Ionizing radiation is used to treat a variety of primary tumors, as well as to palliate metastatic disease. Dermatologists are no strangers to this modality of therapy and, since the discovery of x-rays by Roentgen in 1895, have incorporated radiation into their practice to treat malignant skin tumors, as well as benign skin diseases such as acne, eczema, and cutaneous fungal infections. In the past 30 years, other therapeutic modalities have largely supplanted radiation in the treatment of these benign disorders. Dermatologists today are more commonly called on to treat the cutaneous repercussions of radiation therapy (RT), which are a function of technique, target, total dose, volume, as well as individual variations.\textsuperscript{1,2} RT, either as monotherapy or in combination with other treatment modalities, is a powerful tool in tumor control, limited primarily by injury adjacent to normal tissue.

Radiation-induced skin changes were recognized soon after the discovery of x-rays and were scientifically reported as early as 1902.\textsuperscript{3} Even when the skin is not the primary target, it may be injured as an “innocent bystander” and develop profound alterations on functional, gross, and molecular levels. This is not only true after therapeutic radiation, but also after interventional procedures. Serious radiation-induced skin injuries have been reported after unexpectedly high doses of kilovoltage irradiation exposure during fluoroscopic imaging, including cardiac catheterization.\textsuperscript{4,5} Increasingly sophisticated therapeutic regimens and modern equipment have improved the delivery and ameliorated, but not eliminated, these adverse effects. Increased awareness of potential interactions between RT and concomitant chemotherapy has led to new treatment schedules designed to maximize antineoplastic effects while minimizing skin toxicity. However, radiation dermatitis remains a serious side effect, which may limit the duration of treatment and the dose delivered.

Many of the skin changes after RT are minor and reversible. When cutaneous changes do develop, they are commonly graded as acute, consequential, or chronic and may appear at both the entrance and exit portals. Utilizing a team approach (dermatologist, radiation oncologist, and wound care specialist), we discuss the clinical manifestations of radiation dermatitis, review the pathophysiology, and discuss possible treatment options.

### ACUTE RADIATION DERMATITIS

After RT or accidental exposures, the acute changes usually occur within 90 days. The National Cancer Institute common toxicity criteria version 3.0 has become the standard for evaluation (Table 1). Generalized erythema, sometimes undetectable without special instrumentation, may occur hours after radiation exposure, and fade within hours to days.\textsuperscript{6,7} A second phase of more sustained erythema is apparent 10 to 14 days after dosing, and is characterized by a Blanchable reactive pink hue, without other epidermal changes, most likely mediated by cytokines.\textsuperscript{8
Grade 1 changes include follicular or mild generalized erythema and dry desquamation (Fig 1). Other changes include pruritus, epilation, scaling, and dyspigmentation. The dryness and hair loss are secondary to injury to sebaceous glands and hair follicles.

Grade 2 changes, consisting of persistent tender or edematous erythema (Fig 2), may progress to focal loss of the epidermis, producing moist desquamation in skin folds (Fig 3). This usually occurs after 4 to 5 weeks of therapy, with radiation doses to the skin of 40 Gy or greater. Moist desquamation is characterized by epidermal necrosis, fibrinous exudates, and, often, considerable pain. Bullae, if present, may rupture or become infected. Histologically, arterioles are obstructed by fibrin thrombi and edema is prominent. Depending on the body site, this reaction peaks 1 to 2 weeks after the last treatment and gradually heals, accompanied by increased expression of epidermal growth factor receptors. Epidermal regeneration occurs about the third to fifth week after radiation with complete healing

within 1 to 3 months. Throughout this process, it is important to identify any superinfection, especially with organisms that may act as superantigens, such as *Staphylococcus aureus* (Fig 4). Superantigens up-regulate cytokine production and inflammation by activating antigen-presenting cells and T cells, resulting in increased inflammation and skin damage.

Grade 3 dermatitis is characterized by confluent moist desquamation in locations other than skin folds (Fig 5). The formation of ulcers, hemorrhage, and necrosis heralds grade 4 changes. When acute changes do not resolve, they can result in chronic skin ulceration, fibrosis, or necrosis of underlying structures, including bone—so-called “consequential” late effects (Fig 6). The severity of the acute radiation response may also lead to a late effect in the gut, bladder, and oral mucosa. Disruption of the epithelial basement membrane and breakdown of the barrier function substantially increase the risk for these injuries.

As epidermal function becomes increasingly impaired, the permeability of the skin, as measured by transepidermal water loss, increases. Topical treatment may ameliorate radiation dermatitis, as

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**Table I. Classification of radiation dermatitis**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Faint erythema or dry desquamation</td>
</tr>
<tr>
<td>2</td>
<td>Moderate to brisk erythema or patchy moist desquamation, mostly confined to skin folds and creases; moderate edema</td>
</tr>
<tr>
<td>3</td>
<td>Confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema</td>
</tr>
<tr>
<td>4</td>
<td>Skin necrosis or ulceration of full-thickness dermis; may include bleeding not induced by minor trauma or abrasion</td>
</tr>
</tbody>
</table>

*From National Cancer Institute Common Terminology Criteria for Adverse Events version 3.
measured by this parameter. A “comedo reaction,” consisting of whiteheads and blackheads, is more predisposed to develop after head and neck radiation or radiation of cutaneous cancers. Lesions resembling keratoses called pseudorecidives sometimes appear in the immediate postradiation period, may resemble tumor recurrences, and often spontaneously resolve without treatment. Hair loss may be transient after therapy, and new hair may continue to return for up to a year. Alopecia due to follicular fibrosis may be permanent.

