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.

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- or

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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 coexistent 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, and the connective tissues.[3-21] Factors associated with a greater risk of RIF include combining other treatment modalities with radiotherapy (ie, surgery and/or chemotherapy), large-volume radiotherapy plans, high total radiotherapy dose, unusually high dose per fraction regimens, coincident infection or operative complications (eg, seroma, wound drainage, and extensive hematoma), and inhomogeneity of dose delivery including poor match zones or field abutments.

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.[22] The risk of telangiectasia appears more strongly linked to the occurrence of moist desquamation, with loss of the endothelial cell's epidermal protection and potential exposure to infectious/inflammatory, chemical, or mechanical stresses.[22,23] Some cases of telangiectasia may represent a consequential late reaction after a severe early reaction.[14] Random processes superimposed on the subclinical residual injury may also trigger the onset of clinically apparent late tissue effects.[24]

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[5] 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.[5] 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[12] specified the skin-absorbed dose at a depth of 4.1 mm (d4.1-mm_{depth}) in the field center according to the recommendations of Bentzen et al.[5] They found that the d4.1-mm_{depth} 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_{depth}, fractionation, and systemic agents are also evident (Fig 1).[12]

Latency and Assessment

Data from Jung et al[24] indicate an apparent lifelong risk of developing late complications, without a plateau, suggesting that different kinetic

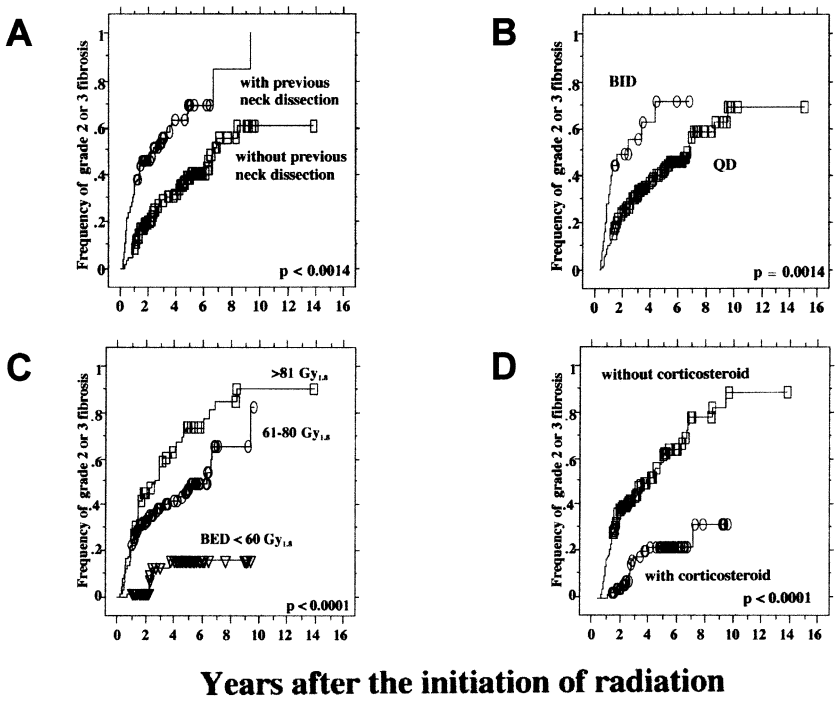

Figure 1. Cumulative incidence curves for the risk of grade 2 or 3 subcutaneous fibrosis. Open circles and open rectangles indicate censored data, (A) with and without previous neck dissection and (B) according to twice daily (BID) or once-a-day (QD) fractionation. Note that the mean prescribed dose in the BID group was significantly higher than in the QD group ($P < .0001$) indicating relative sparing from fractionation, (C) according to a biologically equivalent dose (BED) of d4.1-mm_{depth} with an assumed alpha/beta ratio of 1.8, (D) with and without corticosteroid administration. The authors indicated a source of bias in these data (that patients who received corticosteroids received lower doses of radiotherapy), although the parameter was not included in the multivariate analysis for the risk of fibrosis (see text). A borderline effect was present for the influence of concurrent chemotherapy although the risk was only significant for grade 3 toxicity alone ($P = .0313$, data not shown). (Reproduced with permission.[12])

mechanisms are in play.[24] 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.[4] To monitor and understand these issues, prospectively collected data with consistent assessment methods and understanding of treatment parameters are needed.[5] 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.[25]

