to demise from pulmonary metastases.
- Anterior abdominal wall drains into the femoral and inguinal nodes but this sector of skin is rarely involved with skin cancers.
- Posterior abdominal wall or skin of the lower back is an infrequent site of malignancy and also drains to femoral and inguinal nodes anteriorly.
- Lower extremity is not a common site for skin cancers. Burns or chronic inflammation may cause lesions to evolve from hyperplasia to dysplasia and on to neoplasia. Popliteal nodes drain the foot and leg and ultimately drain into superficial femoral lymph nodes, which also drain the thigh.

Skin cancers are predominantly located on and in the face. To fully appreciate the anatomy, it is important to be aware of the surrounding structures and especially underlying muscle and nerves. As the cancer advances and invades, the reconstruction is more than cosmesis. A particularly troublesome area is over the parotid gland because perineural invasion of the widely branching facial nerve is a major concern.

N-oncoanatomy of the skin surfaces emphasizes the anterior location for most if not all lymph node stations.

The skin lymphatics of the face are different from head and neck cancers, since the drain to a ring of nodes that hang like a necklace from the occiput to below the ear, the parotid and anteriorly to the submaxillary and submandibular region. Once the cancer invades and advances involving deeper underlying structures then the deeper cervical nodes can become at risk for involvement.

There is a rich network of venous channels beneath all skin surfaces that allows for venous hematogenous spread once the dermal and hypodermal layers are penetrated by invading cancers (Fig. 2). These venous collateral channels and plexus are rich and appear once obstruction occurs. Metastatic spread via superficial and deep jugular vein is to lung predominantly. With extensive recurrent and destructive basal cancers which seldom metastasize early, aspiration into lung has been postulated but is an unlikely mechanism. Squamous cell cancers as they invade lymph nodes disseminate via focal veins. Merkel cell cancers are more virulent and are more prone to become metastatic (Rubin and Hansen 2008).

2.1.1 Skin Functional Unit

The smallest unit of skin that retains all the characteristics of skin (a unit of skin structure) consists of a microvessel

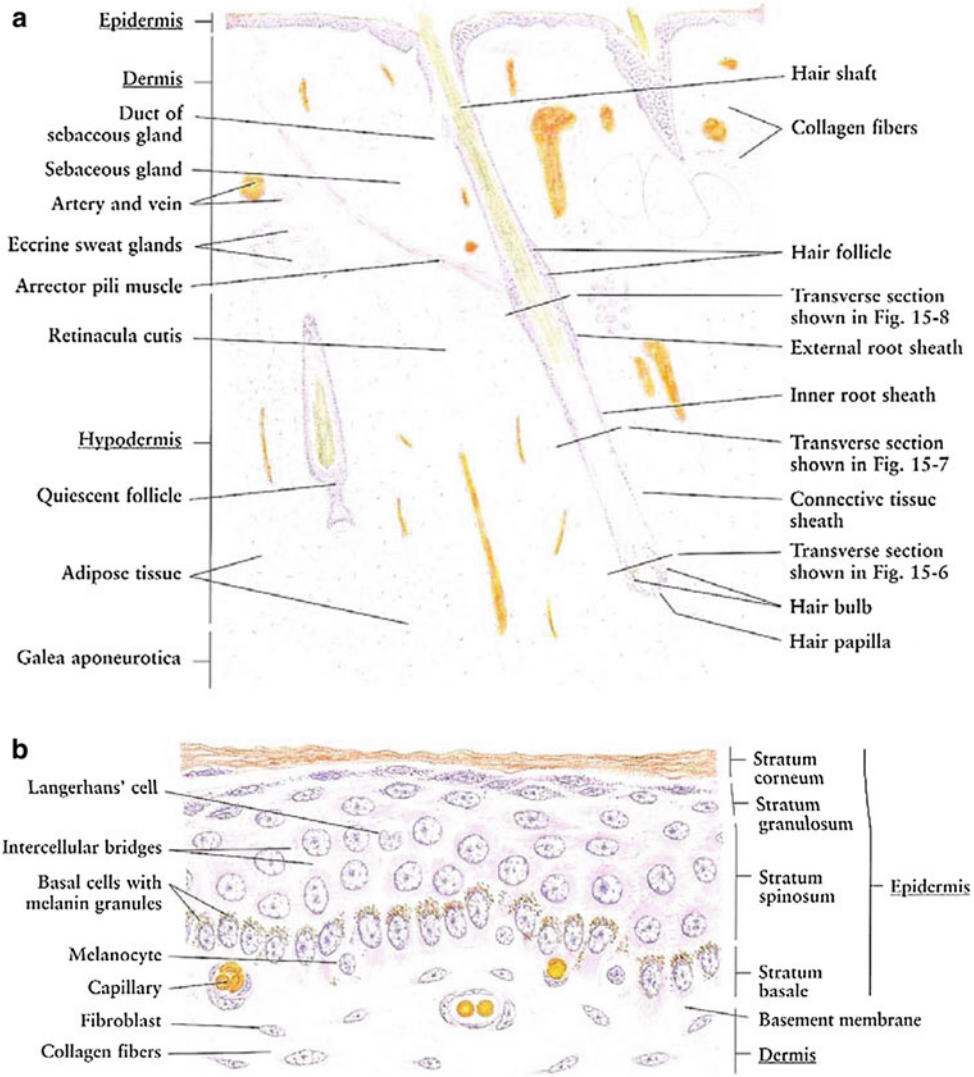

Fig. 3 **a** Scalp low magnification longitudinal section. **b** Thin skin: abdomen. High magnification (with permission from Zhang 1999)

with associated epidermis and dermis. This element of skin is referred to as a "skin functional unit" (FU_s). The FU_s is a core about 30 μm in diameter and 350 μm in length. There are an estimated 30,000 FU_ss per cm^2 in swine, with an associated 135 basal cells overlying a microvessel tuft 80–150 μm long. The skin configuration model emphasizes that the dose response of the FUs defines the dose response of the skin.

2.2 Histology

The skin is a multifunctional organ composed of three layers: the epidermis, dermis, and underlying hypodermis (Fig. 3a). The skin provides protective barrier function, and serves as an important role in hydration, temperature balance, and immunity (Fig. 3a).

The epidermis is the outer layer of the skin, composed of stratified squamous epithelium (Fig. 3b). It varies in thickness from 0.05 (on the eyelids) to 1.5 mm (on the soles of the feet). There are five cell layers in the epidermis: from deep to superficial these are the strata basale, spinosum, granulosum, lucidum, and corneum. The stratum basale, or basal layers, contain mitotically active basal cells, which migrate superficially to replace the nondividing outer layers. As the cells migrate away from the vascular supply in the dermis, they lose their cytoplasm, change shape and composition, and begin to accumulate keratin. The outer stratum corneum is composed of layers of flattened dead skin cells that continuously shed. This keratinized layer of the skin is responsible for barrier function, retaining water and shedding chemical irritants and pathogens. In addition to keratinocytes, the epidermis contains specialized elements such as melanocytes, Langerhans cells, and Merkel cells.

The dermis is composed of connective tissue and is connected to the epidermis by a basement membrane. The dermal layer contains blood and lymphatic vessels, sensory receptors, and skin adnexa (hair follicles, sweat and

sebaceous glands, and apocrine glands) (Fig. 3a). The microvasculature in the dermal layer regulates body temperature by dilation and constriction. The papillary region of the dermis is more superficial, and is composed of looser connective tissue arranged in projections or papillae. The underlying reticular dermis is thicker and composed of denser connective tissue. The reticular dermis contains the largest concentrations of extracellular matrix proteins, as well as the adnexal structures.

2.2.1 Hair

- Each hair arises in a tubular invagination of the epidermis into the dermis. The epithelium of the hair is arranged in three concentric layers: the medulla, the cortex, and cuticle. The hair follicle is tubular sheath composed of an inner epithelial sheath continuous with the epidermis and an outer connective tissue sheath. At the lower end, the root and follicle form a hair bulb connected to a papilloma consisting of fibroblasts, collagen, and rich in capillaries. Normal hair is divided into three parts: the infundibulum, the isthmus, and the inferior segment described above.
- Hair growth is cyclical and is divided into three separate and distinct phases: anagen, telogen, and catagen.
  - Anagen Phase is mitotically active and there is rapid growth i.e., scalp hair.
  - Telogen Phase is a dormant and mitosis is arrested i.e., eyebrows, pubic hair, and axillary hair. This phase lasts for months to years.
  - Catagen Phase occurs when the root is separated from the hair bulb, pigment is terminated and the hair root is separated from the bulb.
- Radiation in modest does to scalp (10–20 Gy) can initiate hair loss within 2–4 weeks and if the total dose is less than TD50; hair will regenerate. It is important to note that telogen hairs in eyebrows are often spared when scalp hair is shed.

2.2.2 Sebaceous Glands

Sebaceous glands are lined by actively proliferating stratified epithelium continuous with the germinal layer of skin. Mitoses are frequent in cells close to walls of excretory duct; newly produced cells move into secretory regions. Modest low doses of radiation have utilized to treat skin acne on face and chest when sebaceous gland activity is stimulated in adolescents.

2.2.3 Sweat Glands

Sweat Glands are simple coiled tubular glands deep in the dermis with its secretory merocrine myoepithelial cells which are specialized post mitotic cells. Sweat glands are more radioresistant and require large doses comparable to producing acute moist dermatitis to ablate. This can occur when the axilla is in the field when irradiating breast cancers.

The hypodermis or subcutis connects the dermal layer to the underlying muscle, bone, and fascia and is, by volume, composed primarily of fat. This layer serves as one of the major sites of fat storage by the body, and also contains macrophages, fibroblasts, and larger caliber blood vessels. The subcutaneous layer normally provides a loose layer of connective tissue to allow for cushioning and articulation during body movement. It is the primary site of fibrotic replacement following high-dose radiation.

3 Physiology and Biology

Skin has been utilized for numerous radiobiologic studies to characterize its radioresponsiveness (Table 1). Pig skin was initially favored because of its histologic characteristics being similar to humans however, more recently mouse leg has been adopted more widely. Radiation reactions have reproducible grading scales and dose time fractionation has been well studied. The clinical course of radiation skin murine reactions is similar to humans and useful for studying the genetic and molecular basis for radiosensitive versus radioresistant strains (Hall and Okunieff).

The pathophysiologic mechanism of late changes, particularly fibrosis, in response to radiation is incompletely understood. Transforming Growth Factor Beta (TGF-β) is a secreted protein that serves a regulatory role in normal tissue inflammation and remodeling by controlling proliferation, differentiation, and secretory functions. TGF-β is expressed in irradiated tissue within hours of exposure (Rodemann and Bamberg 1995; Rubin et al. 1992; Rodemann et al. 1991), and has been correlated with late fibrotic changes in several tissue types (Anscher et al. 1998, 2003), including skin (Kumar et al. 2008). Abrogation of downstream mediator Smad3, a pro-inflammatory signaling molecule induced in response to TGF-β, appears to protect tissue from late fibrotic changes after radiation exposure (Arany et al. 2007; Flanders et al. 2008, 2002; Martin et al. 2000).

TGF-β serves a complex regulatory role in wound healing and tissue remodeling. It is synthesized and secreted by several cell types including tissue macrophages, epithelial and endothelial cells, and fibroblasts. The most prominent isoform (TGF-β1) is synthesized and secreted in an inactive form, and activated by various proteases in the extracellular matrix. It then binds to serine/threonine kinase receptors on the cell surface of mature and immature fibroblasts, endothelial cells, and hematopoietic cells, among others (Rodemann and Blaese 2007).