CHRONIC RADIATION DERMATITIS

The skin may appear relatively normal for a varying duration after RT, and chronic changes may not develop for months to years after exposure. These changes are sometimes transient, like the edematous peau d’orange appearance that appears in the postirradiated breast and that often resolves in the first year. Postinflammatory hypopigmentation and hyperpigmentation are commonly seen after any disruption of the dermoepidermal junction and, depending on the severity of the initial reaction and skin type of the patient, may persist or slowly normalize (Fig 7). Certain body sites such as the scalp exhibit more tolerance for radiation than the skin of the face, neck, trunk, and extremities. Textural changes, including xerosis, scale, and hyperkeratosis are common, and hair follicles and sebaceous glands may appear to be absent in the field. Persistent telangiectasia (Fig 8) is more common after boost dosing, acute grade 3 injury, and moist desquamation, possibly secondary to microvasculature damage. However, the development of moist desquamation does not seem to predispose to the development of subcutaneous fibrosis, and the boost is not associated with any other late changes. Pulsed dye laser treatment has been beneficial in clearing such radiation-induced telangiectasia.

True late radiation-induced changes may occur years after treatment (Fig 9) and are differentiated from consequential late effects, which reflect persistent, nonhealing acute radiation dermatitis.

Persistent poikilodermatous changes, characterized by hyperpigmentation and hypopigmentation (dyspigmentation), atrophy, and telangiectasia, are
indicative of significant cutaneous injury. There may be permanent loss of nails and skin appendages, alopecia, and decreased or absent sweating. The latter is especially significant when large surface areas are treated, as in the case of electron beam therapy for mycosis fungoides. Fibrosis in response to growth factors, such as transforming growth factor-β (TGF-β), may be focal or widespread, producing tissue retraction, limitation of movement, and pain.

Pathologically, the dermis and subcutaneous adipose tissue are replaced by atypical fibroblasts and fibrous tissue. Eccentric myointimal proliferation of the small arteries and arterioles may progress to thrombosis or obstruction, increasing the predisposition for ulcers and skin breakdown. Skin atrophy, related to decreased population of dermal fibroblasts and the reabsorption of collagen also causes fragility and predisposes to erosions and ulcerations, which may be painful, slow to heal, and predisposed to superinfection. Subungual splinter hemorrhages have been reported on occasion.

Radiation necrosis is more commonly a late-consequential injury associated with high-dose RT, failure to heal, acute dermatitis, and dermal ischemia. It is particularly difficult to manage, as impaired healing and superinfection are common in tissues rendered relatively avascular. These problems are exacerbated by peripheral vascular disease, diabetes, hypertension, and connective tissue disease.

**PATHOPHYSIOLOGY**

The skin is a continuously renewing organ, and radiotherapy not only interferes with normal maturation, reproduction and repopulation of germinative epidermal and hair matrix cells, but also targets fibroblasts and the cutaneous vasculature. The radiation-induced injury has been termed a "complex wound," in which structural tissue damage occurs instantaneously, mediated by a burst of free radicals resulting in DNA damage and alteration of proteins, lipids, and carbohydrates. Each additional
exposure or fraction contributes to inflammatory cell recruitment as well as to direct tissue injury. Wound healing is further impaired by inhibition of normal granulation tissue, fibrogenesis, and angiogenesis. Acute injury is, therefore, a consequence of reduction and impairment of functional stem cells, endothelial cell changes, inflammation, and epidermal cell apoptosis and necrosis.

Cutaneous radiation syndrome, occurring after accidental radiation exposure, is also mediated by a combination of inflammatory processes. Alteration of cellular proliferation occurs as a result of a specific pattern of transcriptionally activated proinflammatory cytokines and growth factors. Interaction between epithelial and mesenchymal cells is, at least in part, initiated by interleukin 1α (IL-1α) secreted by the activated epithelial cell during skin injury. This in turn may modulate the synthesis of other proinflammatory mediators and proteases in surrounding fibroblasts.

Repetitive radiation exposure delivers a series of tissue insults to skin that has not had time to repair existing damage. During dose fractionation schedules with gaps (extension of the nontreatment period), tissue-specific repopulation is initiated after a lag period. When accelerated repopulation is initiated, there is an increase in the radiosensitivity of the surviving stem cells and a decrease in the time required for cells to repair sublethal irradiation-induced damage. Ionizing radiation also produces epidermal basal cell and endothelial cell damage, vascular injury, and loss of Langerhans cells. Up-regulation of epidermal growth factor receptor may aid in epithelial repair, whereas alterations in epidermal Langerhans cells may further impair immunologic integrity. These events, combined with the intensive inflammation promoted by up-regulation of adhesion molecules such as intercellular adhesion molecule 1, contribute to impairment of cutaneous barrier function, bacterial colonization, superinfection, and superantigen production.

Acutely irradiated skin demonstrates a perivascular inflammatory infiltrate around dilated blood vessels with swelling and sloughing of epithelial cells and growth arrest. Lower doses produce clumping of nuclear chromatin, swelling of the nucleus, and apoptosis. Higher doses cause nuclear disfiguration or loss of the nuclear membrane, mitochondrial distortion, and degeneration of the endoplasmic reticulum, as well as direct cellular necrosis. Mitotic activity in the germinal cells of the sebaceous glands, hair follicles, and epidermis is inhibited, and basal layer stem cells are depleted. Prostaglandins and thiol compounds are potentially radioprotective agents that have been used to protect normal tissue, with varying degrees of success. In animal models, both have been used to protect hair follicles and other skin structures. Celecoxib, a COX-2 inhibitor, has been shown to reduce skin damage after radiation in mice, exhibiting selective reduction of chemokine and receptor messenger RNA expression in irradiated skin but not in irradiated tumor.