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 once the radiotherapy was administered, events were pre-

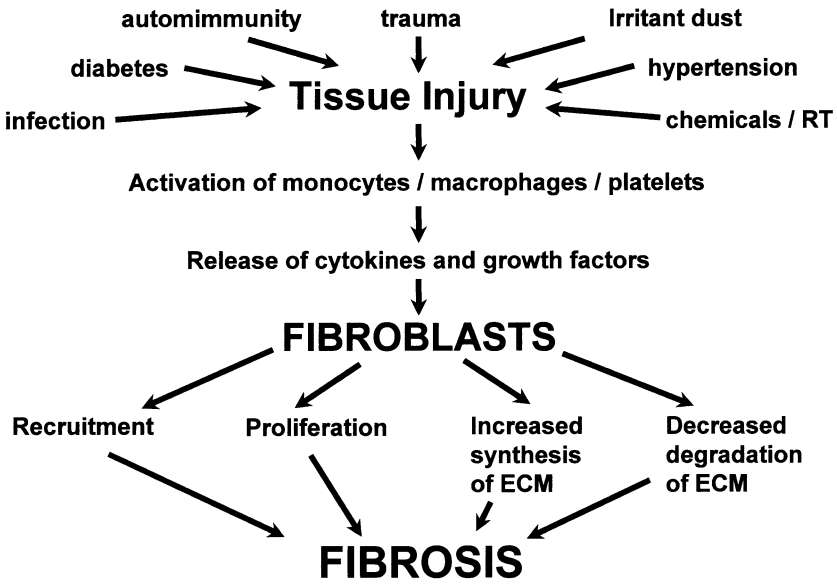

Figure 2. Generalized sequence of events leading from tissue injury to fibrosis. Like other sources of tissue injury, radiotherapy (RT) features prominently in this generic model. (Reproduced with permission.[28])

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-

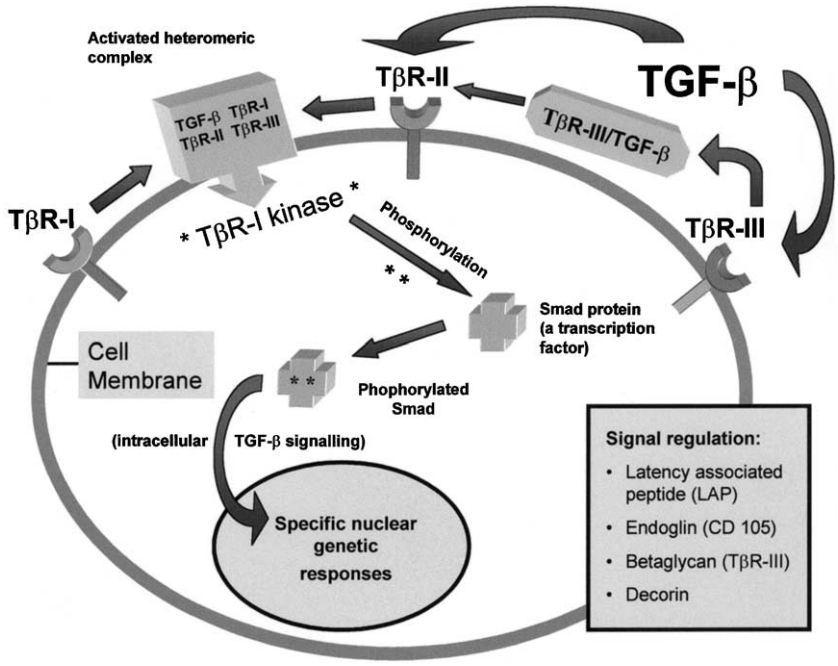

Figure 3. Simplified model of signal transduction interactions of transforming growth factor-β (TGF-β) with its cell surface receptors, termed type III (TβR-III), the most abundant, and types I (TβR-I), and II (TβR-II), that both exhibit signaling activity. TGF-β initially binds to the type III receptor 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 **).