TGF-β regulates extracellular matrix remodeling by increasing fibroblast proliferation, differentiation, and activation (Rodemann et al. 1991, 1996; Lara et al. 1996; Burger

Table 1 Cytokines and growth factors implicated as mediators for the development of late radiation effects on skin

Cytokines, growth factors, and other proteins	Potential mechanisms of actions
IL-1 beta	Stimulates proliferation of keratinocytes and fibroblasts (Shenkier and Gelmon 1994; Yeo et al. 1997) Stimulates metallomatrix proteases (Shenkier and Gelmon 1994; Yeo et al. 1997) Increases dermal angiogenesis (Schwartz et al. 2003) Inflammatory mediator (Vujaskovic et al. 2002; Camidge and Price 2001; Cassady et al. 1975)
IL-6	Inflammatory mediator (Vujaskovic et al. 2002; Camidge and Price 2001; Cassady et al. 1975)
IL-8	Chemokine (Saif et al. 2008)
Eotaxin	Chemokine (Saif et al. 2008)
TGF-B1	Enhances collagen production in response to radiation (Denham and Hauer-Jensen 2002; Cassady et al. 1975; Khanfir and Anchisi 2008) Accelerates the terminal differentiation of progenitor fibroblast to postmitotic functional fibrocytes Stimulates the synthesis of extracellular matrix proteins and MMPs (Bostrom et al. 1999)
PDGF	Induces fibroblast differentiation (Hird et al. 2008)
CCN2	Involved with TGF-B1 in stimulating fibrosis (Hird et al. 2008)
TNF-α	Inflammatory mediators (Vujaskovic et al. 2002; Camidge and Price 2001; Cassady et al. 1975)
CTGF	Promotes fibrosis and secreted by fibroblasts and endothelial cells (Greco et al. 1976)
Smad3	Transduces signaling effects through TGF-B1 (increases chemoattraction and elaboration of extracellular matrix by fibroblasts, inhibitory effects of keratinocyte proliferation, and migration) (Cassady et al. 1975)

Human radiation injury (Table 44.2, p.501). CTGF, connective tissue factor; IL, interleukin; MMPs, matrix metalloproteinases; PDGF, platelets derived growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor

et al. 1998; Herskind et al. 1998; Hakenjos et al. 2000), and thereby increasing secretion of extracellular matrix component proteins (Canney and Dean 1990; Vozenin-Brotons et al. 1999; Schultze-Mosgau et al. 2002). TGF-β promotes its own secretion by fibroblasts in a self-amplifying cascade (Burger et al. 1998). In response, the secretion of most matrix proteins, including collagen, is increased, and matrix proteinases are decreased (Mayer 1990; Hageman et al. 2005; Zhao et al. 2001). Epithelial cell proliferation is diminished, and there is chemotaxis of mast cells and macrophages. The result is increasing production, processing, and deposition of collagen (fibrosis), and loss of epithelial reconstitution of normal tissue structure.

The initiating event in TGF-β activation in response to radiation is poorly understood. Latent TGF-β in the extracellular matrix may be activated by exposure to ionizing radiation (Rodemann and Blaese 2007; Barcellos-Hoff et al. 1994; Barcellos-Hoff 1998). This may involve proteolytic enzymes which act in the presence of radiation-induced reactive oxygen species. This is supported by experimental evidence that free radical scavengers may prevent TGF-β increases as well as fibrosis in irradiated lung (Vujaskovic et al. 2002; Epperly et al. 1999). Other potential sources of TGF-β include endothelial cells, which may release TGF-β in direct response to radiation, or from normal dermal components such as fibroblasts, epithelial cells, macrophages, or endothelial cells as a response to tissue damage. The latter may be the predominant mechanism of consequential late fibrosis following severe acute skin injury, as the severe acute epidermal and dermal tissue injury activates a generalized fibrotic response.

Endothelial cell damage may be a direct result of radiation exposure (endothelial apoptosis or necrosis) or indirectly thorough loss of epithelial barrier function or adjacent tissue necrosis. Damaged endothelial cells secrete TGF-β, which then promotes fibrotic replacement of the damaged dermis. It also increases endothelial permeability, which results in inflammation, and activates the coagulation cascade (Denham and Hauer-Jensen 2002). The inflammatory response includes the chemotaxis and proliferation of macrophages and mast cells which is then direct neovascularization. The histologic result is hypovascular, fibrotic dermis, with a network of tortuous vessels, and telangiectasia. Cytokines that have been implicated in late skin effects from RT are summarized in Table 1.

4 Pathophysiology

Following a large single or fractionated dose there is a linear loss of basal cells, reaching a nadir at ~21 days, followed by exponential reepithelialization to control levels and above by 28–32 days (Fig. 4). The mitotic index and labeling index are increased during this period of

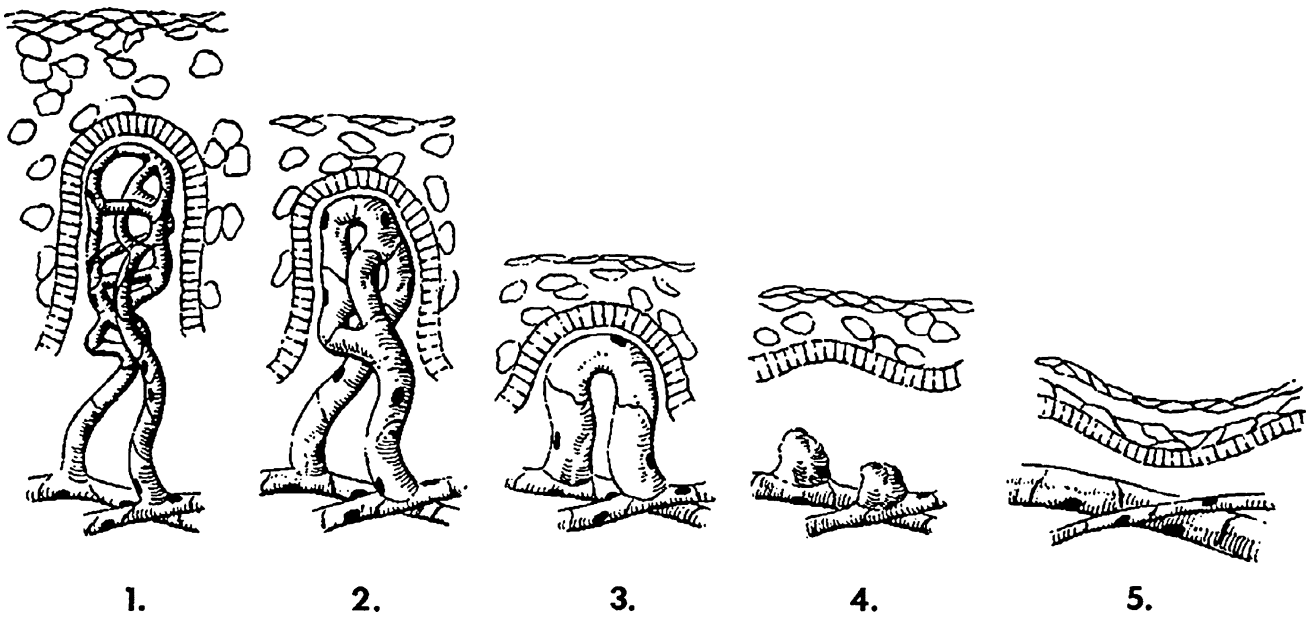

Fig. 4 A diagram of the sequence of microvessel changes in the skin functional unit in time following irradiation. The microvessel tuft is shown as a folded manifold. This model incorporates the loss of cells with vessel shortening and the loss of cells with loss of the short branch of the manifold. A time scale is ignored but must be represented by months and years with the development of telangiectasia. The telangiectasia produced is represented as formed in the vessels of the rete plexus that supplied the tuft. (From Archambeau et al. 1995, IJROBP LENT SOMA)

regeneration. The generation time for this period is estimated to be 15 h. Complete regeneration of the epidermis is produced at all dose fractions up to 45 Gy. Reepithelialization at 32–36 days can then be followed by a second ulceration and necrosis. During the period of basal cell degeneration and regeneration the endothelial population parameters do not change.

Change produced by irradiation in the microvessel endothelium, which exits as a line of 10–20 single cells without supporting adventitia, is not well documented. Endothelial proliferation has not been observed; therefore, the principle change is one of cell loss without replacement. The changes documented histologically are cell loss, a decreased in the number of vessel lumens seen on microscopic section (representing vessel shortening), decrease in tuft density and dilatation. The turnover time or replacement time of endothelial cells is not known, but is estimated to take months of years as evidenced by the time required for late effects to be produced.

A diagram of the sequence of microvessel changes in the skin functional unit in time following irradiation. The microvessel tuft is shown as a folded manifold. This model incorporates the loss of cells with vessel shortening and the loss of cells with loss of the short branch of the manifold (Fig. 3b). A time scale is ignored but must be represented by months and years with the development of the telangiectasia. The telangiectasia produced is represented as formed in the vessels of the rete plexus that supplied the tuft.

5 Clinical Syndromes

5.1 Acute Erythema Phase

Hyper-acute reactions (within hours of RT): Skin changes after radiation exposure follow a predictable course dictated by radiation dose, timing, and the biology of the human inflammatory reaction (Tables 2, 3). The earliest clinically evident reaction is erythema that may occur and resolve within hours, and is normally only evident after relatively high-dose exposure. The threshold dose is 2 Gy or greater, and this effect is noted in therapeutic courses aimed at cutaneous targets, lower energy treatment courses (kilovoltage), or hypofractionated treatment regimens. Histologically, there is a vasodilation and a transient permeability increase in capillaries that results in mild erythema and edema at 2–24 h following exposure (Hall and Giaccia 2005).

Prior to adoption of the Roentgen (R), and later the Gray (Gy), as a measure of radiation dose, skin erythema dose (SED) was used as a crude clinical measure of patient radiation exposure (Khan 2003). For lower energy radiation, this was a reasonable measure of the total dose deposited because the maximum dose was deposited at the skin surface. This transient acute reaction is no longer commonly noted due to the increased use of multiple or rotational fields and megavoltage therapy, high-energy, relatively skin sparing, radiation treatment beams, and the use of fraction size of $\leq$ 2 Gy per day. Acute, transient skin erythema is still commonly

Table 2 LENT SOMA Skin/Subcutaneous tissue

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Scaling/roughness sensation	Present/ asymptomatic Hypersensitivity, pruritus	Symptomatic Intermittent pain	Require constant attention Persistent pain	Debilitating dysfunction
Objective				
Edema Alopecia(scalp) Pigmentation change Ulcer/Necrosis Telangiectasia Fibrosis/Scar Atrophy/Contraction (depression)	Present/ asymptomatic Thinning Transitory, slight Epidermal only Minor Present/ asymptomatic Present/ asymptomatic	Symptomatic Patchy, permanent Permanent, marked Dermal Moderate < 50 % Symptomatic Symptomatic/ $< 10\%$	Secondary dysfunction complete, permanent Subcutaneous Gross ≥ 50 % Secondary dysfunction Secondary dysfunction/ 10–30 %	Total dysfunction Bone exposed Total dysfunction Total dysfunction/ > 30 %
Management				
Dryness Sensation Ulcer Edema Fibrosis/Scar		Intermittent medical intervention	Medical intervention Continuous medical intervention Medical intervention Medical intervention Medical intervention	Surgical intervention/ amputaion Surgical intervention/ amputaion Surgical intervention/ amputaion
Analytic				
Color photographs	Assessment of changes in appearance			

Table 3 Late skin changes may be broadly, and somewhat arbitrarily, segregated into categories and associated examples as shown

	Focal	Global
Subclinical	1. Latent reduced capacity to tolerate future insults (e.g., difficulty with wound healing) 2. Imaging abnormalities	1. Reduced tolerance to alterations in temperature
Clinical	1. Ulceration 2. Fibrosis/retraction 3. Hair loss 4. Atrophy and skin thinning	1. Cosmetic changes and secondary challenges with socialization 2. Reduced mobility of joints underlying fibrotic areas of skin 3. Abnormalities in thermoregulation

Table 4 Gross skin changes produced by irradiation

Acute changes	Late changes
Erythema	Atrophy
Pigmentation	Scaling
Dry desquamation	Pigmentation
Moist reaction	Atrophy
That heals	Fibrosis
Heals partially	Telangiectasia
Does not heal	Necrosis

reported following interventional diagnostic and therapeutic procedures with prolonged fluoroscopy screening times, due to less penetrating kilo-voltage beams. The SOMA LENT system provides a systematic manner to assess, categorize and grade acute reactions to the skin (Table 2), and to specific organs where the skin reaction is a prominent component (e.g., the Breast, see "Breast Cancer"). Skin changes may also be broadly, and somewhat arbitrarily, segregated into focal versus global, and clinical versus subclinical (Table 3).