TGF-β, a peptide which has a fundamental role in controlling proliferation of many cell types, is intricately involved in the development of chronic radiation dermatitis. This cytokine acts as a “master switch” for tissue fibrosis, activating fibroblasts to secrete extracellular matrix protein. In the irradiated tissue of pigs, TGF-β1 also plays an important role in promoting and regulating the late fibrotic process. Its main effect on connective tissues in vivo is to stimulate growth. Endothelial cell proliferation is also stimulated, but epithelial cell growth is inhibited. Mice lacking a downstream mediator of TGF-β, Smad3, demonstrate decreased tissue damage and fibrosis after irradiation, as well as accelerated healing. Up-regulation of TGF-β has been found in fibrotic tissue of irradiated patients, but not in the nonirradiated controls, confirming that its induction is a general response of cells to ionizing radiation. It is also chemotactic for mast cells, possibly increasing angiogenesis by inducing macrophages to release factors that lead to neovascularization.

Radiation-induced endothelial cell damage activates components of the coagulation system, which in turn promotes inflammation and cytokine overproduction. Thrombin, which is a regulator of cell proliferation, may also modulate the synthesis of TGF-β, vascular endothelial permeability, inflammation, and tissue remodeling. Subsequent matrix accumulation, fibrosis, endothelial cell dysfunction, and increased measurable cytokines may ultimately delay reepithelialization.

Long-lasting impairment of the reparative process ultimately affects the integrity of the “healed” radiation-induced wound. Although healed traumatic wounds in nonirradiated skin remodel continuously for years after injury, this capacity is often compromised after RT because of persistent cellular dysfunction or changes in the supporting stroma. Fibroblasts may be permanently altered, causing cutaneous atrophy, contraction, and fibrosis. Although total dose is certainly critical in producing skin problems, late effects may be more dependent on the type of radiation, area, volume, fraction size, and dose/fraction schedules. The underlying pathogenesis of the development of telangiectasia is unknown, but may be due in part to inflammatory damage to the microvasculature during the acute injury and the production of platelet-derived growth
factor (PDGF) and fibroblast growth factor by damaged endothelial cells or macrophages. Both vascular sclerosis and radiation fibrosis are, in part, related to endothelial cell damage and vascular injury. The identification of genes by microarray analysis may further define the molecular mechanisms of this microvascular insult. Leukocyte infiltration, mediated in part by cell adhesion molecules, is also commonly observed at sites of irradiation and is likely to lead to parenchymal atrophy, fibrosis, and necrosis in normal tissues.

RISK FACTORS
Dose fractionation schedules
The total dose, dose/fractionation, type and quality of the beam, volume, and surface area exposed influence the degree of damage to the epidermis, dermis, adnexal structures, and microvasculature. When photons are absorbed, single- and double-strand DNA breakage may occur. In addition, ionized water molecules form free radicals, which then have the potential to diffuse and further damage DNA. In the case of acute radiation dermatitis, the clinical consequences of this reaction are expressed during or immediately after therapy. Usually, these acute changes heal with mild changes. Rarely, the acute dermatitis never completely heals, resulting in consequential late changes leading to chronic wounds and necrosis. Alternatively, chronic or true late radiation dermatitis may develop despite minimal acute radiation dermatitis. Unlike acute effects, true late reactions are unlikely to be self-repairing.

Physical factors
The severity of the skin reaction is both treatment-and patient-related. Physical factors, including smoking, poor nutritional status, problems with skin integrity, actinic damage, as well as body site, obesity, and overlapping skin folds, predispose patients to radiation dermatitis. Fig 1 demonstrates increased radiation-induced erythema in the inframammary crease and axillae compared with that seen on the breast after the same 50-Gy dose. Approximately 25% of patients receiving parallel-opposed lateral fields will have skin reactions. The intentional use of boost doses to treat malignancies or nodal basins unavoidably produces overlapping fields, as illustrated in Fig 1, where increased erythema is seen at the junction between the electron and photon field. The use of bolus material also often results in an increase in the skin dose. When the skin is purposefully targeted, as in the case of inflammatory breast cancer, primary skin cancers, or mycosis fungoides, and when dose escalation is used to treat regionally recurrent disease, cutaneous problems should be anticipated. The larger the targeted tumor, the more likely a severe skin reaction is to develop. Tissue expanders, especially in the breast, present a unique dilemma both in delivering the desired dose and in maintaining skin integrity. Positioning the patient to reduce apposition of skin folds, using skin shields in sensitive areas, and delaying treatment until preexisting skin problems have been addressed may decrease the frequency and severity of radiation-induced skin problems. Deliberate exposure to ultraviolet (UV) radiation in treatment areas should be avoided, as this may up-regulate cytokine production, as well as serve as a cocarcinogen. Temperature extremes should also be avoided.

Genetic factors
As ionizing radiation produces DNA damage, patients with impaired cellular DNA repair capabilities are at increased risk. Those persons with ataxia telangiectasia, a rare autosomal-recessive disorder resulting from mutations in both copies of the ATM gene, are especially predisposed to develop severe cutaneous complications after RT. It has been suggested that patients who develop serious, unanticipated radiation dermatitis may actually harbor a previously undetected abnormality in the ATM gene or may be heterozygous for this trait. ATM heterozygosity occurs in approximately 1% of the general population, and a single mutated copy of the DNA repair gene may predispose patients to cutaneous complications, necessitating dose alterations to reduce cutaneous toxicity. Because of their increased cellular radiosensitivity, heterozygous ATM breast cancer patients may qualify for dose and volume reduction trials.

Other diseases with reduced cellular DNA repair capability call for dose alteration or avoidance of therapeutic radiation entirely. Patients with hereditary nevoid basal cell carcinoma (BCC) syndrome (Gorlin syndrome) develop multiple BCCs as well as a variety of phenotypic abnormalities. The occurrence of abnormalities in the human homologue Patched (PTCH) gene has been identified as the impaired tumor suppressor gene associated with this syndrome, and increased cellular proliferation occurs via the Hedgehog signaling pathway. Ptc heterozygous mice exhibit increased radiation-induced teratogenesis, suggesting a role of ptc in the response to ionizing radiation. Nucleoli in fibroblasts of affected persons are increased after x-ray radiation, apparently corresponding to increased RNA synthesis and metabolism. Radiation of affected patients
may produce devastating results, with the production of widespread cutaneous tumors (Fig 10).