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 β 2.[34] 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.[35] 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.[35] After radiotherapy, Li et al[36] 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.[36]

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;

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

Proposed Mechanism	*Resulting Process*
Repeated tissue exudates	Unresolved fibrin deposition due to deficiency in tissue plasminogen activator
EC injury leads to plasma exudates	Stimulation of collagen synthesis
Detachment of ECs leads to FGF activation and loss of mitogenic control of SMCs	Overproduction of collagen
Radiation-induced EC expression of TNF-alpha and PDGF	Stimulates SMC proliferation and production of collagen
Downregulation of EC NOS activity	Unopposed SMC proliferation
Downregulation of EC thrombomodulin	SMC activation enabled by thrombin with assistance of TGF-β
Prolonged epithelial barrier breakdown	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
Permanent RT induced fibroblast phenotypic alterations	Overproduction of matrix
Alteration of the normal fibroblast population profile	Accumulation of post-mitotic fibrocytes to produce matrix elements
Proliferation of alveolar macrophages and type II pneumocytes (if lung irradiated)	Expression of TGF-β leads to pulmonary fibrosis

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.
Modified with permission.[31]

however, their reassociation inhibits activity offering the prospect of a therapeutic target using recombinant technologies.[28] Other fascinating possibilities include the ability of neutralizing antibodies to TGF-β[26] 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.[37]

Multifactorial Biological Response to Radiation

The evolution of the radiotherapeutic injury, intriguingly termed a complex "wound" by Denham and Hauer-Jensen,[31] 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 (eg, 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).[31] 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.[26]

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

Table 2. Possibilities to avert delayed radiation injury based exclusively on cell killing by 'target cell theory', where damage is 'sealed' after the event

Identification of radiosensitive individuals for avoidance of radiotherapy
Restriction of radiation target volumes through dose-sculpting techniques such as conformal radiotherapy or intensity modulation
Altered fractionation schedules designed to minimize normal tissue injury
Replenishment or enhancement of stem cell numbers through growth factor administration

Data from reference Denham and Hauer-Jensen.[31]

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).[38] 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 3. Selected Studies of Molecules Used in Vivo in Therapeutic Strategies Against Established Fibrotic Disorders of Various Etiologies

Molecule Availability	*Therapeutic Use*	*Beneficial Effect*	*Inhibition of Matrix Synthesis*	*Reduction of Inflammation*	*Growth Factor Antagonism*	*Reference*
Colchicine, available	Experimental	Fibrosis	+			Dubrawsky et al[77]
Interferon-γ, not available	Experimental	Fibrosis	+	+		Grossman et al[78] Cales[79]
	Clinical	Fibrosis				Peter et al[80]
Interferon-α, available	Experimental	Fibrosis				Moreno et al[81]
	Clinical	Hypertrophic scars		+	TGF-β	Tredget et al[82]
	Clinical	Fibrosis				Dufour et al[83]
Glucocorticoids, available	Experimental	Fibrosis	+	+		Cutroneo et al[84]
Essential fatty acids, not available	Experimental	Fibrosis				Hopewell et al[85]
SOD, not available	Clinical	Fibrosis	+	+		Delanian et al[38]
	Clinical	Fibrosis				Perdereau et al[40]
	Experimental	Fibrosis	+	+		Lefaix et al[39]
Pentoxifylline, available	Clinical	Pain		+		Werner-Wasik et al[43]
	Clinical	Pain		+		Futran et al[45]
	Experimental	No effects on fibrosis	−			Lefaix et al[51]
Vitamin E, available	Clinical	Fibrosis				Baillet[86]
Pentoxifylline with vitamin E, available	Clinical	Fibrosis	+	+		Delanian et al[52]
	Experimental	Fibrosis	+	+	TGF-β	Lefaix et al[51]
Direct TNF-a antagonists	Experimental	Fibrosis	+		TNFR-β	Piguet et al[87]
Antibodies to integrins	Experimental	Fibrosis	+	+		Piguet et al[88]

Abbreviations: TGF, transforming growth factor; SOD, superoxide dismutase; TNF, tumor necrosis factor; TNFR-β; TNF receptor beta.
Reproduced with permission.[33]