5.2 Detection and Diagnosis

Since the integument is readily visible on physical examination, the gross skin changes produced by irradiation are summarized in Table 4.

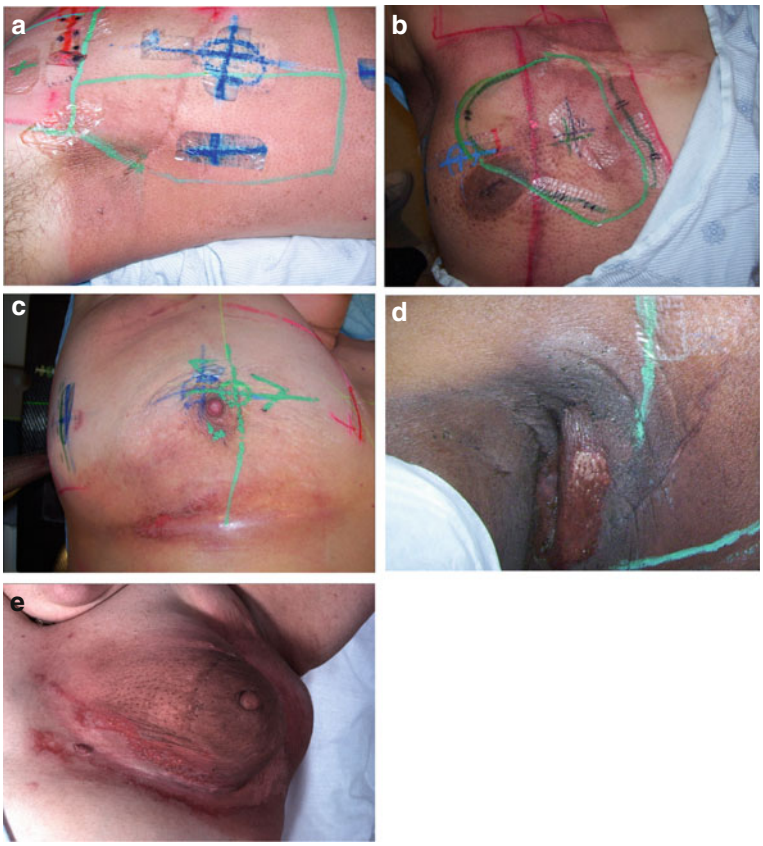

Fig. 5 Acute Dermatitis. **a** Early erythema during radiation therapy for breast cancer. **b** Hyperpigmentation as an early manifestation of radiation dermatitis. Note that the scar tissue in the upper inner quadrant is spared. **c** Dry desquamation of the inframammary fold. **d** Patchy moist desquamation in an axillary skin fold. **e** Confluent moist desquamation

5.2.1 Acute Moist Dermatitis

The more sustained, common, and relevant reactions take place over a matter of weeks following initial exposure (Fig. 5a, b, c, d, e). Acute radiation dermatitis progresses through stages of severity based on the accumulation of radiation-induced changes to dermal vascular and appendageal structures, epidermal stem cells, and activation of inflammatory pathways. The severity of dermatitis is a function of accumulated damage and therefore related to radiation dose. Dermatitis may be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). This scale is symptom-based, and does not inherently distinguish between acute and late reactions based on the timing of the symptom in relation to radiation exposure. Common acute and late dermatologic symptoms not included as radiation dermatitis by the CTCAE.

Grade 1 dermatitis manifests as faint skin erythema within the treatment area, or dry desquamation. Erythema is seen in two contexts: first, as discussed above, there may be a transient vasodilation in the hours after a single fraction skin exposure of 2 Gy or higher. More commonly, erythema develops over the first two to three weeks of fractionated radiation with accumulated exposure (Fig. 5a). In some patients, this manifests as hyperpigmentation (Fig. 5b). With continuing or higher dose radiation exposure, damage to the basal cells in the epidermis may progress until this stem cell population is lost in localized areas, resulting in dry desquamation (Fig. 5c).

Further and more widespread damage to the basal layer leads to further desquamation, and the production of a fibrinous exudate due to increased arteriole permeability and edema in the underlying dermis. This is moist desquamation. The CTC differentiates moist desquamation based on whether it is patchy and localized to skin folds (grade 2, Fig. 5d), or confluent affecting a more widespread area (grade 3, Fig. 4e). Skin folds and creases are particularly susceptible to such reactions since the local dose may be increased due to a "local loss of skin sparing". Additionally, these areas may be subject to additional trauma associated with friction between the two "opposing sides" of the skin fold during normal movement, and/or overlying clothing (e.g., waist-bands of pants or a women's brassiere). More widespread moist desquamation in areas less prone to mechanical trauma is indicative of additional accumulated damage.

The outer strata of the epidermis are composed of fully differentiated and nondividing epithelial cells, which are continuously renewed from proliferating cells in the basal layer of the epidermis. Newly formed daughter cells in the basal layer migrate outward as they differentiate, over approximately 14 days, to reconstitute the outer strata. The turnover time is a function of the local thickness of the

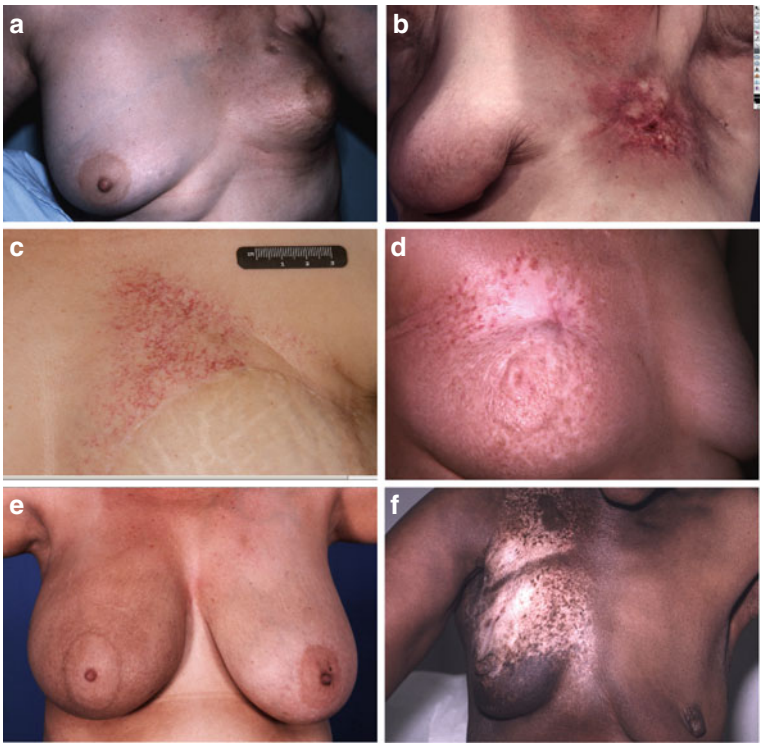

Fig. 6 Chronic Fibrosis. In panel **a**, there is retraction of the treated left breast, with mild to moderate overlying fibrosis. **b** More significant and localized fibrosis with loss of normal skin markings, pigmentation changes, skin retraction, and early ulcerative changes. **c** Telangiectasia which have developed years after radiation. **d** Pigmentation changes -mixed hypo- and hyperpigmented areas. **e** Hyperpigmentation one year after completion of radiation. **f** Hypopigmentation

epidermis, and can vary from 10 to 40 days. Desquamation occurs due to radiation-induced loss of this basal layer, and manifests in the second or third week of fractionated radiation, as the loss of basal stem cells becomes clinically evident. Moist desquamation is an indication of more complete loss of the basal layer; the fibrinous exudate is a result of increased permeability in the dermal vasculature, along with loss of normal epidermal basement membrane integrity.

5.2.2 Dermis

The underlying dermis is composed of connective tissue and houses the vascular and lymphatic network, as well skin adnexa including hair follicles, sweat and sebaceous glands, and sensineural structures. Acutely, most clinically evident changes in the dermis occur due to vascular changes. Vasodilation and increasing vascular permeability occur early (Fajardo and Berthrong 1988), and the resulting perivascular inflammation results in clinically characteristic erythema and edema. Skin adnexal cells are relatively radiosensitive as well, and may not regenerate following exposure. The process of epilation begins within days of radiation exposure (Sieber et al. 1993). Sebaceous glands have similar sensitivity, and eccrine sweat glands become dysfunctional shortly afterwards in a fractionated radiation treatment course. Histologically, these glandular structures demonstrate apoptosis, necrosis, and loss of normal mitotic activity (Malkinson and Keane 1981). Clinically, this leads to either acute and chronic hypohydrosis or anhidrosis.

5.2.3 Regeneration

Regeneration of areas of moist desquamation occurs primarily through replacement of epidermal basal cells either from islands of intact cells within the epidermis or by the migration of such cells from adjacent, uninvolved areas. Normal healing of the radiation wound becomes clinically evident approximately 2 weeks after exposure, consistent with the basal cell turnover time. Widespread confluent mucositis (CTCAE grade 3), or more severe toxicity such as necrosis of the epidermis or underlying dermis, may not undergo complete regeneration of the structural and adnexal elements. Instead, there is prolonged inflammation and progression to early fibrosis. Histologically, the normal epidermis is replaced by fibroblasts and a collagen scar. This is in contrast to the more common late fibrosis, which arises following the regeneration of relatively normal-appearing skin. "Consequential late effects" (Dorr and Hendry 2001) are those directly related to the severity and extent of acute events, and result from the failure of normal healing of the radiation wound, rather than the more commonly noted chronic toxicity, the severity of which is not always predicted by the extent and severity of acute events.

5.2.4 Late Changes of Atrophy and Fibrosis

Late radiation toxicity occurs months to years following exposure, following a period during which the skin may not exhibit significant abnormalities (Figs. 6a, b, c, d, e, f, and 7a, b, c, d, e). Unlike consequential late effects, the risk and severity of true late skin changes are not thought to be

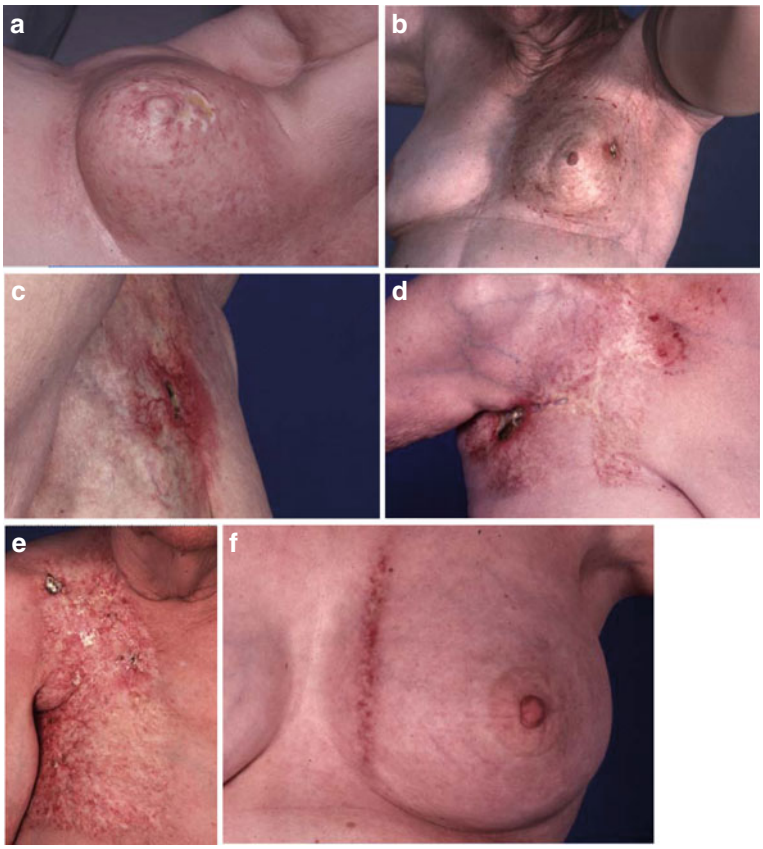

Fig. 7 Late radiation necrosis. **a** A superficial area of necrosis. **b** A necrotic ulceration in the background of marked fibrosis. **c** Necrosis with superficial erosion into the subcutaneous layer. **d** Advanced necrosis. **e** A large area of severe fibrosis. **f** Match line fibrosis at the junction of a breast tangent field with an internal mammary field. The most significant skin changes are limited to the area of overlap, which received radiation from both fields

associated with the risk and severity of acute dermatitis, except that both occur as a function of radiation dose. The clinical hallmarks of late radiation dermatitis are fibrosis, atrophy, and telangiectasia.

The late skin toxicity with the most functional consequence is subcutaneous fibrosis. Activation of growth factors induces replacement of the subcutaneous adipose tissue with fibrous tissue, leading to limitations in range of motion, contraction, pain, and poor cosmesis (Fig. 6a, b). Fibrosis of hair follicles may lead to permanent alopecia. Even in cases where dermal and subcutaneous fibrosis is not clinically evident, there may be atrophy of the skin adnexa. Hair follicles, sebaceous, and sweat glands may be absent in previously irradiation skin because these are not regenerated during normal radiation wound repair.

Loss of glandular elements leads to anhidrosis when extensive skin areas are irradiated, such as in total skin electron therapy. The microvasculature of the dermis and subcutis may develop excess myointimal proliferation, leading to a functional hypovascularity. Tortuosity within small vessels, and microthrombi, results in visible telangiectasia (Fig. 6c). Irregular regeneration of the basal layer of the epidermis may be evident as dyspigmentation (Fig. 6d, e, f).

Paradoxically, there may be a decrease in the population of resident skin fibroblasts in atrophic skin, with loss of the normal collagen structure leading to increased skin fragility and poor wound healing. Necrosis can occur in response to minor trauma or spontaneously, as a consequence of poor tissue perfusion, because of impaired normal tissue repair (Fig. 7a, b, c, d). Care should therefore be taken when considering a biopsy or other procedure involving irradiated skin.

The pathologic severity of late fibrosis is dependent on the radiation dose and volume, and may be modified by underlying comorbid illness and the genetic background. The clinical severity may range from poor cosmesis to significant loss of function, and additionally depends on the anatomic restrictions to motion that result from the underlying fibrosis (Fig. 7e).

6 Radiation Tolerance

6.1 Dose Time Fractionation

One of the earliest reports to systematically document time dose fractionation, was by Strandquist (1944), who treated many skin cancer patients with superficial (100 kv) and orthovoltage (2–400 kv) radiation. The biologic effect in skin was suggested to be proportional to the total dose delivered, under specified conditions of fractionation of dose. The series of isoeffect lines were plotted based on the cure of the skin cancer versus the healing of the skin. This clinical study is the

first observation of a therapeutic ratio, mainly there is a fractionated radiation schedule that can heal the skin cancer as well as the skin. When the doses exceeded the level for ablating the skin cancer, the larger doses resulted in skin necrosis. This was the beginning of establishing favorable radiation therapeutic ratios, wherein cancers can be eradicated without producing severe late effects.

6.2 Radiation Dose and Volume Relationships

Acute and late cutaneous toxicity following radiation therapy is a function of both the inherent radiation sensitivity of the epidermal and dermal structures, as well as the radiation energy, fractionation, and field size. One of the earliest attempt to systematically and comprehensively examine the tolerance of cutaneous tissue to megavoltage-energy radiation was published by Emami et al. (1991). The authors examined retrospective data from patients and compiled estimates of radiation doses that would confer 5 and 50 % risk of late side effects at 5 years—the TD5/5 and TD50/5, respectively. For skin toxicity, they used telangiectasia and necrosis as endpoints, and estimated dose tolerances for treatment of 10, 30, and 100 cm^2. For the endpoint of necrosis and for a 100 cm* field, the estimated TD 3/5 was 5100 cGy, TD 5/5 5500 cGy, and TD 50/5 was 7000 cGy. For a 30 cm* field, the estimated TD 3/5 was 5700 cGy. For a 10 cm^2 field, the TD 3/5 was 6900 cGy. For the endpoint of telangiectasia with an area of approximately 100 cm*, the TD 10/5 was 5000 cGy, TD 30/5 was 5900 cGy, and the TD 50/5 was 6500 cGy (Table 5).

A subsequent review summarized the dose-dependent changes in gross appearance, function, and histology following radiation (Table 5; Archambeau et al. 1995). Larger and more modern series have corroborated these doses. In a series of 468 patients treated for primary skin cancer, in which the prescription dose was delivered to the skin surface, the risk of late skin necrosis was 5.8 % (Locke et al. 2001). The dose delivered was 40 to greater than 60 Gy in fraction sizes of 2–4 Gy per day, and patients were treated with kilovoltage photons and/or electrons with appropriate bolus material to bring the skin dose to 100 %. Notably, the risk of late necrosis correlated with increasing field size and appeared to be increased when the dose was delivered to greater depth.

Interpreting toxicity data from series of noncutaneous malignancy, in which the skin exposure is incidental, is more problematic because the skin dose is rarely measured or reported, and the relative skin dose is a function of radiation energy and technique. For example, a dosimetric study undertaken specifically to compare the skin dose with various radiation techniques in breast cancer patients found the measured skin dose to be 58–71 % of the prescription dose (Selvaraj et al. 2007). Most clinically apparent radiation fibrosis in breast cancer patients is noted in areas of radiation field junctions, where there was unintended overlap (Fig. 6f). Other late effects in breast cancer, such as telangiectasia, which can occur at lower doses, can be seen in the inframammary area or other regions of localized excess dose. A randomized trial in extremity soft tissue sarcoma was conducted specifically to evaluate late radiation morbidity, including subcutaneous fibrosis. Patients were randomized to 50 Gy preoperative radiation or 66 Gy posteroperative. Late grade 2 or greater fibrosis was significantly higher in the postoperative arm, likely due to both increased dose and the prior surgery (Davis et al. 2005). Taken together, the available evidence suggests that doses in excess of approximately 60 Gy increased the risk and severity of clinically significant fibrosis. Additionally, the latency the period between cessation of radiation and clinically apparent skin changes may be shorter in patients exposed to higher doses (Herrmann and Baumann 2006).

More complex methods of predicting normal tissue complications have evolved for many tissue types, particularly lung and liver, related to an effort to escalate radiation dose using more complex beam arrangements (Kong et al. 2007; Milano et al. 2007). These efforts acknowledge that the risk and severity of early and late side effects are a function of not only the maximum radiation dose but also the volume of normal tissue exposed to both high and intermediate doses. The metrics that have evolved range from the addition of low-dose or mean-dose thresholds to the calculation of normal tissue complication probability (NTCP) using mean equivalent dose. No such formalism is in widespread use for evaluating dose to the skin, and data to suggest parameters for similar relationships are lacking. Examination of a large series of skin cancers treated with primary radiotherapy does suggest that increasing tumor size (and by extension, increasing field size) does correlate with an increasing risk of poor cosmesis (Locke et al. 2001), independent of the prescription dose, and this supports a similar volume effect to that seen in other anatomic sites.

Normal tissue dose limits are determined by both the total dose and the fractionation schedule. Most of the clinical experience regarding normal tissue dose tolerance is based on daily treatment with fraction size in the range of 1.8–3 Gy. Equivalent dosing can be estimated for modest alterations in dose using well-accepted models; for more significant increases in daily dose these models may not provide accurate estimates. As stereotactic body radiotherapy, and other hypofractionated treatment regimens, are more commonly employed, normal tissue dose constraints for one to five high-dose fractions are becoming more important. In a recently published series from Memorial Sloan–Kettering Cancer Center, skin toxicity was examined in 50 patients treated in 3 or 4 fractions, from 44 to 60 Gy

for pulmonary tumors (Hoppe et al. 2008). Grade 2 or greater skin toxicity (by the NCI-CTC criteria) correlated with skin dose of greater than 50 % of prescription (i.e., 22–30 Gy). One patient had Grade 4 changes (necrosis) and the authors estimated a skin dose of close to 90 % of prescription (54 Gy) in 3 fractions.

7 Chemotherapy Tolerance

7.1 Systemic Radiosensitization

Concurrent chemoradiatiotherapy is often administered in an effort to exploit the synergistic interaction between radiation and specific radiosensitizing chemotherapy agents (Table 6). Most such agents are nonspecific radiosenstizers; that is, they both increase the effect of the radiation on the tumor target and exacerbate the acute radiation effects on normal tissue. This has been clinically demonstrated in randomized trials of chemoradiotherapy versus radiotherapy alone, in which a significant increase in acute radiation-related mucosal toxicity has been noted in the treatment of esophageal cancer (Cooper et al. 1999), and head and neck cancer (Adelstein et al. 2003). Common chemotherapy drugs identified as radiosensitizers are listed in Table 6.

Concurrent radiosensitizing chemotherapy is indicated for selected lung, gastrointestinal, and gynecologic malignancies (among others) in which the radiation planning is relatively skin-sparing, and therefore the severity of the dermal reaction is typically mild. Dermatitis is more common, and more severe, during chemoradiation for head and neck cancer where the superficial dose may be focally high. Randomized trials assessing the benefit of concurrent chemotherapy have not demonstrated an increase in clinically significant dermatitis, however (Adelstein et al. 2003). This may reflect the fact that the superficial dose varies significantly due to both patient factors as well as treatment technique. Breast cancer may be a superior model, since the skin dose is relatively consistent among patients. Randomized and nonrandomized studies have examined the role of concurrent, rather than sequential, chemoradiation for patients with high-risk breast cancer (Bellon et al. 2004; Livi et al. 2008; Isaac et al. 2002). In one large, retrospective review of concurrent chemoradiotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) compared to breast radiotherapy alone, the addition of concurrent therapy doubled the incidence of grade 2 or greater dermatitis (Livi et al. 2008), although not to clinically significant levels. The ARCOSEIN study is a large multicenter trial that enrolled 297 breast cancer patients and randomized the subjects to either concurrent or sequential chemotherapy. Toxicity assessment was blinded. There was no increase in acute radiation toxicity with concurrent therapy, but the risk of late subcutaneous fibrosis was significantly increased (Toledano et al. 2006).

Tamoxifen is a hormonal agent given during or shortly after radiation in many patients with receptor-positive breast cancer and ductal carcinoma in situ. Tamoxifen is not a classic radiosensitizer, and there is no evidence that tamoxifen given concurrently with breast radiation increases the risk of acute dermatitis (Ahn et al. 2005). Interestingly, tamoxifen may induce TGF-β, which is implicated in the development of radiation fibrosis. A retrospective analysis of 147 patients, 90 of whom had concurrent rather than sequential tamoxifen, has found that late radiation fibrosis is increased in patients who received the drug during their breast radiation (Azria et al. 2004). This has not been a consistent finding; an analysis of 458 patients undertaken to determine the patient and treatment factors impacting on long-term cosmesis failed to find any effect of tamoxifen (Taylor et al. 1995).

7.2 Alopecia

Alopecia is very traumatic because sudden loss of hair is a precursor to loss of self image and identity. Alopecia occurs with numerous cytotoxic agents, acting in anagen phase when hair is mitotically active. The hair becomes thin and brittle shedding resulting in baldness. Immediate anagen release, forcing hair into telogen, and leading to premature shedding occurs. The resulting telogen effluvium is dividing into subcategories:

- Acute with hair loss beginning in 2–3 weeks up to 2–3 months
- Chronic with hair shedding for $\geq$6 months.

Intravenous chemotherapy acts more rapidly versus oral intake. Once chemotherapy is completed, hair returns in 2–3 months. Numerous therapeutic interventions have been implemented with varying degrees of success.

8 Special Topics

8.1 Radiation Recall

Radiation recall is a phenomenon first described several decades ago (D'Angio et al. 1959), describing a cutaneous reaction in the area of previous radiation exposure, in response to specific systemic agents (Table 7). The most

Table 5 Changes produced by increasing total dose (adapted from Archambeau et al. 1995 with permissions)

Schedule dose range dose fraction single (cGy)	Multiple (200 cGy/ day)	Gross Change	Onset of change	Functional change	Histologic change
500–700	~2,000	Epilation	~18days	–	Empty follicle
1000–2000	2000–4000	Erythema	12–17 days	Hyperemia	None noted
2000–3000	–	–	2–6 days	–	–
1000–2000	~4500	Pigmentation		None	Increased melanin
1000–2000	~4500	Dry desquamation	30–70 days	–	Hyperplasia
2000–2400	4500–5000	Moist desquamation that heals	30–50 days	Serum leakage; healing regenerates functional barrier	Linear decrease in cell density exponential cell replacement
>2400	>5000 >6000	Moist Desquamation does not heal > 50 %	30–50 days	Loss of protective Barrier	Linear decrease in cell density
1700–2400	4500–5000	Telangiectasia	6 months–years	None	Cell and vessel Loss; lumen dilatation
>2700	> 6000	Necrosis nonhealing	Months, years	Loss of protective barrier	Necrosis

commonly cited chemotherapeutic agents are anthracyclines (Camidge and Price 2001; Cassady et al. 1975; Greco et al. 1976), taxanes (Shenkier and Gelmon 1994; Yeo et al. 1997), and gemcitabine (Schwartz et al. 2003). The relative incidence of a recall reaction, with regard to any specific system agent, is difficult to discern. There is likely a reporting bias reflecting the relative prevalence of administration of certain agents in patients who have received radiation treatment that includes the skin (i.e., the use of anthracyclines and taxanes in breast cancer patients). Additional systemic agents implicated in radiation recall reactions (listed in Table 7) include standard chemotherapeutic agents, newer targeted therapeutics (Saif et al. 2008; Khanfir and Anchisi 2008), hormonal therapy agents (Parry 1992; Bostrom et al. 1999), as well as non-oncologic medications (Hird et al. 2008).

The clinical manifestations of radiation recall occur with the inital administration of the systemic agent, within minutes to days with intravenous drug, or days to weeks with oral medication. The timing of presentation may be related to the drug dose (Cassady et al. 1975), and both the severity and timing of the reaction may be related to the prior radiation dose (Stelzer et al. 1993). The duration of the responses reported ranges from weeks to months. Interestingly, readministration of the same systemic agent does not consistently lead to recurrence of the phenomenon.

While a recall reaction can occur in any organ, skin is the most common site. It occurs in a well-demarcated area defined by the borders of the previous treatment field, and can occur despite the lack of any clinically significant skin reaction during the previous radiation treatment. The clinical signs and symptoms mimic acute radiation hypersensitivity dermatitis, and this can range from erythema and a maculopapular rash to desquamation and necrosis. The pathogenesis is not well understood. An early hypothesis was that tissue stem cells remained depleted long after radiation, making the tissue more sensitive to cytotoxics. This does not explain, however, radiation recall reactions elicited by noncytotoxics or the lack of a reaction to subsequent drug exposure in some cases. The clinicopathologic manifestations are best explained by a local, acquired drug hypersensitivity reaction. Prior radiation therapy may locally alter the normal dermal immunologic response by changing basal and stimulated cytokine production (Azria et al. 2005; Hallahan et al. 1989). This is consistent with histologic findings of acute inflammation (vasodilation, infiltration of inflammatory cell mediators) in affected tissue, as well as the response of recall dermatitis to treatment with corticosteroids.

8.2 Secondary Malignancy

Radiation exposure is an established cause of solid and non-solid tumors in animals and humans. Some of the earliest of evidence of this link was the observation of an increased risk of skin malignancies in radiation workers including uranium miners and radiologists (Hall and Giaccia 2005). Basal and squamous cell skin cancers were also noted to occur in excess in survivors of Hiroshima and Nagasaki, and their incidence significantly related to radiation exposure with an excess relative risk of 1.0 per sievert (Thompson et al. 1994).

Table 6 Non-specific radiosensitizers

Chemotherapy Agents
Bleomycin
Capecitabine, 5-Fluorouracil
Cisplatin, Carboplatin, Oxaliplatin
Dactinomycin, Doxorubicin
Docetaxel, Paclitaxel
Gemcitabine
Gemcitabine
Methotrexate

Chemotherapeutic agents which enhance acute radiation toxicity when given concurrently

The role of therapeutic radiation in the induction of nonmelanoma skin cancer has been established in several large retrospective studies. An analysis of 1805 patients enrolled on a skin cancer prevention trial found that prior radiation therapy predicted a significantly higher risk of basal cell tumors, with a relative risk of 2.3. The risk of squamous cell cancers was not elevated, although the overall incidence was lower than that of basal cell. The relative risk of developing a basal cell cancer was highest in those treated at a younger age, and increased with time since radiation exposure (greatest at 20 years (Karagas et al. 1996)). These cancers occurred within the radiation field, and the risk appeared to be highest for those who were treated to the face and neck, raising the possibility that sun exposure may increase the risk of radiation-induced skin cancer. A case–control study from the New Hampshire Skin Cancer Study Group included 592 cases of basal cell cancer and 289 cases of squamous cancer, with age- and gender-matched controls (Lichter et al. 2000). There was an increased risk of both basal and squamous cell cancer in patients who reported a history of radiotherapy (relative risk of 3.3, and 2.94, respectively).

8.3 Genetic Syndromes

Several genetic syndromes are associated with an increased risk of cutaneous toxicity following radiation exposure. Many of these involve impaired DNA damage repair pathways, and most patients are predisposed to excess normal tissue effects in all organs.

Ataxia telangiectasia (AT) is a rare autosomal-recessive disorder in which both copies of the ATM gene are mutated. This leads to a loss of recruitment of DNA damage repair proteins to double-strand breaks, and enhances cellular radiation sensitivity. Patients with AT are prone to severe cutaneous side effects. Patients who are heterozygotes for the mutant AT trait do not demonstrate any of the characteristic neurologic or cutaneous manifestations of the syndrome, but may be predisposed to excess radiation toxicity. A high rate of late skin complications has been observed in breast cancer patients with an ATM mutation (Iannuzzi et al. 2002). Since the prevalence of the heterozygous mutation may be as high as 1 % in the U.S. population, this has been posited to explain part of the observed heterogeneity in patient sensitivity to radiation. This observed increase in sensitivity has not been consistently demonstrated, however (Bremer et al. 2003).

Other syndromes associated with defects in DNA repair are less prevalent. These include Fanconi's anemia, Bloom and Gardner's syndrome, and Dysplastic Nevus Syndrome. Although an increase in radiation-mediated DNA damage has been demonstrated in some of these syndromes, there is no compelling evidence that this generally translates into a clinically significant risk of increased tissue effects.

Basal cell nevus syndrome (BCNS, Gorlin's syndrome) is a hereditary disorder associated with the abnormalities in the PTCH gene, a tumor suppressor in the Hedgehog signaling pathway (Bale 2002). The syndrome is characterized by skeletal abnormalities, an elevated risk of childhood medulloblastoma, and a predilection for developing multiple basal cell carcinomas of the skin beginning at an early age. In murine models of BCNS, animals have an increased risk of secondary malignancy following exposure to radiation therapy (Hahn et al. 1998). In human patients with BCNS who are treated with therapeutic radiation, there is a markedly increased risk of secondary malignancy. Published reports include secondary brain tumors and innumerable basal cell skin cancers arising within the radiation field of adults who were treated with radiation therapy for childhood medulloblastoma (O'Malley et al. 1997; Atahan et al. 1998).

8.4 Comorbid Medical Illness

The severity of late radiation dermatitis may be increased in the presence of any of several comorbid medical conditions. The clinical manifestations of radiation fibrosis are a function of the extent of the fibrotic response, and the ability of the impaired dermal microvasculature to perform normal cutaneous organ function. Conditions that impair the normal microvasculature are expected to exacerbate fibrotic replacement of the normal epidermis and dermis, and worsen the clinical symptoms of late radiation injury such as poor wound healing, contracture, loss of range of motion, atrophy, and dyspigmentation. Hypertension and diabetes are both associated with diminished dermal microvasculature, and are implicated in worsening late radiation injury (Baker and Krochak 1989). In particular, the combination of hypertension and diabetes is a predictor of more severe late radiation toxicity (Chon and Loeffler 2002). Other patient

Table 7 Agents reported to induce a radiation recall reaction

Cytotoxic chemotherapy	Targeted or hormonal agents	Non-oncologic systemic
Arsenic Trioxide	Bevacizumab	Gatifloxacin
Bleomycin	Pemetrexed	Isoniazid
Capecitabine	Tamoxifen	Levofloxacin
Cyclophosphamide		Simvastatin
Cytarabine		
Dacarbazine		
Dactinomycin		
Daunorubicin		
Docetaxel		
Doxorubicin		
Epirubicin		
Etoposide		
Fluorouracil		
Gemcitabine		
Hydroxyurea		
Idarubicin		
Lomustine		
Melphalan		
Methotrexate		
Paclitaxel		
Vinblastine		

factors, such as advanced age, tobacco use, and distal extremity location may similarly increase the risk.

The presence of active collagen vascular disease (CVD) is often cited as a relative contraindication to radiation treatment, due to concern for severe late fibrosis (Holscher et al. 2006). This loosely defined family of disorders, including systemic lupus erythematosus (SLE), scleroderma, rheumatoid arthritis (RA), polymyositis or dermatomyositis, and mixed connective tissue disorders (MCTD) among others, share a propensity for an inappropriately active immune response. SLE and scleroderma in particular are often associated with cutaneous fibrotic manifestations. Several retrospective and case–control studies have examined the incidence of late cutaneous toxicity in these populations. Because of the relatively low prevalence of some disorders, the occasional uncertainty of diagnoses, and the range of clinical severity, a clear evaluation of the effect on radiation sensitivity is not always feasible. In a study in breast cancer patients, severe late fibrosis was found in irradiated patients with scleroderma, but not other CVDs (Chen et al. 2001). Similar finding were made regarding more generally defined late toxicity in patients who received radiation to other sites, that non-RA CVDs, most commonly SLE and scleroderma, predicted for worse late toxicity (Morris and Powell 1997; Phan et al. 2003). One case–control study found that all CVDs, including RA, predicted for an increased severity of late toxicity, but that the most severe effects were seen in patients with scleroderma and SLE (Lin et al. 2008). These authors also examined radiation responses in patients with systemic vasculitides (polymyalgia rheumatica, temporal arthritis, Wegener's granulomatosis) and found a similar increase in late toxicity. It is important to note that the diseases most strongly correlated to increasing late fibrosis are those that commonly manifest with skin abnormalities. There has been no clear correlation with an increase in acute effects in this population, and as there are no reports of fatal or life-threatening sequelae, this remains a relative, rather than an absolute, contraindication to radiation treatment.

8.5 Wound Healing

Ionizing radiation can impair all stages of wound healing, depending on the anatomic area of skin irradiated, total radiation dose delivered, and the timing of exposure with respect to wound formation. Potential targets of such effects include local inflammatory cells and fibroblasts.

Wound healing within previously irradiated skin is impaired to an extent dependent upon the previous radiation dose, as well as the interval since exposure (Gorodetsky et al. 1990). The effects are mediated predominantly through fibroblasts, which are decreased in number, have decreased proliferative capacity, and are functionally insufficient in skin which is atrophied and fibrotic due to radiation treatment (Tibbs 1997). There is an attenuation of the normal fibroblast response to growth factor-induced chemotaxis and activation. There is both a decrease in collagen gene expression and failure of complete extra-cellular maturation (Bernstein et al. 1993a). There is some evidence that the latter may be mediated through alterations in growth factor expression, especially TGF-β (Bernstein et al. 1993b). The clinical consequence of this is a significant decrease in wound bursting strength, and an increased risk of wound dehiscence. Studies of wound integrity in irradiated skin demonstrate the most significant compromise in the 3–4 weeks following injury. The clinical manifestations may represent merely a delay in normal tissue remodeling, especially in skin which retains much of its normal microstructure and function. At later time points the strength of such wounds can approach that of wounds in unirradiated tissue.

The vasculature is also permanently altered by prior radiation. Acutely there is an increase in vascular

permeability, but in the long term there is vascular stasis, occlusion, and edema of vessel walls. This results in poor vascular supply to the irradiated area, which can lead to late dermal fibrosis and resultant loss of elasticity. The loss of vascularity also predisposes to infection, and impairs the supply of monocytes and fibroblasts available for wound healing (Doyle et al. 1996). Wounds in previously irradiated tissue are slow to heal, prone to dehisce and more frequently require skin grafting. Grafts are more prone to breakdown, and tissue flaps more likely to fail, especially when the site of origin also lies within the radiation field.

Wounding followed by radiation. After wounding, there is an acute rapid response (over several days) of the normal tissues to initiate wound repair. The "foundation" of successful wound healing is the laying down of a collagen network within the wound that occurs during this time. However, it takes many weeks to months for that collagen network to mature/remodel into a strong healed scar. The period of the initial rapid laying down of the foundation is typically a few days, and irradiating the wound during that time will manifest as a slower/blunted wound healing in the following weeks/months. However, if the radiation is given after this rapid laying down of a foundation (but before the foundation matures to a strong wound), the maturation of the scar, and the ultimate strength of the scar, will be less effected. Thus, the effects of radiation treatment on existing wounds is primarily timing dependent. Early irradiation can impair the proliferation, migration, and activation of fibroblasts, resulting in decreased collagen formation and cross-linking. Observed complications include decreased wound strength and dehiscence (Drake and Oishi 1995; Springfield 1993). In contrast, if irradiation is delayed until three to four weeks after wound formation, there is a much lower likelihood of complication (Tibbs 1997). At least one study has demonstrated that delaying as little as five to eight days results in a reduction of complications to the expected normal level, implying that a critical threshold of collagen formation and cross-linking has been completed. Even with such a delay, however, impaired neo-vascularization may occur, leading to late effects including skin atrophy, scar contraction, and fibrosis. The probability of such effects seems to be dose dependent (Gorodetsky et al. 1990), and thus there is a high incidence of such late complications after high dose radiation, and a lower but significant risk following low doses such as those used in the treatment of benign proliferative processes.

8.6 Skin Grafts

One of the commonly stated concepts in radiation therapy is that grafted skin tolerates irradiation poorly. Since the need for reconstructive surgery is increasing with the advent of more radical surgical procedures for various carcinomas, consideration of postoperative irradiation in grafted sites is not unusual. Very definite differences occur in the reaction to radiation between normal and grafted skin sites (Rubin et al. 1960).

Grafts less than 3 months old demonstrate greater radiosensitivity than normal skin. In grafts of intermediate age, the response to and recovery from irradiation parallels that of normal skin. In grafts older than 1 year, no reaction to irradiation is generally elicited, but in one instance, graft necrosis ensued at the 16th week.

On the basis of an experimental program (Rubin et al. 1960) with Chester White and Yorkshire pigs subjected to full thickness and split thickness grafts, the following conclusions were drawn:

1. Fresh grafts tend to react to ionizing irradiation more vigorously and earlier than normal skin, and they recover more slowly.
2. Split thickness grafts tend to react less vigorously than full thickness grafts.
3. The intensity of the reaction is inversely proportional to the quality of the radiation.
4. Fractionation and protraction have less impact on response, but the value of fractionation is aiding full recovery and is clearly established.
5. Irradiation should not be begun immediately after grafting.

Careful clinical observations and experimentation have clearly shown that, in a wide variety of circumstances, alteration in capillary anatomy and physiology has a profound effect on irradiated tissue and tumors. Knowledge of the changing blood supply pattern of an autograft is essential. The stages in graft union to host tissues are four: the stage of plasmic circulation, the state of vascularization, the stage of organic union, and the stage of cicatrization.

It is logical to anticipate that the more vascularized a graft is, the more sensitive the graft will be to irradiation. The injection of small quantities of radioisotopes intradermally or subcutaneously and the observation of the rate of their disappearance from the local site constitute a recognized method of studying vascular integrity.

The half-time of disappearance can be used as an expression of the vascular function of the graft site injected.

Therefore, the differences in vascularization of grafted skin and normal skin form a reasonable basis to explain the differences in the radiation responses of these structures. The radioisotopes half-time of disappearance following subcutaneous injection is an index of vascularity or vascular function of a graft and serves as a parameter to predict its radioresponsiveness.

1. Irradiation during the stage of plasmic circulation, prior to union of the graft, produces necrosis suppression of the budding of new capillaries from the host vascular bed, a process which is essential to graft survival.

2. Irradiation during the stage of vascularization elicits a greater reaction in the graft by virtue of the excessive capillary sprouting and in growth of vessels.
3. Irradiation during the stage of organic union evokes a reaction in the graft approximate that in normal skin as the fibroblastic and collagen responses progress. Normally vascularity of the graft at this stage is decreased as compared with the previous stage, and in transition it approximates that of normal skin.
4. Irradiation during the stage of cicatrization usually evokes no response in the graft, since vascularization is less than that in normal skin, and scar tissue is relatively radioresistant. If a reaction is elicited, the decreased vascularity may sufficiently compromise recovery powers so that necrosis may ensue.

On the basis of the results, the recommendations are:

1. Limit the total dose to a graft as much as possible, consistent with good treatment.
2. Exclude as much of the graft as possible from the radiation port, consistent with good treatment.
3. Fractionate and protract the dose as much as is practical, since fuller recovery is thus insured.
4. Employ megavoltage irradiation, because its skin-sparying effect lessens the severity of graft reaction.
5. Allow time for a good "take" of the autograft rather than begin irradiation immediately. Usually this is within 3–4 weeks after grafting.

9 Prevention and Management

Acute cutaneous toxicities are managed with preventative and supportive care measures. Prior to treatment, patients should be instructed to avoid chemical irritants, sun exposure, the application of extremes of heat or cold, and to minimize mechanical trauma within the treatment field. The topical application of moisturizers is often recommended prophylactically, and used to treat the dryness associated with early desquamation. During grade 2 and 3 toxicity, normal epidermal barrier function is disrupted, which makes the skin more prone to infection, and less able to retain moisture. Moisture exuding dressings may be applied to prevent or slow progressive dermal damage. Close observation for superinfection, and symptomatic management of discomfort should be part of standard on-treatment care. None of these measures has been demonstrated to lessen the severity of dermatitis, but are rather intended to support prompt tissue re-epithelialization.

Late cutaneous changes may occur long after radiation treatment, and may continue to progress over months to years. Although atrophy, telangiectasia, and dyspigmentation may contribute to poor cosmetic outcomes, cutaneous and subcutaneous fibrosis are the most likely to cause significant limitations to function and quality of life. The best method of primary prevention is to use the appropriate radiation techniques to limit the area and dose of skin exposure. Consequential late effects may be limited by both avoidance and appropriate supportive care of severe acute side effects.

The treatment of fibrosis may begin either during the early symptomatic period or during the latent period between the resolution of acute side effects and before the development of late ones. Preventative measures such as active and passive range of motion exercises are used to prevent loss of range of motion due to neck fibrosis in patients treated for head and neck cancer, or of the limbs in patients treated to the extremities or joints. Fibrosis may be exacerbated by further tissue trauma, so surgical procedures should be avoided in radiated areas when possible.

Pharmaceutical treatment of fibrosis has been successful with pentoxifylline and vitamin E. Pentoxifylline is a xanthine derivative that is currently approved for the treatment of intermittent claudication due to peripheral vascular disease. It decreases platelet aggregation, and increases microvascular blood flow. Laboratory evidence also suggests that it may decrease proliferation of fibroblasts, and decrease deposition of extracellular matrix proteins (Delanian and Lefaix 2007). Vitamin E is a free radical scavenger, which may diminish the ongoing inflammatory response.

Pentoxifylline and vitamin E have been tested concurrently with radiation in a randomized trial in the prevention of lung fibrosis due to chest radiation (Ozturk et al. 2004). Forty patients with lung or breast cancer were enrolled and randomized to receive pentoxifylline or placebo concurrently with radiation. There was a significant improvement in diffusion capacity, a clinical measure of lung fibrosis, in the patients receiving drug. Two randomized trials have tested pentoxifylline given prophylactically after radiation, specifically examining whether it decreased the development of cutaneous fibrosis. In 83 breast cancer patients (Magnusson et al. 2009) and 78 head and neck cancer patients (Aygenc et al. 2004), administration of the drug following radiation decreased fibrosis and improved post-treatment range of motion.

The combination of pentoxifylline and vitamin E has been most thoroughly evaluated in the treatment of established fibrosis, both in skin and other organs. Several retrospective series examines the effect of the combination in patients with radiation-induced fibrosis. Delanian et al. reported on 43 patients treated with pentoxifylline (800 mg per day) and vitamin E (1000 U per day) for 6 months, and found decreased area of fibrosis, and improved symptoms (Delanian et al. 1999). A decrease in the area of fibrosis has been similarly reported in other small series (Haddad et al. 2005;

Futran et al. 1997). Randomized trial results are promising, but not definitive, however. Delanian et al. conducted a two-way randomized trial of pentoxifylline and vitamin E, each versus placebo, in 24 patients treated for 6 months (Delanian et al. 2003). The patients that received both drugs had significantly decreased fibrosis compared to those in the arm that received two placebos; there was no improvement in the patient who received either of the drugs alone. A trial in 68 breast cancer patients with fibrosis treated with the same drug dose and duration failed to show any difference, however, in either arm volume or improved fibrosis. The disparate findings may reflect differences in outcome measures, patient selection, or duration of follow-up. A systematic, retrospective, evaluation of 44 patients treated with pentoxifylline and vitamin E for 6–48 months found that the regression of fibrosis was best seen after longer treatment intervals. Patients had 2/3 of the maximum response at 24 months treatment duration. Those patients treated for shorter duration (3–6 months) were prone to significant rebound increase in fibrosis after drug combination was discontinued.

Pentoxifylline has also been administered as a single agent in attempt to treat existing radiation-induced fibrosis. One prospective trial of 1200 mg per day for 8 weeks reported a one-third improvement in range of motion, and decreased edema (Okunieff et al. 2004). A randomized trial of 12 patients, treated for 6 months, failed to demonstrate any benefit of single-agent therapy (Delanian et al. 2003). The same trial examined Vitamin E alone versus placebo, and again showed no benefit.

Other strategies have been used in an empiric attempt to ameliorate the symptoms of subcutaneous fibrosis. Corticosteroids, nonsteroidal anti-inflammatories, and other immunosuppressives have been used, based on their activity in slowing the progressive fibrosis of some connective tissue disorders. Antioxidants other than vitamin E, including superoxide dismutase, have been tested in the laboratory in mice, but there are to date no clinically available active agents (Delanian and Lefaix 2007). Curcumin is an antioxidant that has been tested in mice, and found to decrease the early cytokine response to radiation (Okunieff et al. 2006). Hyperbaric oxygen has been used in two prospective studies in women with lymphedema after breast radiation therapy. In both, there was an improvement in patient-reported symptoms. One study reported a decrease in indurations in 8 of 15 patients (Gothard et al. 2004), the other reported no improvement in fibrosis (Carl et al. 2001). Angiotensin converting enzyme inhibitors and ethanol have some efficacy in decreasing late effects in other tissue, but have not been tested in skin (Delanian and Lefaix 2007). Given the lack of a compelling benefit to any standard medical therapy for radiation-induced fibrosis, all of these approaches warrant further study.

10 Future Research

The importance of skin research response to radiation has been heightened by the atomic age we live in currently. The "Cutaneous Syndrome" (CS), in reference to non-therapeutic exposure includes: Japan's nuclear reactor explosions, Chernobyl nuclear accident, threat of nuclear bomb terrorists, and warfare. Radiation deaths in 50 % of survivors occurred in Cutaneous Syndrome due to eventual skin-related reactions i.e., severe erythema and persistent pain, hemorrhagic desquamation, necrosis, and complete oncolysis. Regeneration of skin by stem cell grafts may be a future approach.

11 Review of Historic Literature

1898 Gassmann: Described histologic changes in two chronic roentgen ulcers.

1909 Wolbach: In a thorough description of chronic radiodermatitis, introduced the concept that vascular changes are progressive.

1927 Quimby: Determined that skin erythema is affected by both the quality and quantity of radiation.

1937 MacComb and Quimby: Developed the concept of cumulative dose, i.e., that the injurious effects of radiation accumulate in fractionated dose schedules.

1944 Strandqvist: Introduced a concept central to modern radiotherapeutic techniques—an isoeffect plot in which a relationship is demonstrated between time and dose.

1955 Devik: Beautifully correlated the epithelial and vascular changes after local roentgen irradiation of the skin of mice and concluded that the main cause of the acute skin reaction is epithelial cellular injury and that the secondary cause is injury to the stromal capillaries.

1956 Paterson: constructed tables and graphs to guide radiotherapists utilizing orthovoltage irradiation on time-dose-area levels that produce moist desquamation.

1960 Rubin, Casarett and Grise: Noted the difference in response between normal and grafted skin to irradiation and explained this on a pathophysiologic basis.

1968 Rubin and Casarett: Introduced the "biocontinuum" of radiation injury from acute to subacute to chronic and late changes i.e. carcinogenesis.

1984–1991 Turrensen and Notter: In clinical studies investigated a variety of radiation dose/time/fractionation studies on acute/late skin responses.

1992 Rubin et al.: LENT-SOMA Toxicity scales introduced for grading radiation induced reactions in skin.

1995 Archambeau: Meticulous presentation of microvessel changes in papillary dermis induced by radiation over time.

2003 Trotti and Rubin: Developed the CTC V3 toxicity scales for skin to be applicable to multimodality treatment of skin during cancer treatment.

References

Adelstein DJ, Li Y, Adams GL et al (2003) An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemo radiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 21(1):92–98

Ahn PH, Vu HT, Lannin D et al (2005) Sequence of radiotherapy with tamoxifen in conservatively managed breast cancer does not affect local relapse rates. J Clin Oncol 23(1):17–23

Anscher MS, Kong FM, Andrews K et al (1998) Plasma transforming growth factor beta 1 as a predictor of radiation pneumonitis. Int J Radiat Oncol Biol Phys 41(5):1029–1035

Anscher MS, Marks LB, Shafman TD et al (2003) Risk of long-term complications after TFG-beta1-guided very-high-dose thoracic radiotherapy. Int J Radiat Oncol Biol Phys 56(4):988–995

Arany PR, Flanders KC, DeGraff W, Cook J, Mitchell JB, Roberts AB (2007) Absence of Smad3 confers radioprotection through modulation of ERK-MAPK in primary dermal fibroblasts. J Dermatol Sci 48(1):35–42

Archambeau JO, Richard P, Todd W (1995) Pathophysiology of irradiated skin and breast. Int J Radiat Oncol Biol Phys 31(5):1171–1185

Atahan IL, Yildiz F, Ozyar E, Uzal D, Zorlu F (1998) Basal cell carcinomas developing in a case of medulloblastoma associated with Gorlin's syndrome. Pediatr Hematol Oncol 15(2):187–191

Aygenc E, Celikkanat S, Kaymakci M, Aksaray F, Ozdem C (2004) Prophylactic effect of pentoxifylline on radiotherapy complications: a clinical study. Otolaryngol Head Neck Surg 130(3):351–356

Azria D, Gourgou S, Sozzi WJ et al (2004) Concomitant use of tamoxifen with radiotherapy enhances subcutaneous breast fibrosis in hypersensitive patients. Br J Cancer 91(7):1251–1260

Azria D, Magne N, Zouhair A et al (2005) Radiation recall: a well recognized but neglected phenomenon. Cancer Treat Rev 31(7):555–570

Baker DG, Krochak RJ (1989) The response of the microvascular system to radiation: a review. Cancer Invest 7(3):287–294

Bale AE (2002) Hedgehog signaling and human disease. Annu Rev Genomics Hum Genet 3:47–65

Barcellos-Hoff MH (1998) How do tissues respond to damage at the cellular level? The role of cytokines in irradiated tissues. Radiat Res 150(5 Suppl):S109–S120

Barcellos-Hoff MH, Derynck R, Tsang ML, Weatherbee JA (1994) Transforming growth factor-beta activation in irradiated murine mammary gland. J Clin Invest 93(2):892–899

Bellon JR, Shulman LN, Come SE et al (2004) A prospective study of concurrent cyclophosphamide/methotrexate/5-fluorouracil and reduced-dose radiotherapy in patients with early-stage breast carcinoma. Cancer 100(7):1358–1364

Bernstein EF, Salomon GD, Harisiadis L et al (1993a) Collagen gene expression and wound strength in normal and radiation-impaired wounds. A model of radiation-impaired wound healing. J Dermatol Surg Oncol 19(6):564–570

Bernstein EF, Sullivan FJ, Mitchell JB, Salomon GD, Glatstein E (1993b) Biology of chronic radiation effect on tissues and wound healing. Clin Plast Surg 20(3):435–453

Bostrom A, Sjolin-Forsberg G, Wilking N, Bergh J (1999) Radiation recall–another call with tamoxifen. Acta Oncol 38(7):955–959

Bremer M, Klopper K, Yamini P, Dix-Waltes R, Dork T, Karstens JH (2003) Clinical radiosensitivity in breast cancer patients carrying pathogenic ATM gene mutations: no observation of increased radiation-induced acute or late effects. Radiother Oncol 69(2):155–160

Burger A, Loffler H, Bamberg M, Rodemann HP (1998) Molecular and cellular basis of radiation fibrosis. Int J Radiat Biol 73(4):401–408

Camidge R, Price A (2001) Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol 59(3):237–245

Canney PA, Dean S (1990) Transforming growth factor beta: a promotor of late connective tissue injury following radiotherapy? Br J Radiol 63(752):620–623

Carl UM, Feldmeier JJ, Schmitt G, Hartmann KA (2001) Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery. Int J Radiat Oncol Biol Phys 49(4):1029–1031

Cassady JR, Richter MP, Piro AJ, Jaffe N (1975) Radiation–Adriamycin interactions: preliminary clinical observations. Cancer 36(3):946–949

Chen AM, Obedian E, Haffty BG (2001) Breast-conserving therapy in the setting of collagen vascular disease. Cancer J 7(6):480–491

Chon BH, Loeffler JS (2002) The effect of nonmalignant systemic disease on tolerance to radiation therapy. Oncologist 7(2):136–143

Cooper JS, Guo MD, Herskovic A et al (1999) Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85–01). Radiat Ther Oncol Group. JAMA 281(17):1623–1627

D'Angio GJ, Farber S, Maddock CL (1959) Potentiation of x-ray effects by actinomycin D. Radiology 73:175–177

Davis AM, O'Sullivan B, Turcotte R et al (2005) Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 75(1):48–53

Delanian S, Lefaix JL (2007) Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. Semin Radiat Oncol 17(2):99–107

Delanian S, Balla-Mekias S, Lefaix JL (1999) Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. J Clin Oncol 17(10):3283–3290

Delanian S, Porcher R, Balla-Mekias S, Lefaix JL (2003) Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. J Clin Oncol 21(13):2545–2550

Denham JW, Hauer-Jensen M (2002) The radiotherapeutic injury—a complex 'wound'. Radiother Oncol 63(2):129–145

Dorr W, Hendry JH (2001) Consequential late effects in normal tissues. Radiother Oncol 61(3):223–231

Doyle JW, Li YQ, Salloum A, FitzGerald TJ, Walton RL (1996) The effects of radiation on neovascularization in a rat model. Plast Reconstr Surg 98(1):129–135

Drake DB, Oishi SN (1995) Wound healing considerations in chemotherapy and radiation therapy. Clin Plast Surg 22(1):31–37

Emami B, Lyman J, Brown A et al (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21(1):109–122

Epperly MW, Travis EL, Sikora C, Greenberger JS (1999) Manganese [correction of Magnesium] superoxide dismutase (MnSOD) plasmid/liposome pulmonary radioprotective gene therapy: modulation of irradiation-induced mRNA for IL-I, TNF-alpha, and TGF-beta correlates with delay of organizing alveolitis/fibrosis. Biol Blood Marrow Transpl 5(4):204–214

Fajardo LF, Berthrong M (1988) Vascular lesions following radiation. Pathol Annu 23(Pt 1):297–330

Flanders KC, Sullivan CD, Fujii M et al (2002) Mice lacking Smad3 are protected against cutaneous injury induced by ionizing radiation. Am J Pathol 160(3):1057–1068

Flanders KC, Ho BM, Arany PR et al (2008) Absence of Smad3 induces neutrophil migration after cutaneous irradiation: possible contribution to subsequent radioprotection. Am J Pathol 173(1):68–76

Futran ND, Trotti A, Gwede C (1997) Pentoxifylline in the treatment of radiation-related soft tissue injury: preliminary observations. Laryngoscope 107(3):391–395

Gorodetsky R, Mou XD, Fisher DR, Taylor JM, Withers HR (1990) Radiation effect in mouse skin: dose fractionation and wound healing. Int J Radiat Oncol Biol Phys 18(5):1077–1081

Gothard L, Stanton A, MacLaren J et al (2004) Non-randomized phase II trial of hyperbaric oxygen therapy in patients with chronic arm lymphoedema and tissue fibrosis after radiotherapy for early breast cancer. Radiother Oncol 70(3):217–224

Greco FA, Brereton HD, Kent H, Zimbler H, Merrill J, Johnson RE (1976) Adriamycin and enhanced radiation reaction in normal esophagus and skin. Ann Intern Med 85(3):294–298

Haddad P, Kalaghchi B, Mouzegar-Hashemi F (2005) Pentoxifylline and vitamin E combination for superficial radiation-induced fibrosis: a phase II clinical trial. Radiother Oncol 77(3):324–326

Hageman J, Eggen BJ, Rozema T, Damman K, Kampinga HH, Coppes RP (2005) Radiation and transforming growth factor-beta cooperate in transcriptional activation of the profibrotic plasminogen activator inhibitor-1 gene. Clin Cancer Res 11(16):5956–5964

Hahn H, Wojnowski L, Zimmer AM, Hall J, Miller G, Zimmer A (1998) Rhabdomyosarcomas and radiation hypersensitivity in a mouse model of Gorlin syndrome. Nat Med 4(5):619–622

Hakenjos L, Bamberg M, Rodemann HP (2000) TGF-beta 1-mediated alterations of rat lung fibroblast differentiation resulting in the radiation-induced fibrotic phenotype. Int J Radiat Biol 76(4):503–509

Hall EJ, Giaccia AJ (2005) Radiobiology for the Radiologist, 6th edn. Lippincott Williams & Wilkins, Philadelphia

Hall and Okunieff. Human radiation injury

Hallahan DE, Spriggs DR, Beckett MA, Kufe DW, Weichselbaum RR (1989) Increased tumor necrosis factor alpha mRNA after cellular exposure to ionizing radiation. Proc Natl Acad Sci U S A 86(24):10104–10107

Herrmann T, Baumann M, Dorr W (2006) Clinical radiation biology. Elsevier, Munich

Herskind C, Bentzen SM, Overgaard J, Overgaard M, Bamberg M, Rodemann HP (1998) Differentiation state of skin fibroblast cultures versus risk of subcutaneous fibrosis after radiotherapy. Radiother Oncol 47(3):263–269

Hird AE, Wilson J, Symons S, Sinclair E, Davis M, Chow E (2008) Radiation recall dermatitis: case report and review of the literature. Curr Oncol 15(1):53–62

Holscher T, Bentzen SM, Baumann M (2006) Influence of connective tissue diseases on the expression of radiation side effects: a systematic review. Radiother Oncol 78(2):123–130

Hoppe BS, Laser B, Kowalski AV et al (2008) Acute skin toxicity following stereotactic body radiation therapy for stage I non-small-cell lung cancer: who's at risk? Int J Radiat Oncol Biol Phys 72(5):1283–1286

Iannuzzi CM, Atencio DP, Green S, Stock RG, Rosenstein BS (2002) ATM mutations in female breast cancer patients predict for an increase in radiation-induced late effects. Int J Radiat Oncol Biol Phys 52(3):606–613

Isaac N, Panzarella T, Lau A et al (2002) Concurrent cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy and radiotherapy for breast carcinoma: a well tolerated adjuvant regimen. Cancer 95(4):696–703

Karagas MR, McDonald JA, Greenberg ER et al (1996) Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. For the skin cancer prevention study group. J Natl Cancer Inst 88(24):1848–1853

Khan FM (2003) The physics of radiation therapy, 3rd edn. Lippincott Williams & Wilkins, Philadelphia

Khanfir K, Anchisi S (2008) Pemetrexed-associated radiation recall dermatitis. Acta Oncol 47(8):1607–1608

Kong FM, Pan C, Eisbruch A, Ten Haken RK (2007) Physical models and simpler dosimetric descriptors of radiation late toxicity. Semin Radiat Oncol 17(2):108–120

Kumar S, Kolozsvary A, Kohl R, Lu M, Brown S, Kim JH (2008) Radiation-induced skin injury in the animal model of scleroderma: implications for post-radiotherapy fibrosis. Radiat Oncol 3:40

Lara PC, Russell NS, Smolders IJ, Bartelink H, Begg AC, Coco-Martin JM (1996) Radiation-induced differentiation of human skin fibroblasts: relationship with cell survival and collagen production. Int J Radiat Biol 70(6):683–692

Lichter MD, Karagas MR, Mott LA, Spencer SK, Stukel TA, Greenberg ER (2000) Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire skin cancer study group. Arch Dermatol 136(8):1007–1011

Lin A, Bu-Isa E, Griffith KA, Ben-Josef E (2008) Toxicity of radiotherapy in patients with collagen vascular disease. Cancer 113(3):648–653

Livi L, Saieva C, Borghesi S et al (2008) Concurrent cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy and radiotherapy for early breast carcinoma. Int J Radiat Oncol Biol Phys 71(3):705–709

Locke J, Karimpour S, Young G, Lockett MA, Perez CA (2001) Radiotherapy for epithelial skin cancer. Int J Radiat Oncol Biol Phys 51(3):748–755

Magnusson M, Hoglund P, Johansson K et al (2009) Pentoxifylline and vitamin E treatment for prevention of radiation-induced side-effects in women with breast cancer: A phase two, double-blind, placebo-controlled randomised clinical trial (Ptx-5). Eur J Cancer 45(14):2488–2495

Malkinson FD, Keane JT (1981) Radiobiology of the skin: review of some effects on epidermis and hair. J Invest Dermatol 77(1):133–138

Martin M, Lefaix J, Delanian S (2000) TGF-beta 1 and radiation fibrosis: a master switch and a specific therapeutic target? Int J Radiat Oncol Biol Phys 47(2):277–290

Mayer M (1990) Biochemical and biological aspects of the plasminogen activation system. Clin Biochem 23(3):197–211

Milano MT, Constine LS, Okunieff P (2007) Normal tissue tolerance dose metrics for radiation therapy of major organs. Semin Radiat Oncol 17(2):131–140

Morris MM, Powell SN (1997) Irradiation in the setting of collagen vascular disease: acute and late complications. J Clin Oncol 15(7):2728–2735

Okunieff P, Augustine E, Hicks JE et al (2004) Pentoxifylline in the treatment of radiation-induced fibrosis. J Clin Oncol 22(11):2207–2213

Okunieff P, Xu J, Hu D et al (2006) Curcumin protects against radiation-induced acute and chronic cutaneous toxicity in mice and decreases mRNA expression of inflammatory and fibrogenic cytokines. Int J Radiat Oncol Biol Phys 65(3):890–898

O'Malley S, Weitman D, Olding M, Sekhar L (1997) Multiple neoplasms following craniospinal irradiation for medulloblastoma in a patient with nevoid basal cell carcinoma syndrome. Case report. J Neurosurg 86(2):286–288

Ozturk B, Egehan I, Atavci S, Kitapci M (2004) Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomized trial. Int J Radiat Oncol Biol Phys 58(1):213–219

Parry BR (1992) Radiation recall induced by tamoxifen. Lancet 340(8810):49

Phan C, Mindrum M, Silverman C, Paris K, Spanos W (2003) Matched-control retrospective study of the acute and late complications in patients with collagen vascular diseases treated with radiation therapy. Cancer J 9(6):461–466

Rodemann HP, Bamberg M (1995) Cellular basis of radiation-induced fibrosis. Radiother Oncol 35(2):83–90

Rodemann HP, Blaese MA (2007) Responses of normal cells to ionizing radiation. Semin Radiat Oncol 17(2):81–88

Rodemann HP, Peterson HP, Schwenke K, von Wangenheim KH (1991) Terminal differentiation of human fibroblasts is induced by radiation. Scanning Microsc 5(4):1135–1142

Rodemann HP, Binder A, Burger A, Guven N, Loffler H, Bamberg M (1996) The underlying cellular mechanism of fibrosis. Kidney Int Suppl 54:S32–S36

Rubin P, Casarett GW (1968) Clinical radiation pathology, vol I. W. B. Saunders Company, Philadelphia

Rubin P, Hansen JT (2008) TNM staging atlas, 1st edn, vol 52. Lippincott Williams & Wilkins, Philadelphia, pp 449–450

Rubin P, Casarett G, Grise JW (1960) The vascular pathophysiologoy of an irradiated graft. Am J Roentgenol Radium Ther Nucl Med 83:1096–1104

Rubin P, Finkelstein J, Shapiro D (1992) Molecular biology mechanisms in the radiation induction of pulmonary injury syndromes: interrelationship between the alveolar macrophage and the septal fibroblast. Int J Radiat Oncol Biol Phys 24(1):93–101

Saif MW, Ramos J, Knisely J (2008) Radiation recall phenomenon secondary to bevacizumab in a patient with pancreatic cancer. JOP 9(6):744–747

Schultze-Mosgau S, Wehrhan F, Grabenbauer G et al (2002) Transforming growth factor beta1 and beta2 (TGFbeta2/TGFbeta2) profile changes in previously irradiated free flap beds. Head Neck 24(1):33–41

Schwartz BM, Khuntia D, Kennedy AW, Markman M (2003) Gemcitabine-induced radiation recall dermatitis following whole pelvic radiation therapy. Gynecol Oncol 91(2):421–422

Selvaraj RN, Bhatnagar A, Beriwal S et al (2007) Breast skin doses from brachytherapy using MammoSite HDR, intensity modulated radiation therapy, and tangential fields techniques. Technol Cancer Res Treat 6(1):17–22

Shenkier T, Gelmon K (1994) Paclitaxel and radiation-recall dermatitis. J Clin Oncol 12(2):439

Sieber VK, Wilkinson J, Aluri GR, Bywaters T (1993) Quantification of radiation-induced epilation in the pig: a biological indicator of radiation dose to the skin. Int J Radiat Biol 63(3):355–360

Springfield DS (1993) Surgical wound healing. Cancer Treat Res 67:81–98

Strandquist M (1944) A study of the cumulative effects of fractionated X-ray treatment based on the experience gained at the radium-hemmet with the treatment of 280 cases of carcinoma of the skin and lip. Acta Radiol 55(Suppl):300–304

Stelzer KJ, Griffin TW, Koh WJ (1993) Radiation recall skin toxicity with bleomycin in a patient with Kaposi sarcoma related to acquired immune deficiency syndrome. Cancer 71(4):1322–1325

Taylor ME, Perez CA, Halverson KJ et al (1995) Factors influencing cosmetic results after conservation therapy for breast cancer. Int J Radiat Oncol Biol Phys 31(4):753–764

Thompson DE, Mabuchi K, Ron E et al (1994) Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. Radiat Res 137(2 Suppl):S17–S67

Tibbs MK (1997) Wound healing following radiation therapy: a review. Radiother Oncol 42(2):99–106

Toledano A, Garaud P, Serin D et al (2006) Concurrent administration of adjuvant chemotherapy and radiotherapy after breast-conserving surgery enhances late toxicities: long-term results of the ARCO-SEIN multicenter randomized study. Int J Radiat Oncol Biol Phys 65(2):324–332

Vozenin-Brotons MC, Gault N, Sivan V et al (1999) Histopathological and cellular studies of a case of cutaneous radiation syndrome after accidental chronic exposure to a cesium source. Radiat Res 152(3):332–337

Vujaskovic Z, Feng QF, Rabbani ZN, Anscher MS, Samulski TV, Brizel DM (2002) Radioprotection of lungs by amifostine is associated with reduction in profibrogenic cytokine activity. Radiat Res 157(6):656–660

Yeo W, Leung SF, Johnson PJ (1997) Radiation-recall dermatitis with docetaxel: establishment of a requisite radiation threshold. Eur J Cancer 33(4):698–699

Zhang S (1999) An atlas of histology. Springer, New York

Zhao W, Spitz DR, Oberley LW, Robbins ME (2001) Redox modulation of the pro-fibrogenic mediator plasminogen activator inhibitor-1 following ionizing radiation. Cancer Res 61(14):5537–5543