Patients with other chromosomal breakage syndromes, including Fanconi's anemia, Bloom syndrome, as well as disorders characterized by defects in DNA repair such as xeroderma pigmentosum, may experience increased frequency of chromatid breaks and gaps in skin fibroblasts when compared with normal controls after G2 phase x-irradiation. This has also been reported with familial polyposis, Gardner's syndrome, hereditary malignant melanoma, and dysplastic nevus syndrome. However, even in patients without known genetic disorders, there may be individual differences in early and late radiation response in the skin. Whether these differences are determined by heterogeneity in intrinsic cell radiosensitivity or by other factors has yet to be elucidated. Attempts have been made in breast cancer patients to predict radiosensitivity and subsequent fibrosis by measuring the number of lethal chromosome aberrations of in vitro irradiated lymphocytes, but there is no clinically standardized method of predicting individual variations in response to therapy. Measurements of DNA damage by p53 and p21 protein accumulation have been assayed in the irradiated breast, where no association between the p53 response and degree of erythema was found. Therefore epidermal p53 response does not reliably predict the degree of radiation-induced epidermal injury. Individual responses to radiation-induced DNA damage vary widely and may be independent of the type of radiation.

Connective tissue disease

Preexisting connective tissue or autoimmune disease, including scleroderma, systemic lupus erythematosus (SLE), and perhaps rheumatoid arthritis (RA), unpredictably predispose patients to the development of severe radiation dermatitis. Although the mechanism is not known, lymphocytes from patients with RA, SLE, and polymyositis are more radiosensitive than those from healthy volunteers or patients with conditions not associated with autoimmunity. Peripheral blood lymphocytes from patients with SLE, juvenile RA, and systemic sclerosis have significantly greater DNA damage after irradiation than do those from control subjects. Because of this, the presence of connective tissue disease is a relative contraindication to RT.

Infectious disease

Patients with HIV-related disease may demonstrate a decreased tolerance of skin and mucous membranes to treatment, independent of their risk of infection. They tend to develop cutaneous reactions at a lower dose, as well as more significant systemic problems.

Radiosensitizers

An increase in adverse events is well documented after the use of “radiosensitizers.” These are drugs given immediately either immediately before, during, or less than 7 days after radiation, causing increased cellular damage and impaired repair. It is now known that the timing and dose of any such agents are crucial. For example, when paclitaxel or docetaxel are used in conjunction with radiotherapy in the treatment of breast cancer, they produce synergistic cutaneous toxicity that is both schedule- and dose-dependent. The concomitant use of tamoxifen with RT has been implicated in the development of an increased incidence of subcutaneous fibrosis by some investigators.

DIFFERENTIAL DIAGNOSIS

Common cutaneous problems, including dermatitis or infection, may become manifest during or after treatment. Fig 11 demonstrates a contact dermatitis to the marking pens used to draw fiducials, or field lines. Even after the immediate effects of radiation have subsided, the treated skin may manifest a host of physical and functional changes. Compromised integrity and impaired barrier function may produce a “locus minoris resistentiae,” a Latin phrase meaning “a place of less resistance,” demonstrated by the asthetotic eczema confined to the radiation port shown in Fig 12. There are case reports of localized infection or Sweet’s syndrome in the irradiated skin of the breast as well as lichen planus confined to a radiation port. Reports of pemphigus, an autoimmune bullous disease, occurring after ionizing radiation exposure are rare. Common to these cases is a
prodromal persistent nonspecific dermatitic eruption, which is often interpreted as radiation dermatitis, and latency of variable duration before the onset of a vesiculobullous eruption that begins at the portal of irradiation.90

Cutaneous hypersensitivity syndromes, including erythema multiforme, have been reported to start in irradiated skin and generalize from there.91 Localized Stevens-Johnson syndrome confined to radiation ports has been reported in conjunction with the administration of oral agents, such as phenobarbital.92 Other severe complications including toxic epidermal necrolysis, a skin condition characterized by complete epidermal necrosis, has been reported to occur more frequently when phenytoin and related anticonvulsants are combined with cranial radiation. These reactions also have, on occasion, started in the radiation port,92-97 prompting some clinicians to avoid phenytoin during RT.91 Non-specific hypersensitivity reactions including urticaria may also be seen during RT (Fig 13). Delayed breast cellulitis, presenting as breast inflammation that is not responsive to antibiotics, is an aseptic inflammatory process occurring after breast-conserving therapy. It may appear before or after radiation and be caused by impairment or occlusion of the lymphatic circulation.98

Radiation recall refers to the phenomenon of cutaneous inflammation, limited to the site of radiation, occurring at least 7 days after treatment or after the acute dermatitis has healed.99 It is graded according to its severity, ranging from erythema to necrosis, ulceration, or hemorrhage. Increasingly, severe recall dermatitis tends to occur when the offending drugs, usually cytotoxic agents, are introduced shortly after the cessation of RT.99 It has also been reported after the administration of nonsteroidal antiinflammatory agents and antituberculosis medications.100 Radiation recall occurs minutes to days after drug exposure and may occur weeks to years after radiation. Radiation recall occurs unpredictably recur on reexposure, but usually flares after the first exposure to the inciting drug. The longest well-documented hiatus between treatment and recall is 2 years after radiation exposure.101,102 The origin of this well-documented phenomenon is uncertain. Impaired cellular repair, gene mutation,vascular damage, epidermal stem cell inadequacy, and depletion, drug hypersensitivity, cumulative direct DNA damage and oxidative stress, koebnerization, nonimmune activation, and up-regulation of cytokines have all been implicated.100 The latter theory is supported by cases of radiation recall that occur minutes after parenteral infusion, whereas it takes a median of 8 days to manifest after oral medications. Although anecdotally beneficial, the role of topical or systemic steroids, mast cell inhibitors, and antihistamines in prevention and treatment of this problem has not been evaluated in a controlled setting.99

Finally, recurrent or secondary tumor should be considered if atypical plaques and nodules develop

Fig 11. Contact dermatitis from pens used to paint fiducials (field lines).

Fig 12. Dermatitis in locus minoris resistentiae after radiation.

Fig 13. Urticaria during radiation therapy.
within the radiation field. Although irradiated skin may present some difficulty in healing, a biopsy is useful in this clinical situation.

TREATMENT OF ACUTE RADIATION DERMATITIS

Early changes (grade 1) characterized by erythema and dry desquamation are best treated symptomatically. The affected area is washed gently with plain water alone or combined with a mild, low pH—cleansing agent that does not exacerbate the existing dermatitis. This has proven to be both physically and psychologically more beneficial than older practices of not washing at all. Washing may also reduce the bacterial load and thereby reduce potential superantigen-induced inflammation. Patients should wear well-fitting, nonbinding clothing and avoid unnecessary topical irritants and friction. When required, soft burn nets or other modalities that hold dressings in place without adhesives should replace tape. In the case of breast cancer patients, a sports bra can be used for this purpose. While patients are actively undergoing therapy, aluminum or magnesium salts such as those found in antiperspirants and talcs should not be used in the treated area because they can increase the radiation dose to the superficial skin. UV exposure in the treated area because they can increase the radiation dose to the superficial skin. UV exposure should be avoided, and photoprotection in the form of clothing, hats, and sunscreen should be utilized as tolerated.

TOPICAL THERAPY AND WOUND CARE

Many of the recommendations for skin care are derived from the wound care literature. The goal of treating the erythema and dry desquamation is to avoid a bolus effect, minimize transepidermal water loss, decrease pain, and prevent progression to moist desquamation. Petroleum-based emollients are commonly used, with or without hydrogel dressings. Radioemulsions containing trolamine were hoped to be “radioprotective” because they are macrophage cell stimulators that remove necrotic tissue, promote fibroblast proliferation, and, ex vivo, reduce vascular alterations, restore CD34 expression, promote epithelial cell proliferation, and decrease IL-1 expression and collagen secretion. The oil-in-water formulation also softens nonviable tissues. Although controlled studies show no clinical radioprotective effect over control agents, many patients express satisfaction with these ointments and find them soothing. Newer non-petroleum-based products combining castor oil, balsam of Peru, and trypsin purportedly stimulate the capillary bed, improve epithelialization, and provide cutaneous protection.

Recommendations for use of other topical skin agents are largely anecdotal, and few randomized studies have been performed. Consequently, a great variety of products have been used, and many recommendations have emerged. Aloe vera, D-panthenol, hydrophobic and hydrophilic ointments, chamomile, and almond ointment have been tried with variable results. The role of antioxidants, including vitamin C, has not been established, and topical ascorbic acid does no better than placebo in preventing skin toxicity after cranial RT. However, when antioxidants were given systemically to mice, higher doses of radiation were required to obtain skin desquamation. Sucralfate (sucrose aluminum), a widely used antiulcer drug, has anti-inflammatory properties and activates cellular proliferation. In a double-blind, randomized study comparing the efficacy of sucralfate cream to a base cream in 50 breast cancer patients who received postoperative electron beam therapy to the chest wall, acute radiation dermatitis was decreased and the recovery of the skin was also significantly faster in the group that received sucralfate cream. However, in another study comparing vehicle with vehicle plus 10% sucralfate, there was no significant difference in time to healing or pain relief. Topical hyaluronic acid has been helpful in some patients undergoing RT, demonstrating improved healing compared with placebo, as has calendula, an extract from a plant of the marigold family. Barrier films may also prove useful when compared with glycerine cream. Skin care products containing antioxidants such as hydroxytyrosol are used for stasis dermatitis, but whether they are useful in the treatment of radiation dermatitis is not known.

The general consensus is that the majority of patients do not need specific therapy and symptomatically benefit from bland moisturizers as tolerated. However, as with other forms of dermatitis, creams and ointments are generally better tolerated than lotions in irritated, dry skin. Since approximately 10% of patients have allergic-type reactions with topical agents, this should be considered if exacerbation of the dermatitis occurs.

The use of topical corticosteroids to prevent or treat radiation dermatitis is somewhat controversial. Because these agents have documented anti-inflammatory effects and have been shown to inhibit the up-regulation of IL-6 in response to ionizing radiation, they have been utilized for both treatment and prevention. Comparisons of different topical steroids, instituted either before or during the onset of acute dermatitis, show conflicting results. Some studies show no statistically significant difference between steroid (0.2% hydrocortisone valerate)
versus placebo, whereas other groups demonstrate decreased acute radiation dermatitis in the topical steroid group. Comparison of two different steroid creams, 1% hydrocortisone cream and 0.05% clobetasone butyrate, in a double-blind trial was carried out in 54 patients undergoing RT for breast cancer. The majority of patients using either cream derived benefit from its soothing effect, but patients using clobetasone butyrate developed more severe skin reactions. Although there is no consensus, at best steroids may ameliorate the dermatitis, but steroids do not prevent it. It is not known whether the incidence of infection, telangiectasia, or skin atrophy, which are known side effects of this group of topical agents, is increased. Other anti-inflammatory agents such as 1% indomethacin cream were not found to be helpful in preventing radiation-induced erythema. The new topical calcineurin inhibitors (topical tacrolimus and pimecrolimus) are potent down-regulators of cytokine production and are currently approved for use in atopic dermatitis. To date there have been no controlled trials documenting their usefulness in radiation dermatitis.

Wound care for erosions and ulcers

Although irradiated skin is significantly altered, the care of radiation dermatitis is generally not specific and is adapted from the generic wound care experience (Table II). From a prognostic standpoint, it may be helpful to distinguish consequential late injury from secondary injury in an irradiated field. Wound dressings are used for multiple reasons, including handling wound secretions and pain control, as well as protecting the skin from outside contamination. In addition, preserving a moist environment enhances re-epithelialization, lyse necrotic tissue and encourages phagocytosis of necrotic debris and bacteria. To enhance barrier function, hydrophilic and lipophilic creams and ointments are often used alone or with hydrogel dressings. These dressings are soothing, but, because they are not self-adherent, must be held in place and removed just before treatment. They may be cleaned and reapplied, especially on nonexudative wounds. When the dressings are refrigerated before use and applied while still cool, patients often find them soothing.

Hydrocolloid dressings provide minimal absorption of secretions and hydrate the wound. Additional benefits include healing of established wounds, simplification of wound care, and pain control. They are self-adherent, which may present a problem when the adhesive is placed on already damaged skin. These dressings are commonly left in place for several days and therefore are more useful after completion of RT.

Table II. Treatment of radiation dermatitis

<table>
<thead>
<tr>
<th>Acute</th>
<th>Erythema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Emollients (lotions, creams, or ointments)</td>
</tr>
<tr>
<td></td>
<td>Avoid friction, UV radiation, temperature extremes, trauma</td>
</tr>
<tr>
<td></td>
<td>Treat symptoms</td>
</tr>
</tbody>
</table>
| Dry desquamation | }

|       | Emollients (creams or ointments) |
|       | Petrolatum based |
|       | Castor oil/balsam of Peru/trypsin |
|       | Trolamine |
|       | Miscellaneous (see text) |
| Gentle cleansing | }

| Topical corticosteroids—controversial |
| Moist desquamation during RT |
| As above with the addition of: |
| Hydrogel dressings |
| Hydrocolloid dressings for minimally exudative wounds |
| Burn pads, alginate, or foam dressings for highly exudative wounds |
| Bacterial culture: treat infected wounds topically or systemically based on results |

| Moist desquamation after RT |
| As above with the addition of: |
| Film dressings for minimally exudative erosions |
| Infected wounds |
| Ionic silver pads or powder |
| Topical antibiotics |
| Cadexomer iodine |
| Maltodextrin powder |

| Chronic |
| Ulcers |
| Control secretions, limit bacteria and debris |
| As above with the addition of: |
| Careful and selective debridement |
| Mechanical |
| Enzymatic |
| Autolytic—moist matrix |
| Biosurgical |
| Recombinant PDGF |
| Biologic preparations: growth factors |
| Low-intensity helium laser |
| Hyperbaric oxygen |
| Telangiectasia |
| Vascular laser |
| Fibrosis |
| Pentoxifyllin, pentoxifylline plus vitamin E |
| Interferon gamma |
| Superoxide dismutase |

PDGF, Platelet-derived growth factor; RT, radiation therapy.

* Adapted from reviews of the wound care literature and clinical experience.

1 Case reports.

2 Controlled human trial.

3 Animal models.
Persistent eschars can be removed manually with the patient under local anesthesia or treated with enzymatic debridement or autolytic dressings. Biosurgical debridement with sterile live maggots removes necrotic, infected tissue, leaving healthy tissue untouched. Unfortunately, these techniques often leave significant skin and soft-tissue defects. Biosynthetic dressings, artificial skin, and bioengineered skin have proved useful in the setting of persistent, nonhealing ulcerations. Novel therapies, including low-intensity helium-neon laser, have benefited some patients with recalcitrant chronic skin ulcers after RT, perhaps by enhancing metabolic pathways, cell proliferation, and motility of fibroblasts and keratinocytes, as well as improving skin circulation and inducing angiogenesis. Recombinant PDGF and hydrophilic copolymer membranes have also been utilized to treat chronic radiation-induced ulcers.

Topical or oral antibacterial agents should be considered in the treatment of wounds that are at high risk or are already infected. Silver-based dressings are antibacterial and have proven to be effective for this purpose. Patients with anal canal tumors or some types of gynecologic tumors undergoing RT and chemotherapy experience close to 100% incidence of dermatitis, often of grade 3 or 4. This not only interferes with quality of life, but also mandates a hiatus in RT, potentially with a negative impact on patient outcome. In patients in whom the tumor was not close to the skin, silver leaf nylon dressings, removed during treatments, have been found to be helpful, probably secondary to their antibacterial effects. Because of the potential to increase the skin dose, caution should be used with any metal-based dressing during therapy. Cadexomer iodine–based dressings promote autolytic debridement, absorb exudates, control drainage, and are nontoxic to fibroblasts in vitro. Maltodextrin powder or gel, a macrophage activator, reduces bioburden by increasing local osmolality and is helpful in odor control.

**Targeted biologic therapy**

Targeted therapy and biologic preparations may be useful in some types of radiation dermatitis. A series of 24 patients with acute radiation-induced vulvar dermatitis found topical granulocyte-macrophage–colony-stimulating factor plus topical steroids more useful than steroids alone in reducing the severity and duration of the problem. The presumed mechanism of action is the promotion of chemotaxis of monocytes into tissues and the maturation of monocytes into macrophages.

PDGFs are chemotactic for neutrophils, monocytes, macrophages, and fibroblasts. Theoretically they also stimulate the synthesis of extracellular matrix components, collagen, and additional growth factors. These have shown anecdotal success in producing enough granulation tissue in a chronic radiation wound on the neck to support a skin graft. Chronic radiation ulcers after electron beam therapy were treated successfully with PDGF gel and hydrophilic copolymer membrane. If there is active tumor, there may be some theoretical risk in the use of growth factors, and some topical dressings may partially absorb or inactivate this expensive product.

**Treatment of chronic fibrosis**

Chronic fibrosis is probably the most difficult cutaneous complication to treat. Long thought to be irreversible, chronic fibrosis often requires supportive measures to avoid skin breakdown and infection. Multidisciplinary teams including specialists in wound care, physical therapy, and pain management often work together to address important cosmetic and quality-of-life issues. Physical therapy, deep massage, as well as active and passive range of motion exercises are important techniques utilized to maintain mobility and to minimize contractures. Chronic nonhealing ulcers and suspect lesions may need histopathologic examination to exclude the possibility of secondary skin malignancy. Unfortunately, these sites may heal poorly.

Alternative approaches include the use of pentoxifylline (PTX), a methylxanthine derivative in common use as an inhibitor of platelet aggregation. This drug may also increase phagocytic activity of polymorphonuclear leukocytes and monocytes, as well as antagonizing tumor necrosis factor-α and -β. By decreasing cytokines granulocyte-macrophage–colony-stimulating factor and interferon gamma, as well as modulating intercellular adhesion molecule-1 expression, PTX had a significant antifibrotic effect in vivo in reversing gamma ray–induced fibrosis in pigs. The combination of PTX and the antioxidant vitamin E (α-tocopheryl acetate) may further down-regulate TGF-β expression by myofibroblasts and actually reverse the abnormal fibroblast phenotype that perpetuates fibrosis. Other effects of PTX include inhibition of certain constitutive and TNF alpha-induced biosynthetic activities of fibroblasts as well as lowering the levels of type I...
Studies examining the effect of prophylactic administration of PTX are ongoing. It may reduce late soft tissue disease but does not affect acute radiation reactions in animals. In patients, late skin changes, fibrosis, and soft tissue necrosis were less severe in PTX-treated groups than in controls, possibly because of a protective effect with the use of PTX against vascular disease.\textsuperscript{152} PTX also accelerated healing of soft-tissue necrosis and reversed some late radiation injuries.\textsuperscript{139,153} There was no positive effect on acute skin reactions or pain in some studies,\textsuperscript{152} whereas in others the use of PTX showed a decrease in pain.\textsuperscript{139,153} When PTX was used with vitamin E, lymphedema of the arm occurring after axillary surgery and lymphatic radiotherapy was not prevented.\textsuperscript{154} However, both in patients and in the pig model, some antifibrotic action of this combination was found in established disease.\textsuperscript{49,140} In a pig model, there was less subcutaneous fibrotic scar tissue and decreased immunostaining for TGF-\( \beta \)1 in the residual fibrotic tissue.\textsuperscript{45,49,154} Lipid peroxidation and certain lipid peroxidation products induce genetic overexpression of fibrogenic cytokines, the key molecules in the pathogenic mechanisms of fibrosis, as well as increased transcription and synthesis of collagen.\textsuperscript{45,155} Both of these events can be down-regulated, at least in experimental models, by the use of antioxidants. The effect of oxidative stress on cytokine gene expression appears to be an important mechanism by which connective tissue deposition is promoted.\textsuperscript{156,157}

Other modalities in the treatment of treat chronic radiation fibrosis have included intramuscular injections of liposomal copper/zinc superoxide dismutase twice a week for 3 weeks in 34 patients, who showed some clinical regression of fibrosis that began in the third week and was at maximal by 2 months.\textsuperscript{143} Liposomal superoxide dismutase may down-regulate TGF-\( \beta \) secretions by myofibroblasts, functioning as an antioxidant and anti-inflammatory agent.\textsuperscript{45} Early animal studies show that superoxide dismutase may have an immediate radioprotective effect if given before radiation, possibly changing genetic programming of cell differentiation and proliferation;\textsuperscript{142} it also has been shown to reverse the radiation-induced fibrotic process in experimental animals and to permit the regeneration of normal tissue in a zone of well-established postirradiation fibrosis.\textsuperscript{142}

Another proinflammatory cytokine, interferon gamma, may inhibit collagen production in dermal fibroblasts. When used subcutaneously 3 times a week for 6 months, then once per week for 6 months in 5 patients with chronic-stage cutaneous radiation syndrome, low-dose interferon gamma was found to be useful in the treatment of cutaneous fibrosis and of the chronic infection in fibrosed skin.\textsuperscript{141}

In chronic radiation dermatitis, hyperbaric oxygen therapy (HBOT) can result in re-epithelialization of small areas as well as reduce pain, edema, erythema, or lymphedema.\textsuperscript{32} but no effect on fibrosis or telangiectasia was noted.\textsuperscript{158} However, when HBOT was used as a prophylactic in an animal model, it has been shown that tissue fibrosis may be reduced.\textsuperscript{159,160} HBOT may also be useful in radiation-induced hypovascularity, and HBOT has been used since the 1970s because of its ability to induce neovascularization in the irradiated bed.\textsuperscript{157} Numerous mechanisms have been implicated, including the enhanced activity of prolyl hydroxylase in the production of collagen, and recent data have demonstrated that HBOT modulates the signal transduction pathway that regulates the gene expression for the PDGF-\( \beta \) receptor. HBOT also stimulates osteoclast and osteoblast function, which is impaired under hypoxic conditions. Improved neutrophil function results in increased resistance to infection, and HBOT has bacteriostatic effects on anaerobic and even aerobic bacteria. Therefore Medicare covers HBOT as part of the treatment of the late effects of RT, and an evidence-based review of its use in irradiated tissue is available from the Undersea and Hyperbaric Medical Society.\textsuperscript{161}

**Secondary cutaneous malignancy**

Ionizing radiation may be used to treat established cutaneous malignancies, but it also increases the frequency of skin cancer and its precursor lesions. The strongest case can be made for the increased incidence of BCC, and all available studies show that skin cancer risk is greater from radiation exposure at young ages\textsuperscript{162-165} and greater for Caucasians compared with African Americans.\textsuperscript{163} When the average age at irradiation for tinea capitis was 12 years, the latent period of radiation-induced skin cancer was 36 years.\textsuperscript{166} These tumors arise not only in areas with typical changes associated with long-term radiation, but also on normal-appearing irradiated scalp in patients who were treated for tinea capitis.\textsuperscript{166} The increased risk of nonmelanoma skin cancer (NMSC) may last for a lifetime after irradiation, is dose related, and after exposure grows over time.\textsuperscript{162,165,167} These BCCs may present with aggressive or unusual variants, including keloidal, scarring, or aggressive varieties. Genetic instability may occur in irradiated cells many generations after treatment, possibly accounting for these tumors,\textsuperscript{168} and mutations of...
tumor-suppressor genes may play a role in some cases.\textsuperscript{166,169}

The growth of other tumors including radiation keratoses, squamous cell carcinoma (SCC), fibrosarcoma, dermatosarcoma, angiosarcoma, and melanoma has not been as well documented. The observation that fewer skin cancers develop among irradiated African Americans as compared with Caucasians, despite a comparable dose of ionizing radiation, implies that skin susceptibility to UV exposure may modify the risk from ionizing radiation. Available evidence indicates that the excess risk of skin cancer lasts for 45 years or more after treatment.\textsuperscript{162} Most of the studies reporting an increase of NMSC have not distinguished between patients who received radiotherapy versus those receiving chemotherapy. Some, but not all, follow-up studies of cancer patients have reported excesses of malignant melanoma as second malignant neoplasms. It is not clear from the studies how much, if any, of the excess melanoma risk is attributable to radiotherapy.\textsuperscript{162,164} However, the fact remains that the most common malignancy in the survivors of Hiroshima and Nagasaki was NMSC. SCC in radiation fields or scars is often ill defined and exhibits aggressive behavior and metastases. Because of this, surgical excision is the preferred modality of treatment. Microscopically monitored surgery with margin control (Mohs surgery) has a high cure rate, is well tolerated, and usually performed with the patient under local anesthesia in an office setting.

Angiosarcomas are a heterogeneous group of tumors with differing pathogenesis. They may be classified as primary in breast parenchyma, often in younger patients. When found after radical mastectomy with axillary node dissection, Stewart-Treves syndrome, they appear to be associated with chronic edema rather than radiation alone. Angiosarcomas developing in radiation sites should be considered in the clinical setting of late skin thickening, induration, edema, or dyspigmentation.\textsuperscript{170} Because breast-conserving therapy followed by RT has become the standard of care for early disease, a recently recognized form of cutaneous postradiation angiosarcoma of the breast has been observed, and incidence of this tumor may increase.\textsuperscript{171} This type of angiosarcoma is frequently multifocal, with a median interval to diagnosis of 59 months; lymphedema was largely absent or mild.\textsuperscript{172}

Because of their premalignant potential, radiation-induced keratoses are often treated. Although there are no studies specifically addressing therapy for irradiated skin, in practice these keratoses are treated like actinically induced lesions. Cryotherapy is widely used for localized lesions, but it is of limited usefulness if it does not address large numbers of lesions in the radiation port. Diffuse ill-defined keratoses are candidates for destruction with physical measures such as chemical peels, dermabrasion, or laser.

Topical 5-fluorouracil, diclofenac, photodynamic therapy, and imiquimod have also proven beneficial. Fluorouracil cream is an antineoplastic, antimetabolite drug that interferes with the synthesis of DNA and RNA, preventing the proliferation of damaged cells.\textsuperscript{173} Newer topical modalities, such as diclofenac, are cyclooxygenase 2 (COX-2) inhibitors, inhibiting the enzymes involved in arachidonic acid metabolism. Arachidonic acid metabolites have been shown to be pivotal in promoting epithelial tumor growth by stimulating angiogenesis, inhibiting apoptosis, and increasing invasiveness of tumor cells.\textsuperscript{174-177} This suggests a possible role for COX-2 inhibitors administered at therapeutically achievable doses in the prevention of radiation-induced malignancy.\textsuperscript{178} Diclofenac, a topical COX-2 inhibitor, is typically applied twice a day for 90 days.

Another modality used in the treatment of actinic keratoses and in situ SCC is topical 5-aminolevulinic acid followed by photodynamic therapy.\textsuperscript{179} This approach utilizes a photosensitizing compound applied to specific lesions and photoactivated by red-light irradiation. Case reports have found this treatment useful for chronic x-ray induced dermatitis and particularly helpful in relief of pain.\textsuperscript{180}

A promising therapeutic option for both keratoses and superficial BCC is topical imiquimod. This immune response modifier affects both the innate and acquired immune responses\textsuperscript{181,182} by binding to toll-like receptor 7.\textsuperscript{183} Subsequent activation of mRNA expression of cytokines, including interferon alfa, TNF-\alpha, and IL-12, promotes a helper T-cell type 1–mediated immune response as well as reduced Bcl-2 expression, which induces Fas-R-mediated apoptosis in BCC.\textsuperscript{181,184} Currently imiquimod is approved by the Food and Drug Administration to treat multiple actinic keratoses\textsuperscript{185} and genital warts.

\section*{FUTURE DIRECTIONS}

The treatment of radiation-induced skin injury continues to be a multidisciplinary effort that focuses on identifying patients at risk, new skin-sparing technology, and wound care of established disease. Technological advances in radiation delivery include conformal RT, which targets the tumor while minimizing exposure of normal tissue. Intensity-modulated radiotherapy utilizes collimators that focus multiple beams on the intended target. This results in a smaller high-dose target, but at the cost of increasing the volume of tissue receiving low doses.
of radiation. The linear accelerator and in-room computed tomography, as well as dedicated operating room suites equipped with a linear accelerator, provide increased precision and convenience for patients as well as for radiation oncologists. The combination of positron emission tomographic scans and computed tomography further defines treatment targets. Newer modalities of therapy, including the utilization of protons, potentially will avoid the skin altogether.

Advancements in immunology, including a better understanding of cytokines, inflammation, and the role they play in producing acute and chronic radiation dermatitis, have prompted ongoing investigation of compounds which may prove to be “cytoprotective.” Finally, advances in basic wound care management have been invaluable in the treatment of acute and chronic radiation dermatitis.

REFERENCES