Table 4. Pentoxifylline Alone in the Treatment of Late Radiation Injury

Author	*Population*	*Intervention*	*Assessment of Response*	*Results*
Futran[45]	N = 26 Patients with soft tissue necrosis (STN) (n = 15), fibrosis (n = 5) and mucosal pain (n = 6)	PTX alone for at least 3 months	STN-reduction of tumor size (0-100%) Fibrosis-reduction in tissue induration and improvement in mobility (0-100%) Mucosal pain-patient assessment of pain reduction (0-100%)	13/26 patients had complete reversal of injury 8/26 patients had an improvement of injury 5/26 patients showed no improvement
Werner-Wasik[43]	N = 1 (anecdotal case report of radiation induced fibrosis)	400 mg PTX tid for 6 weeks	Subjective report of pain and tenderness, clinical examination of fibrotic area	Improvement in symptoms and clinical examination
Cornelison et al[44]	N = 10 (8 evaluable), post radiation fibrosis (neck, chest wall, pelvis, extremities	PTX 400 mg po tid for 8 weeks	Range of motion, Motor strength, Edema, Pain, Fatigue, Tissue compliance	8/8 evaluable patients had improvement in at least 1 evaluation area (only 3/7 had reduced pain)
Dion et al[46]	N = 12 (with 15 sites of soft tissue necrosis), all sites of necrosis were Grade 4-RTOG/EORTC, and all had ulceration	400 mg PTX tid (with escalation to 400 mg q.i.d. if no healing had occurred at 3 months	RTOG/EORTC system Pain assessment Two-dimensional measurement of ulcerations Photographs	13/15 ulcerations were completely healed, 1/15 partially healed, 1/15 unhealed. Mean time to heal = 9.0 wks (range 4-18). All patients needing narcotic analgesics prior to PTX had complete relief of pain.
Chua et al[48]	N = 20 (16 evaluable) NPC patients with severe (dental gap < or = 25 mm) trismus from radiotherapy	400 mg PTX bid to tid for 8 weeks	Dental gap measures (from left upper to lower incisor tooth, before and after PTX course)	10/16 had measured increase in dental gap ranging from 2 to 25 mm. 6 had > 5mm increment. Mean increase from 12.5 to 16.5 mm (P = .023)

Abbreviations: PTX, pentoxifylline; NPC, nasopharyngeal carcinoma; bid, twice daily; tid, 3 times a day; po, by mouth.

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[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.[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.[40]

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

Author	*Population*	*Intervention*	*Assessment of Response*	*Results*
Lefaix[51]	Animal model (N = 15)	3 arms: 1) PTX + α-tocopherol 2) PTX alone 3) Control	Measurement of projected cutaneous surface area of fibrotic block and ultrasound assessment of depth	PTX + α-tocopherol superior, PTX alone and control groups equivalent
Delanian[89]	Case report, 67-year-old woman with fibrosis	PTX 800 mg/d Vitamin E 1000 U/d	Clinical assessment of response SOMA/LENT assessment	Complete clinical response at 18 months
Delanian[52]	Patients with radiation-induced fibrosis N = 40	PTX 800 mg/d Vitamin E 1000 U/d	Measurement of projected cutaneous surface area of fibrotic block SOMA/LENT assessment	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

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

General Approach	*Comments*	*Other Information*
Pharmacological	Variable efficacies Some clinical studies Some experimental studies Some agents unavailable (e.g. SOD) Randomized trials needed	See tables 3-5
Hyperbaric oxygen	Mechanisms poorly understood Signalling pathways possible Reduced edema, pain, erythema No significant effect on fibrosis and telangiectasia Brachial plexopathy RCT: no substantive amelioration improved 'warmth' sensation? improved lymphedema?	See text discussion See reference[71] See reference[72] See reference[72] See reference[73]
Physiotherapy	Maintenance of exercise beneficial Avoids atrophy and disuse Benefit for lymphedema (RCT) Benefit for function (RCT) Need for additional trials	See reference[3] See reference[75] See reference[74]
Microcurrent therapy	Pilot data available: improved function improved pain sustained benefits (>3 month) mechanisms undetermined confimatory studies needed	See reference[76]

Abbreviations: SOD, superoxide dismutase; RCT, randomized controlled trial.

expression resulting in an antifibrotic action in pig and human myofibroblasts.[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[43] and in a small descriptive trial[44] (Table 4). In contrast, other studies of PTX alone have shown its value in soft-tissue necrosis predominantly rather than radiation fibrosis.[45,46] Also, the regression of subcutaneous scar seen in a pig model with SOD could not be reproduced with PTX.[33] Other clinical reports have indicated benefit in radiation mastitis,[47] and of especial interest is the report from Chua et al[48] 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.[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.[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 phopholipids 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[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-β1 was shown in residual fibrotic tissue.[51] These authors also indicate that alpha-tocopherol alone does not appear to have the same efficacy for RIF as the combination with PTX.[51,52]

In their clinical article, Delanian et al[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.[52] Once more, we would add the cautionary need to attempt to confirm these hopeful findings and preferably with a controlled trial.

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-β 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-β and the possibility that malignancy may arise.[53] Thus, in cancer cells, mutations in the pathway may allow uncontrolled cell proliferation arising from resistance to TGF-β growth inhibition.[32] 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,[28] but a detailed discussion of these issues is beyond the scope of this article.

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,[26,54-56] although results may not be confirmed if fibrosis versus inflammation are separated as endpoint[57] or surrogate endpoints are evaluated[58]; however, useful clinical data are much less readily available. Hirota et al[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,[59] and there is anecdotal evidence of its efficacy.[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.[61] Other investigational approaches include the potential offered by angiotensin-converting enzyme inhibitors[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-β. 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.[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.

Hyperbaric Oxygen

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)[63-65] and soft tissue.[66] Some high morbidity situations also benefit in-

cluding laryngeal necrosis in the head and neck[67] and hemorrhagic cystitis, proctitis, and colitis after radiotherapy of the pelvis.[68,69]

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 neoangiogenesis. Edema may be reduced by the resulting decreased capillary filtration pressure.[70] Recently van den Blink et al[71] 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.[71]

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.[66]

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[72] 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.[72]

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.[73] 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.[10]

RIBP is generally associated with 1 or more undesirable treatment variables,[10] 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.[73] 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.[73]

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[3] 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[74] 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.[74] 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.[75]

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.[76] 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.[76]

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

1. Dische S, Warburton MF, Jones D, et al: The recording of morbidity related to radiotherapy. Radiother Oncol 16: 103-108, 1989
2. Overgaard J, Bartelink H: About tolerance and quality. An important notice to all radiation oncologists. Radiother Oncol 35:1-3, 1995
3. Bentzen SM, Overgaard M, Thames HD: Fractionation sensitivity of a functional endpoint: Impaired shoulder movement after post-mastectomy radiotherapy. Int J Radiat Oncol Biol Phys 17:531-537, 1989
4. Bentzen SM, Turesson I, Thames HD: Fractionation sensitivity and latency of telangiectasia after postmastectomy radiotherapy: A graded-response analysis. Radiother Oncol 18:95-106, 1990
5. Bentzen SM, Christensen JJ, Overgaard J, et al: Some methodological problems in estimating radiobiological parameters from clinical data. Alpha/beta ratios and electron RBE for cutaneous reactions in patients treated with postmastectomy radiotherapy. Acta Oncol 27:105-116, 1988
6. Johansson S, Svensson H, Denekamp J: Dose response and latency for radiation-induced fibrosis, edema, and neuropathy in breast cancer patients. Int J Radiat Oncol Biol Phys 52:1207-1219, 2002
7. Borger JH, Kemperman H, Smitt HS, et al: Dose and volume effects on fibrosis after breast conservation therapy. Int J Radiat Oncol Biol Phys 30:1073-1081, 1994
8. Krishnamurthy R, Whitman GJ, Stelling CB, et al: Mammographic findings after breast conservation therapy. Radiographics 19:S53-62, 1999
9. Olivotto IA, Weir LM, Kim-Sing C, et al: Late cosmetic results of short fractionation for breast conservation. Radiother Oncol 41:7-13, 1996
10. Bentzen SM, Dische S: Morbidity related to axillary irradiation in the treatment of breast cancer. Acta Oncol 39:337-347, 2000
11. Trotti A: Toxicity in head and neck cancer: A review of trends and issues. Int J Radiat Oncol Biol Phys 47:1-12, 2000
12. Hirota S, Tsujino K, Oshitani T, et al: Subcutaneous fibrosis after whole neck irradiation. Int J Radiat Oncol Biol Phys 52:937-943, 2002
13. Wratten CR, Poulsen MG, Williamson S, et al: Effect of surgery on normal tissue toxicity in patients treated with accelerated radiotherapy. Acta Oncol 41:56-62, 2002
14. Peters LJ, Ang KK, Thames HD Jr: Accelerated fractionation in the radiation treatment of head and neck cancer. A critical comparison of different strategies. Acta Oncol 27:185-194, 1988
15. van Kampen M, Eble MJ, Lehnert T, et al: Correlation of intraoperatively irradiated volume and fibrosis in patients with soft-tissue sarcoma of the extremities. Int J Radiat Oncol Biol Phys 51:94-99, 2001
16. Robinson MH, Spruce L, Eeles R, et al: Limb function following conservation treatment of adult soft tissue sarcoma. Eur J Cancer 27:1567-1574, 1991
17. Stinson SF, DeLaney TF, Greenberg J, et al: Acute and long-term effects on limb function of combined modality limb sparing therapy for extremity soft tissue sarcoma. Int J Radiat Oncol Biol Phys 21:1493-1499, 1991
18. Karasek K, Constine LS, Rosier R: Sarcoma therapy: Functional outcome and relationship to treatment parameters. Int J Radiat Oncol Biol Phys 24:651-656, 1992
19. O'Sullivan B, Davis AM, Turcotte R, et al: Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 359:2235-2241, 2002
20. O'Sullivan B, Davis AA randomized phase III trial of pre-operative compared to post-operative radiotherapy in extremity soft tissue sarcoma. Proc 43rd Annual Meeting, American Society of Therapeutic Radiology and Oncology. Int J Radiation Oncology Biol Phys 51:151, 2001 (suppl 3)
21. Davis AM, O'Sullivan B, Bell RS, et al: Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. J Clin Oncol 20:4472-4477, 2002
22. Bentzen SM, Overgaard M: Relationship between early and late normal-tissue injury after postmastectomy radiotherapy. Radiother Oncol 20:159-165, 1991

23. Turesson I, Thames HD: Repair capacity and kinetics of human skin during fractionated radiotherapy: Erythema, desquamation, and telangiectasia after 3 and 5 year's follow-up. Radiother Oncol 15:169-188, 1989
24. Jung H, Beck-Bornholdt HP, Svoboda V, et al: Quantification of late complications after radiation therapy. Radiother Oncol 61:233-246, 2001
25. Bentzen SM, Vaeth M, Pedersen DE, et al: Why actuarial estimates should be used in reporting late normal-tissue effects of cancer treatment. . .now! Int J Radiat Oncol Biol Phys 32:1531-1534, 1995
26. Hill RP, Rodemann HP, Hendry JH, et al: Normal tissue radiobiology: From the laboratory to the clinic. Int J Radiat Oncol Biol Phys 49:353-365, 2001
27. Border WA, Noble NA: Transforming growth factor beta in tissue fibrosis. N Engl J Med 331:1286-1292, 1994
28. Franklin TJ: Therapeutic approaches to organ fibrosis. Int J Biochem Cell Biol 29:79-89, 1997
29. Leask A, Abraham DJ, Finlay DR, et al: Dysregulation of transforming growth factor beta signaling in scleroderma: Overexpression of endoglin in cutaneous scleroderma fibroblasts. Arthritis Rheum 46:1857-1865, 2002
30. Ruifrok AC, McBride WH: Growth factors: Biological and clinical aspects. Int J Radiat Oncol Biol Phys 43:877-881, 1999
31. Denham JW, Hauer-Jensen M: The radiotherapeutic injury—A complex 'wound'. Radiother Oncol 63:129-145, 2002
32. Blobe GC, Schiemann WP, Lodish HF: Role of transforming growth factor beta in human disease. N Engl J Med 342:1350-1358, 2000
33. Martin M, Lefaix J, Delanian S: TGF-beta1 and radiation fibrosis: A master switch and a specific therapeutic target? Int J Radiat Oncol Biol Phys 47:277-290, 2000
34. Barbara NP, Wrana JL, Letarte M: Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-beta superfamily. J Biol Chem 274:584-594, 1999
35. Wong SH, Hamel L, Chevalier S, et al: Endoglin expression on human microvascular endothelial cells association with betaglycan and formation of higher order complexes with TGF-beta signalling receptors. Eur J Biochem 267: 5550-5560, 2000
36. Li C, Wilson PB, Levine E, et al: TGF-beta1 levels in pre-treatment plasma identify breast cancer patients at risk of developing post-radiotherapy fibrosis. Int J Cancer 84:155-159, 1999
37. Isaka Y, Brees DK, Ikegaya K, et al: Gene therapy by skeletal muscle expression of decorin prevents fibrotic disease in rat kidney. Nat Med 2:418-423, 1996
38. Delanian S, Baillet F, Huart J, et al: Successful treatment of radiation-induced fibrosis using liposomal Cu/Zn superoxide dismutase: Clinical trial. Radiother Oncol 32: 12-20, 1994
39. Lefaix JL, Delanian S, Leplat JJ, et al: Successful treatment of radiation-induced fibrosis using Cu/Zn-SOD and Mn-SOD: An experimental study. Int J Radiat Oncol Biol Phys 35:305-312, 1996
40. Perdereau B, Campana F, Vilcoq JR, et al: Superoxide dismutase (Cu/Zn) in cutaneous application in the treatment of radiation-induced fibrosis. Bull Cancer 81:659-669, 1994
41. Vozenin-Brotons MC, Sivan V, Gault N, et al: Antifibrotic action of Cu/Zn SOD is mediated by TGF-beta1 repression and phenotypic reversion of myofibroblasts. Free Radic Biol Med 30:30-42, 2001
42. Delanian S, Martin M, Bravard A, et al: Cu/Zn superoxide dismutase modulates phenotypic changes in cultured fibroblasts from human skin with chronic radiotherapy damage. Radiother Oncol 58:325-331, 2001
43. Werner-Wasik M, Madoc-Jones H: Trental (pentoxifylline) relieves pain from postradiation fibrosis. Int J Radiat Oncol Biol Phys 25:757-758, 1993
44. Cornelison TL, Okunieff P, Naydich GB: Trial of pentoxifylline in patients with functional disability caused by radiation-induced advanced regional fibrosis: Preliminary report. Proc Am Assoc Cancer Res Oncol 37:610, 1996
45. Futran ND, Trotti A, Gwede C: Pentoxifylline in the treatment of radiation-related soft tissue injury: Preliminary observations. Laryngoscope 107:391-395, 1997
46. Dion MW, Hussey DH, Doornbos JF, et al: Preliminary results of a pilot study of pentoxifylline in the treatment of late radiation soft tissue necrosis. Int J Radiat Oncol Biol Phys 19:401-407, 1990
47. Steeves RA, Robins HI: Pentoxifylline treatment of radiation mastitis. Int J Radiat Oncol Biol Phys 42:1177, 1998
48. Chua DT, Lo C, Yuen J, et al: A pilot study of pentoxifylline in the treatment of radiation-induced trismus. Am J Clin Oncol 24:366-369, 2001
49. Poli G, Parola M: Oxidative damage and fibrogenesis. Free Radic Biol Med 22:287-305, 1997
50. Simonini G, Pignone A, Generini S, et al: Emerging potentials for an antioxidant therapy as a new approach to the treatment of systemic sclerosis. Toxicology 155:1-15, 2000
51. Lefaix JL, Delanian S, Vozenin MC, et al: Striking regression of subcutaneous fibrosis induced by high doses of gamma rays using a combination of pentoxifylline and alpha-tocopherol: An experimental study. Int J Radiat Oncol Biol Phys 43:839-847, 1999
52. Delanian S, Balla-Mekias S, Lefaix JL: Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. J Clin Oncol 17: 3283-3290, 1999
53. Brattain MG, Markowitz SD, Willson JK: The type II transforming growth factor-beta receptor as a tumor-suppressor gene. Curr Opin Oncol 8:49-53, 1996
54. Evans ML, Graham MM, Mahler PA, et al: Use of steroids to suppress vascular response to radiation. Int J Radiat Oncol Biol Phys 13:563-567, 1987
55. Geraci JP, Mariano MS, Jackson KL: Amelioration of radiation nephropathy in rats by dexamethasone treatment after irradiation. Radiat Res 134:86-93, 1993
56. Kure F: [The radioprotective effects of methylprednisolone and Sho-Saikoto on mouse lung]. Nippon Igaku Hoshasen Gakkai Zasshi 52:96-103, 1992
57. Ward HE, Kemsley L, Davies L, et al: The effect of steroids on radiation-induced lung disease in the rat. Radiat Res 136:22-28, 1993

58. Peterson LM, Evans ML, Graham MM, et al: Vascular response to radiation injury in the rat lung. Radiat Res 129:139-148, 1992
59. Riekki R, Jukkola A, Sassi ML, et al: Modulation of skin collagen metabolism by irradiation: Collagen synthesis is increased in irradiated human skin. Br J Dermatol 142: 874-880, 2000
60. James WD, Odom RB: Late subcutaneous fibrosis following megavoltage radiotherapy. J Am Acad Dermatol 3:616-618, 1980
61. Michalowski AS: On radiation damage to normal tissues and its treatment. II. Anti-inflammatory drugs. Acta Oncol 33:139-157, 1994
62. