Late Radiation-Related Fibrosis: Pathogenesis, Manifestations, and Current Management

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Radiation-induced fibrosis (RIF) represents one of the most common long-term adverse effects of curative radiotherapy. Current cancer treatment approaches, involving more intensive radiotherapy regimens, used in combination with systemic agents, will likely be associated with a higher incidence and greater degree of damage to normal tissues, especially RIF. Traditionally, the development of fibrosis after radiation therapy has been considered static and irreversible. Contemporary understanding recognizes RIF as a continuum of responses mediated by molecular pathways that may be amenable to interventions. Preliminary evidence suggests that pharmacological or other interventions may be possible to reverse the manifestation of the injury and restore function to tissues. A variety of strategies have been tested for the management of RIF, although formal trials of these therapies that permit treatment comparisons are unavailable at this time. It is critical that we formally evaluate new management approaches for RIF with larger patient accrual. To this end, it is also important to develop a means of registering its occurrence for outcome analysis and to refer these patients to colleagues familiar with optimal management and enrollment in clinical trials.

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The influence of radiation-induced fibrosis (RIF) depends on the anatomic site and may range from solely subjective to very objective manifestations. In this article, the proposed underlying mechanisms of fibrosis are briefly reviewed as well as current management options. We discuss the biologic rationale of currently available interventions and explore potential areas of study for the future. One focus that will be emphasized is the dynamic nature of RIF representing a continuum mediated by molecular pathways that may be amenable to modulation.

Detection and Manifestations

Problems in Reporting and Detection of Radiation Fibrosis

The paradox of achieving successful treatment outcome from radiotherapy is that it produces an increase in the number of patients at risk for developing late radiation injuries. As well, the use of concurrent chemoradiation regimens and intensified fractionation schedules is likely to yield a greater incidence of long-term effects.

Assessment of late morbidity is not routinely reported as part of clinical practice, and even clinical trials do not always report long-term effects. Many trials have not systematically performed screening for late effects using accepted grading systems.1 Also, our expectations for the incidence of severe normal tissue damage may be problematic because tolerance doses are often estimates based on modeling.2 Models are frequently based on generalizations that assume uniform whole-organ irradiation, conventional fractionation, normal baseline function, and absence of other cancer treatments. Lastly, the comparison of the incidences of RIF among different institutions may not be valid for various reasons including cancer incidence, patient selection, comorbidity, and survival outcome.

Manifestation of Radiation Injury

Clinical and pathologic features. In most tissues, the predominant pathological effect of radiation is stromal with an interstitial fibrinous exudate preceding the onset of progressive fibrosis. Typically, rigid stromal encasement of capillaries and sinusoids that become distorted and dilated is present in the established (chronic) and severely affected case. Clinically, the earliest features usually comprise loss of tissue elasticity followed by mild induration. A greater degree of injury involves significant induration with rigidity of the surface layers and retraction of surface contours generally related to fibrosis of the dermis and subcutaneous tissue. Additional changes include hyperpigmentation, epilation, hyper-
hypoplasia of the epidermis, loss of vascularity, dryness (generally manifestations of injury to overlying epithelium and integuments, independent of fibrosis) and associated disuse atrophy. In extreme cases, ulceration and necrosis may result in part from extravasation of fibrinous exudate or from vascular compromise exacerbated by trauma or infection. Depending on the radiation dose distribution, more sinister manifestations may result in deeper tissues, including progressive entrapment (eg, of neurologic structures), stenosis, obliteration, or obstruction of parenchymal and hollow structures that accompanies injury to vital anatomy in the pelvis, abdomen, thorax, and head and neck. Fibrosis is often co-existent with local or regional lymphedema, which may also contribute to soft-tissue induration and functional consequences. The pathophysiologic relationship, if any, between these 2 forms of tissue injury is not well understood.

Methods of categorizing (or ranking) the severity of radiation fibrosis are discussed elsewhere in this issue. In addition, different specific anatomic sites may manifest different outcomes because the clinical impact may vary according to anatomy for the same extent of injury. The more common anatomic regions to be affected include the breast, the head and neck. Fibrosis is often co-existent with local or regional lymphedema, which may also contribute to soft-tissue induration and functional consequences. The pathophysiologic relationship, if any, between these 2 forms of tissue injury is not well understood.

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Different targets for radiation soft-tissue injury. The link between the different manifestations of radiation injury and their severity is complex. For example, telangiectasia, often regarded as part of the late tissue fibrosis picture, appears not to be correlated with the late endpoint of fibrosis suggesting that an assay for clinical expression of late injury may have to be specific for that injury. Some cases of telangiectasia may represent a consequential late reaction after a severe early reaction. Random processes superimposed on the subclinical residual injury may also trigger the onset of clinically apparent late tissue effects.

Dosimetry and Radiobiology
Although subcutaneous RIF is probably the most common manifestation of radiation injury, the exact depth in the skin most responsible for the fibrotic process is unclear. Bentzen et al proposed a range of 3.3 to 5.5 mm as acceptable reference points for subcutaneous fibrosis in the breast, with the best estimate at a depth of 4.1 mm. They also suggested a best estimate for the alpha/beta ratio of 1.8 for the fibrosis endpoint. The thickness of the skin is similar for the neck, chest wall, and most areas of the limbs and therefore consistent with these observations. The reason this may be important is that contemporary 3-dimensional radiotherapy planning systems do not model this dose satisfactorily because it exists in the steep dose gradient buildup zone. Unless consistency in describing dose and measuring outcome is used, we will remain at a disadvantage in predicting the true incidence and dose response of RIF. For subcutaneous fibrosis in neck tissues, Hirota et al specified the skin-absorbed dose at a depth of 4.1 mm (d4.1-mm) in the field center according to the recommendations of Bentzen et al. They found that the d4.1-mm was affected by the number of fields used and the application of certain techniques such as electron boosts compared with photons. They showed time dependence in the onset of RIF and that patients undergoing prior surgery (neck dissection) have a higher incidence of subcutaneous fibrosis than those without surgery, confirming that the effects of multimodality treatment in addition to the accuracy of dose calculation must be taken into account in estimating late tissue effects. The influence of other factors including total dose as the biologically equivalent dose (BED) at d4.1-mm fractionation, and systemic agents are also evident (Fig 1).

Latency and Assessment
Data from Jung et al indicate an apparent lifelong risk of developing late complications, without a plateau, suggesting that different kinetic
mechanisms are in play. The incidence of late effects appeared to be governed by nearly exponential kinetics quantifiable by the percentage of patients at risk of developing late morbidity per year. Therefore, serious underestimates of the severity and incidence of fibrosis may result if correct procedures are not used, especially in groups with incomplete follow-up. Also, increasing grades of some toxicities (eg, telangiectasia after breast cancer radiotherapy) are seen at progressively longer follow-up times. To monitor and understand these issues, prospectively collected data with consistent assessment methods and understanding of treatment parameters are needed. It should be acknowledged that rates of toxicity may be artefactually diminished because of death (from cancer or other causes) as a competing event. Improved understanding of the risk of late injury can be obtained by the use of cumulative incidence data and actuarial estimates accounting for death as a censoring event.

Biologic Responses Leading to Late Tissue Fibrosis

Traditional Concepts

The earliest theories attributed all late radiation injury to vascular/endothelial damage that led to permanent hypoxia and nutritional damage from vascular insufficiency. Later it was proposed that the normal tissue response was primarily controlled by the radiosensitivity of parenchymal (or target) cells and could be usefully predicted by the linear quadratic equation. In essence, this mechanism of injury also assumed that the radiotherapy was administered, events were pre-
determined, at least from a biologic standpoint. In fact, cellular radiosensitivity studies in the clinic have shown only weak correlations with the predicted late normal tissue responses, although this has not discouraged the widespread use of the L-Q model for predicting tissue outcomes.26

**Molecular Pathways in the Genesis of Radiation Fibrosis**

Contemporary thinking recognizes that a coordinated cellular response occurs after exposure to radiation. This response involves the interaction of many growth factors (or cytokines) with their receptors and the extracellular matrix (ECM), an aggregate of molecular structures that includes collagen. Continued enzymatic degradation and modification of the matrix results from a multifaceted series of events, mediated by molecular pathways at many levels. Likely, this is amplified after the initial phase of radiation tissue injury both as a result of the direct effects of the radiation on the cells and as a result of an induced inflammatory response. The actions of the involved cytokines can be positive or negative, depending on the influence of signaling from each other and the nature of the tissues involved in the remodeling process.27 In the case of fibrosis, imbalance can occur with accumulation of matrix in tissues as the primary pathologic feature of an aberrant process, usually triggered by external injury and the launch of a cascade of fibrogenic stimulants (Fig 2).28

Transforming growth factor-β (TGF-β), a member of a superfamily of proteins, exists as 3 isoforms (TGF-β 1, 2, and 3) with different functions implicated in organ growth and development, immune modulation, tumor suppression, and response to injury. TGF-β has recently generated considerable interest because of its powerful fibrogenic action. For example, dysregulation of TGF-β signaling with overexpression of endoglin (see later) appears implicated in the pathogenesis of scleroderma,29 and evidence suggests that TGF-β1 is the compelling stimulus behind the fibrotic reaction involving the proliferation of collagen-producing postmitotic fibrocytes from their progenitor fibroblasts. Although our understanding of the biology of TGF-β continues to evolve, it is believed to follow a model of signal transduction involving many receptors and kinase pathways (see summary, Fig 3).26-28,30-35 It is suggested that the type I receptor mediates ECM production, but growth and proliferation are influenced by the type II receptor.27 Also, variations in the gene-governing regulation of TGF-β expression occur naturally,32 and such ge-
netic polymorphisms may explain some of the variability in incidence and severity of RIF after radiotherapy.

**Molecular Complexes and Potential Therapeutic Targets in the TGF-β Pathway**

In reality, the TGF-β1 cytokine driven processes governing radiation injury are substantially more complex and include the functions of CD105 (also called endoglin), a specific vascular membrane glycoprotein with high affinity binding or TGF-β1 and β3 but not β2. At the same time, the type III TGF-β receptor (betaglycan), another membrane proteoglycan, binds TGF-β in the extracellular space and, although lacking signaling function of its own, is involved in the presentation of the cytokine to the type II TGF-β receptor. Furthermore, endoglin may diminish, whereas betaglycan may augment TGF-β signal transduction and the very recently described complexes between endoglin and betaglycan may therefore be involved in positive and negative TGF-β signaling regulation. After radiotherapy, Li et al have postulated that local tissue TGF-β1 activity is dulled by being scavenged by CD105 through the formation of receptor-ligand complexes. They showed that TGF-β1 increases the risk of developing fibrosis after radiotherapy in breast cancer patients, but the risk is lower when there is enhanced formation of circulating CD105–TGF-β1 complexes.

Therefore, formation of molecular complexes may restore balance in the continuous reconstitution of ECM offering potential for antifibrotic therapeutic targets. Also, TGF-β is first secreted as a latent complex and must be released from its latency-associated peptide to become functional.

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**Figure 3.** Simplified model of signal transduction interactions of transforming growth factor-β (TGF-β) with its cell surface receptors, termed type III (TβR-III), the most abundant, and types I (TβR-I), and II (TβR-II), that both exhibit signaling activity. TGF-β initially binds to the type III receptor and presents TGF-β to the type II receptor. Alternatively, TGF-β binds directly to the Type II receptor. In either event the binding of TGF-β to type II receptor is followed by type I receptor binding to form an active heteromeric receptor complex, involving a pair of transmembrane serine/threonine kinases, that activates (phosphorylates) the TβR-I (type I) receptor kinase pathway. The activated TβR-I receptors phosphorylate Smad transcription factors that initiate specific nuclear genetic target responses. Additional functions influence homeostatic signaling involving latency associated peptide (LAP), endoglin, proteoglycan (the type III receptor, also called betaglycan), and decorin (a natural TGF-β inhibitor) (see text). (Phosphorylation illustrated as double **).
however, their reassociation inhibits activity offering the prospect of a therapeutic target using recombinant technologies. Other fascinating possibilities include the ability of neutralizing antibodies to TGF-β and the naturally occurring TGF-β binding protein, decorin (a natural TGF-β inhibitor), to inhibit fibrosis. Indeed gene therapy approaches, using the decorin gene, have proven successful in animal models in sequestering decorin to certain tissues with consequent decrease in TGF-β expression and reversal of fibrosis.

Multifactorial Biological Response to Radiation

The evolution of the radiotherapeutic injury, intriguingly termed a complex “wound” by Denham and Hauer-Jensen, involves a variety of biological mechanisms that include a burst of molecular activity in addition to those of TGF-β. These include a series of complex interactions (e.g., plasminogen activator, angiotensin-converting enzyme, thromboxane, thrombin, and so on) in a dynamic spectrum of cellular injury, ongoing repair, inflammation, and other physiologic responses (Table 1). Appreciating these responses may yield targets for interventions to ameliorate radiation-mediated injury and even potentially reverse it. Finally, one should also not forget Hill et al’s recent caution that the important contribution of inflammatory cytokines in radiation effects does not rule out the importance of parenchymal and/or vascular cell killing.

Management Options for RIF

Interventions to Ameliorate Fibrosis

Earlier, we discussed the target cell theory as a mechanism for understanding the process of late tissue injury. If this were the sole mechanism, there would be limited opportunity to avert the damage (Table 2). However, in the development of RIF, nonlethal cellular injuries and inflammatory responses are important. In fact, most clinical findings are caused by excessively indurated and thickened tissues rather than atrophy. Clinical studies now provide evidence that in some situations reversal of fibrosis seems possible (Tables 3-5).

In the sections that follow, we present a brief overview of interventions that have been used in the clinical setting of RIF in patients (Table 6). It is cautioned that many of the observations are

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Table 1. Some Proposed Mechanistic Processes in the Genesis of Radiation Fibrosis

<table>
<thead>
<tr>
<th>Proposed Mechanism</th>
<th>Resulting Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated tissue exudates</td>
<td>Unresolved fibrin deposition due to deficiency in tissue plasminogen activator</td>
</tr>
<tr>
<td>EC injury leads to plasma exudates</td>
<td>Stimulation of collagen synthesis</td>
</tr>
<tr>
<td>Detachment of ECs leads to FGF activation and loss of mitogenic control of SMCs</td>
<td>Overproduction of collagen</td>
</tr>
<tr>
<td>Radiation-induced EC expression of TNF-alpha and PDGF</td>
<td>Stimulates SMC proliferation and production of collagen</td>
</tr>
<tr>
<td>Downregulation of EC NOS activity</td>
<td>Unopposed SMC proliferation</td>
</tr>
<tr>
<td>Downregulation of EC thrombomodulin</td>
<td>SMC activation enabled by thrombin with assistance of TGF-β</td>
</tr>
<tr>
<td>Prolonged epithelial barrier breakdown</td>
<td>Chronic subepithelial inflammation, including TGF-β production that drives fibroblast and SMC proliferation. TGF-β activation is promoted by mast cell hyperplasia in the gut</td>
</tr>
<tr>
<td>Permanent RT induced fibroblast phenotypic alterations</td>
<td>Overproduction of matrix</td>
</tr>
<tr>
<td>Alteration of the normal fibroblast population profile</td>
<td>Accumulation of post-mitotic fibrocytes to produce matrix elements</td>
</tr>
<tr>
<td>Proliferation of alveolar macrophages and type II pneumocytes (if lung irradiated)</td>
<td>Expression of TGF-β leads to pulmonary fibrosis</td>
</tr>
</tbody>
</table>

Abbreviations: EC; endothelial cell; FGF, fibroblast growth factor; SMC, smooth muscle cell; TNF-α, tumor necrosis factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; RT, radiotherapy; TGF-β, transforming growth factor-β; NOS, nitric oxide synthase.

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based on pilot studies of the type I/II variety, and there is an urgent need for confirmatory trials using randomized design or other attempts to control for bias in selection and outcome assessment.

Pharmacologic Measures

**Superoxide dismutase.** The first effective agent reported to reduce long-standing fibrosis caused by radiotherapy was liposomal Cu/Zn superoxide dismutase (SOD). There are 2 forms of SOD in humans: a mitochondrial isoform (manganese containing SOD, MnSOD) and a copper/zinc containing SOD (Cu/Zn SOD) located in the cytosol of human cells and in intracellular structures including the nucleus. SOD initially captures oxygen-free radicals, enzymatically converting them to hydrogen peroxide \((H_2O_2)\) before further metabolism. Administra-

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Therapeutic Use</th>
<th>Beneficial Effect</th>
<th>Inhibition of Matrix Synthesis</th>
<th>Reduction of Inflammation</th>
<th>Growth Factor Antagonism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colchicine, available</td>
<td>Experimental</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Dubrawsky et al77</td>
</tr>
<tr>
<td>Interferon-(\gamma), not available</td>
<td>Experimental</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Grossman et al78</td>
</tr>
<tr>
<td>Interferon-(\alpha), available</td>
<td>Clinical</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td>TGF-(\beta)</td>
<td>Calès79, Peter et al80</td>
</tr>
<tr>
<td>Glucocorticoids, available</td>
<td>Clinical</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Moreno et al81, Tredget et al82</td>
</tr>
<tr>
<td>Essential fatty acids, not available</td>
<td>Clinical</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Dufour et al83, Cutroneo et al84</td>
</tr>
<tr>
<td>SOD, not available</td>
<td>Clinical</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Delanian et al85</td>
</tr>
<tr>
<td>Pentoxifylline, available</td>
<td>Clinical</td>
<td>Pain</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Delanian et al86</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>Pain</td>
<td>No effects on fibrosis</td>
<td>+</td>
<td></td>
<td>Lefaix et al87</td>
</tr>
<tr>
<td>Vitamin E, available</td>
<td>Clinical</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td>TGF-(\beta)</td>
<td>Piguet et al88</td>
</tr>
<tr>
<td>Pentoxifylline with vitamin E, available</td>
<td>Clinical</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td>TGF-(\beta)</td>
<td>Delanian et al89, Lefaix et al90</td>
</tr>
<tr>
<td>Direct TNF-(\alpha) antagonists</td>
<td>Experimental</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td>TNFR-(\beta)</td>
<td>Piguet et al91</td>
</tr>
<tr>
<td>Antibodies to integrins</td>
<td>Experimental</td>
<td>Fibrosis</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Piguet et al92</td>
</tr>
</tbody>
</table>

Abbreviations: TGF, transforming growth factor; SOD, superoxide dismutase; TNF, tumor necrosis factor; TNFR-\(\beta\), TNF receptor beta.

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tion of SOD is problematic because of its short biological half-life, relatively high molecular weight (33 kDa) and hydrophilic nature. For this reason, a liposome encapsulated version allows a more efficient incorporation of the therapeutic compound, more continuous release, and which compensates for the short half-life. Delanian et al\textsuperscript{38} used bovine liposomal Cu/Zn SOD as twice weekly intramuscular injections of 5 mg for a total of 30 mg in 34 patients, all of whom showed some clinical regression of fibrosis. Regression commenced after 3 weeks and was maximal after 2 months. The same investigators were able to observe similar results using bovine Cu/Zn SOD and human recombinant Mn SOD with equal efficacy in a pig fibrosis model.\textsuperscript{39} Other investigators showed that the use of Cu/Zn SOD ointment applied twice daily showed improvement in breast symptoms, and perhaps more importantly, fibrosis after 6 months of treatment.\textsuperscript{40}

<table>
<thead>
<tr>
<th>Table 4. Pentoxifylline Alone in the Treatment of Late Radiation Injury</th>
</tr>
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<tbody>
<tr>
<td><strong>Author</strong></td>
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<tr>
<td>------------</td>
</tr>
<tr>
<td>Futran\textsuperscript{15}</td>
</tr>
<tr>
<td>Werner-Wasik\textsuperscript{43}</td>
</tr>
<tr>
<td>Cornelison et al\textsuperscript{44}</td>
</tr>
<tr>
<td>Dion et al\textsuperscript{46}</td>
</tr>
<tr>
<td>Chua et al\textsuperscript{48}</td>
</tr>
</tbody>
</table>

Abbreviations: PTX, pentoxifylline; NPC, nasopharyngeal carcinoma; bid, twice daily; tid, 3 times a day; po, by mouth.
Putative mechanisms implicate an effect of oxidative stress on cytokine gene expression as a mechanism of inducing fibrosis. Present evidence suggests that SOD reduces TGF-β1 expression in myofibroblasts, both at the messenger RNA and protein level, resulting in downregulation of collagen chain production. It is suggested that exogenous SOD can enter cells and reduce TGF-β1

Table 5. Pentoxifylline and Alpha Tocopherol (Vitamin E) for Late Radiation Fibrosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Intervention</th>
<th>Assessment of Response</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefaix51</td>
<td>Animal model (N = 15)</td>
<td>3 arms: 1) PTX + α-tocopherol 2) PTX alone 3) Control</td>
<td>Measurement of projected cutaneous surface area of fibrotic block and ultrasound assessment of depth</td>
<td>PTX + α-tocopherol superior, PTX alone and control groups equivalent</td>
</tr>
<tr>
<td>Delanian89</td>
<td>Case report, 67-year-old woman with fibrosis</td>
<td>PTX 800 mg/d Vitamin E 1000 U/d</td>
<td>Clinical assessment of response SOMA/LENT assessment</td>
<td>Complete clinical response at 18 months</td>
</tr>
<tr>
<td>Delanian52</td>
<td>Patients with radiation-induced fibrosis N = 40</td>
<td>PTX 800 mg/d Vitamin E 1000 U/d</td>
<td>Measurement of projected cutaneous surface area of fibrotic block SOMA/LENT assessment</td>
<td>Mean surface area regression (6 months) = 53% 24/40 patients had at least 50% regression Mean SOMA scores decreased from 13.2 to 6.9</td>
</tr>
</tbody>
</table>

Abbreviations: PTX, pentoxifylline.

Putative mechanisms implicate an effect of oxidative stress on cytokine gene expression as a mechanism of inducing fibrosis. Present evidence suggests that SOD reduces TGF-β1 expression in myofibroblasts, both at the messenger RNA and protein level, resulting in downregulation of collagen chain production. It is suggested that exogenous SOD can enter cells and reduce TGF-β1

Table 6. Strategies That Have Been Used for Established Radiation Fibrosis

<table>
<thead>
<tr>
<th>General Approach</th>
<th>Comments</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological</td>
<td>Variable efficacies Some clinical studies Some experimental studies Some agents unavailable (e.g. SOD)</td>
<td>See tables 3-5</td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
<td>Mechanisms poorly understood Signalling pathways possible Reduced edema, pain, erythema No significant effect on fibrosis and telangiectasia</td>
<td>See text discussion See reference71 See reference72 See reference72</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>Maintenance of exercise beneficial Avoids atrophy and disuse Benefit for lymphedema (RCT) Benefit for function (RCT) Need for additional trials</td>
<td>See reference5</td>
</tr>
<tr>
<td>Microcurrent therapy</td>
<td>Pilot data available: improved function improved pain sustained benefits (&gt;3 month) mechanisms undetermined</td>
<td>See reference76</td>
</tr>
</tbody>
</table>

Abbreviations: SOD, superoxide dismutase; RCT, randomized controlled trial.
expression resulting in an antifibrotic action in pig and human myofibroblasts.\textsuperscript{41,42}

SOD as an approved treatment remains unavailable, but the impressive clinical results in human and animal studies has spawned the exploration of alternative treatments that use antioxidant agents.

**Pentoxifylline alone.** Pentoxifylline (PTX) is a methylxanthine derivative originally introduced for the treatment of venous stasis ulcers, intermittent claudication, and cerebrovascular insufficiency. It produces dose-related hemorrheologic effects, lowers blood viscosity, improves erythrocyte flexibility, and increases tissue oxygen levels as well as promoting platelet deaggregation. These effects may be relevant in the treatment of late radiation injury. The enhanced red blood cell deformability allows more ready passage of cells through small vessels and capillaries narrowed by radiotherapy. PTX also inhibits the activation of neutrophils by cytokines, which abrogates oxygen radical formation, and tissue injury. The agent also appears to stimulate prostacyclin release from normal endothelial cells to inhibit some of the cytokine cascade resulting from tissue injury, and it indirectly inhibits the production of thromboxane, a potent vasoconstrictor and a strong stimulator of platelet aggregation.

Reports on the use of PTX as a sole agent for radiation fibrosis appear to be contradictory. Moderate beneficial effects are evident in 1 case report\textsuperscript{43} and in a small descriptive trial\textsuperscript{44} (Table 4). In contrast, other studies of PTX alone have shown its value in soft-tissue necrosis predominately rather than radiation fibrosis.\textsuperscript{45,46} Also, the regression of subcutaneous scar seen in a pig model with SOD could not be reproduced with PTX.\textsuperscript{33} Other clinical reports have indicated benefit in radiation mastitis,\textsuperscript{37} and of especial interest is the report from Chua et al\textsuperscript{40} indicating a modest therapeutic effect in 20 patients with severe radiation induced trismus after therapy for nasopharyngeal carcinoma (Table 4). A randomized open label crossover trial was launched by the Radiation Therapy Oncology Group in 1994, but closed because of poor accrual (A. Trotti, personal communication, 2003). The failure of this trial to accrue points out some of the challenges in conducting toxicity intervention studies.

**Combined pentoxifylline and alpha-tocopherol (vitamin E).** As alluded to earlier, an effect of oxidative stress on cytokine gene expression appears to be an important mechanism in fibrogenesis.\textsuperscript{49} The recognition that SOD could produce regression of fibrosis led to the investigation of alternative antioxidant strategies and explorations of these approaches as novel treatments for scleroderma.\textsuperscript{50} In RIF, the most widely reported regimen is PTX combined with another antioxidant, alpha-tocopherol (vitamin E). The theoretical background to these approaches is that reactive oxygen species are generated during inflammatory reactions and RIF development and should be efficiently scavenged to minimize oxidative stress. Alpha-tocopherol (vitamin E) is the most prominent antioxidant that protects membrane phospholipids from oxidative damage. The need for the drugs to be used in combination is not yet explained. Nevertheless, striking regression has been described in the pig model and in real clinical situations by the same authors who were the prominent advocates for the use of SOD\textsuperscript{51,52} (Table 5). In addition, in the pig model, not only was dramatic regression of the subcutaneous fibrotic scar noted but additionally decreased immunostaining for TGF-\textbeta1 was shown in residual fibrotic tissue.\textsuperscript{51} These authors also indicate that alpha-tocopherol alone does not appear to have the same efficacy for RIF as the combination with PTX.\textsuperscript{51,52}

In their clinical article, Delanian et al\textsuperscript{52} describe objective responses to the combination of PTX and alpha-tocopherol in 23 of 28 (83\%) RIF areas at 12 months with very satisfactory immediate and long-term tolerance. Rare instances of asthenia, vertigo, mild nausea, or dyspepsia were noted that did not significantly interfere with the use of the protocol. In addition, substantial improvement in the pliability of the affected regions was common and arrest of neurologic deficit from RIF was consistent, although actual restoration of neurologic impairment did not occur. Local pain improved rapidly with substantial reduction in the requirement for analgesics. Of interest, continued slow responses were frequent, often extending beyond 12 months and with a centripetal reduction of the edges of the fibrotic block without contraction or atrophy. In the end, however, perhaps the most important deduction from the authors is their strong conviction that the
results challenge the long-held dogma that dense radiation fibrosis is not reversible.\textsuperscript{32} Once more, we would add the cautionary need to attempt to confirm these hopeful findings and preferably with a controlled trial.

\textbf{Reservations about long-term antifibrotic pharmacological intervention.} Other than the approaches mentioned (SOD, PTX alone, or with tocopherol), as yet there have been no other significant clinical data showing significant interference with the RIF process. Nevertheless, the pathophysiological processes described earlier suggest multiple strategies for research into the amelioration of the fibrotic process at the molecular level. However, given the multiple functions of the TGF-\(\beta\) superfamily, some reservation exists about the possibility of malignant induction if there is continuous systemic inhibition of the signaling pathway as would be needed to treat late tissue fibrosis. There is evidence that loss or inactivation of the type II receptor may be associated with loss of the antimitogenic response to TGF-\(\beta\) and the possibility that malignancy may arise.\textsuperscript{53} Thus, in cancer cells, mutations in the pathway may allow uncontrolled cell proliferation arising from resistance to TGF-\(\beta\) growth inhibition.\textsuperscript{52} For this reason, it is useful to consider long-term strategies (eg, decorin gene therapy, already mentioned) when the antifibrogenic activity is restricted to local anatomic regions. Other possibilities include reduction of collagen I and II (the predominant proteins in fibrotic lesions), inhibition of angiotensin-converting enzyme, and enhancement of collagenase activity to achieve reduction in established fibrosis,\textsuperscript{28} but a detailed discussion of these issues is beyond the scope of this article.

\textbf{Corticosteroids and Other Drugs}

Corticosteroids have been long used for the treatment of radiation injuries. They are useful as anti-inflammatory agents, but it is uncertain whether they are capable of useful amelioration of established fibrosis. Likely they exert much of their effect by reduction of symptoms from the inflammatory reaction. Numerous examples exist from the laboratory in which the occurrence of fibrosis is prevented or reduced,\textsuperscript{26,34-36} although results may not be confirmed if fibrosis versus inflammation are separated as endpoint\textsuperscript{27} or surrogate endpoints are evaluated\textsuperscript{56}; however, useful clinical data are much less readily available. Hirata et al\textsuperscript{12} noted that patients in their series who received corticosteroids as part of chemotherapy regimens had significantly lower incidences of severe fibrosis compared with those not receiving these agents. As they point out, these data are likely significantly confounded by the fact that patients receiving corticosteroids had conditions requiring lower radiotherapy doses. Surprisingly, despite the prominent display on univariate analysis (Fig 1C), the authors omitted corticosteroid administration as a parameter in their multivariate analysis for the fibrosis endpoint. The application of topical steroids to downregulate collagen synthesis has been suggested to treat RIF in the skin,\textsuperscript{29} and there is anecdotal evidence of its efficacy.\textsuperscript{60} It would seem that properly controlled clinical trials are necessary to establish the role and efficacy of these approaches and particularly whether the goal is prevention or reversal of fibrosis.

The use of anti-inflammatory drugs will likely continue to have a special place as symptomatic treatment in the management of radiotherapy sequelae.\textsuperscript{61} Other investigational approaches include the potential offered by angiotensin-converting enzyme inhibitors\textsuperscript{62} that block the conversion of angiotensin I to angiotensin II. Angiotensin II increases synthesis and decreases degradation of components of the ECM and appears mediated in part by TGF-\(\beta\). Evaluation of Angiotensin-converting enzyme inhibitors has so far been almost exclusively confined to the laboratory but may offer the opportunity for intervention in damage to the lung or kidney.\textsuperscript{26} Again one must be cautious in interpreting results and particularly avoid confusion about whether treatment is intended to prevent/reduce radiotherapy complications or alternatively achieve reversal of the injury. Other groups of drugs (eg, interferons) offer interesting mechanistic possibilities to reverse fibrosis (Table 3), but their use is limited by their associated toxicities.

\textbf{Hyperbaric Oxygen}

\textbf{Indications for hyperbaric oxygen.} The evidence suggests that the strongest benefit for hyperbaric oxygen (HBO) is in the amelioration of radiotherapy necrosis in bone (especially mandibular osteoradionecrosis)\textsuperscript{63-65} and soft tissue.\textsuperscript{66} Some high morbidity situations also benefit in-
cluding laryngeal necrosis in the head and neck and hemorrhagic cystitis, proctitis, and colitis after radiotherapy of the pelvis.

**Potential mechanisms of HBO.** The marked narrowing of the small blood vessels in radiation damaged tissues results in progressive vascular depletion and insufficient oxygenation of tissues. Additional trauma or infection can precipitate necrosis. Induration and fibrosis develop, presumably linked to molecular mechanisms.

HBO has several effects that include increased oxygen diffusibility, collagen synthesis, and neovascularization. Edema may be reduced by the resulting decreased capillary filtration pressure. Recently van den Blink et al showed that high pressure and hyperoxygenation independently influence enhanced cytokine production and cytokine release, respectively. The altered cytokine production is believed to involve the evolutionary mitogen-activated protein kinase proteins that have pivotal roles in transcription factor phosphorylation and in modulation of cytokine production.

HBO, through repetitive exposure, stimulates angiogenesis resulting in tissue restructuring. It is plausible that HBO-induced neovascularization induces oxygenation and healing of damaged soft tissue, bone, or cartilage, but it is less obvious why established fibrosis should resolve.

**What evidence is there for HBO in RIF?**

Strong evidence for a benefit of HBO in established fibrosis is not apparent in the clinical literature, although a reduction in fibrosis is suggested as a companion to the neovascularization and improvement of radiation-induced soft-tissue ulceration.

Patients with breast cancer frequently suffer temporary symptomatology after partial mastectomy and radiotherapy, but the majority experience complete resolution. In rare instances, symptoms may continue for extended periods. In a small nonrandomized prospective study, Carl et al found that patients with persisting symptomatology treated with HBO showed significant improvement in pain, erythema, and swelling compared with a control group (P < .001), and 25% became asymptomatic compared with none of the control patients. Neither fibrosis or telangiectasia were significantly affected by HBO. Despite this, HBO remains an option for patients with persistent symptomatology in this setting, even if overt amelioration of fibrosis seems unlikely.

**HBO in radiation-induced brachial plexopathy.** A particularly devastating sequel to breast and regional lymph node radiotherapy is radiation-induced brachial plexopathy (RIBP). The underlying pathobiology of RIBP implicates vasculitis and sclerotic narrowing of small blood vessels supplying the brachial plexus. Distal peripheral nerve atrophy and demyelination explain the severe motor and sensory disturbances and pain that result. Often, an associated morbidity triad that includes arm lymphedema, impaired shoulder motion, and brachial plexopathy occurs. They serve to compound each other; moreover, they usually share pathogenetic elements such as fibrosis.

RIBP is generally associated with 1 or more undesirable treatment variables, and, fortunately, with appropriate attention to radiotherapy technique, its incidence should now be very rare. The improvement in radiation-induced symptomatology with HBO treatment, as well in radiation-induced neurologic damage (eg, small groups of patients with optic neuropathy, myelopathy, or sacral plexopathy), prompted a recent randomized trial. HBO (30 sessions) over a period of 6 weeks was compared in a blinded fashion with a control group treated in the same chamber with an inert gas mixture in women with moderate neurologic deficits. At the time of reporting, the investigators observed no reliable evidence to support any evidence of retardation of RIBP with HBO, although improvement in warm sensory threshold (appreciation of warm temperature compared with the opposite unaffected control limb) was noted suggesting a nonsignificant therapeutic effect. Improvement in lymphedema, an unanticipated result, was observed in sufficient patients to justify continued investigation of HBO in patients with severe lymphedema, and an ongoing nonrandomized phase II study is currently underway.

**Physiotherapy**

Active physical exercise intuitively appears the most applicable and physiologic approach possible in the recuperation from physical injury. Surprisingly, we can find only a few scientific reports in the literature exploring principles of rehabilitation and maintenance of function and to safe-
guard against adverse sequelae of radiotherapy in cancer patients.

Previously, Bentzen et al. had observed the beneficial effects of a physical exercise program in patients at risk of impaired shoulder movement after postmastectomy radiotherapy. Moreover, they provided statistical quantification of the apparently considerable value of this approach. Thus, a patient less than 60 years old who develops subcutaneous fibrosis can expect to reduce her risk of impaired shoulder movement from 77% to 36% using systematic exercises. Much more recently, Box and colleagues conducted a randomized trial to determine the effect of elective physiotherapy on shoulder movement after surgery for primary, operable breast cancer. Physiotherapy in the early postoperative period was effective in facilitating and maintaining recovery of shoulder movement over the first 2 years after breast cancer surgery. Moreover, a physiotherapy intervention program that included principles for lymphedema risk minimization and early management of this condition when it was identified reduced the development of secondary lymphedema after axillary dissection and altered its progression in comparison to the control group.

The varied nature of treatments that frequently involve surgery and radiotherapy contribute to adverse outcome of cancer treatment. Although little direct evidence exists that physical therapy contributes to reversal or prevention of fibrosis, it does seem that preservation of strength and mobility and overall function and well being can be enhanced. Therefore, such measures should be encouraged. In addition, clinical research undertaken to determine the optimal approaches and timing of these interventions for patients at risk should be emphasized.

**Impedance-Controlled Microcurrent Therapy**

A beneficial effect of electric current for tissue repair has recently been reported by Lennox et al. They accrued 26 patients with established late RIF in the head and neck to a trial of twice daily impedance-controlled microcurrent therapy for 1 week. Objective range-of-motion measurements appropriate to the anatomic sites were performed, including cervical rotation, extension/flexion, and lateral flexion before therapy at the end of each treatment day and monthly for 3 months. In addition, each patient’s subjective complaints were documented before treatment and reevaluated at last follow-up. No additional physical therapy or electrical stimulation took place. The treatment was well tolerated.

At the end of the course of microcurrent therapy, 92% of the 26 patients exhibited improved cervical rotation, 85% had improved cervical extension/flexion, and 81% had improved cervical lateral flexion. Moreover, at a 3-month follow-up visit the vast majority had maintained ranges of motion greater than their pretherapy measurements. Some patients also reported symptom improvement for tongue mobility, facial asymmetry, xerostomia, cervical/facial muscle spasms, trismus, and soft-tissue tenderness.

The exact mechanism underlying this therapy remains poorly understood. Of note, this was an uncontrolled experiment using a sizable (7.6 cm diameter and 7.6 cm long) metal cylindrical roller that weighed approximately 6 lbs (A Lennox, verbal communication, December 2002) as a movable electrode that was repeatedly rolled manually across the normal and abnormal tissue by a therapist. Electric current transmission took place between the movable electrode and a fixed conducting plate electrode located close to the affected tissues. In the experiment, no attempt to control with sham treatment was used, although a control population might enhance the interpretation of results. Plausible mechanisms could include placebo effects or pain relief from physical massage, including muscle and soft-tissue mobilization. Reduction of edema or even tissue healing might potentially arise from such maneuvers. The authors have suggested mechanisms that include an influence on migration of extracellular calcium ions to penetrate the cell membrane. Higher levels of intracellular calcium encourage increased synthesis of adenosine triphosphate, and increased protein synthesis may encourage cellular repair and replication. Microvoltage may affect the cascade of reactions involved in the responses described earlier that lead to inflammation and potential fibrogenesis.

Additional studies are needed to validate these encouraging, important, and preliminary results of impedance-controlled microcurrent therapy and to optimize the treatment protocol, particularly with respect to treatment schedules and
combining microcurrent therapy with physical and/or drug therapy.

Conclusions
RIF is a common, complex, and potentially debilitating problem for survivors of cancer treatment. All oncologists should know about the risk factors that predispose to the development of RIF and the principles of management. Contemporary understanding of principles of molecular biology brings a whole new understanding that may permit new treatments to be developed for this condition that threatens to be seen with even greater frequency in the future. Ironically, this results from improvements in cancer treatments that achieve higher rates of disease eradication through more intensive cancer therapies. Perhaps the greatest optimism comes from the observations that established RIF appears reversible in some cases. Effort should be expended to have patients who suffer from these problems referred to centers with experience in their management and where the capability may exist to evaluate the role and mechanisms of new treatment approaches.

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References


Late Radiation-Related Fibrosis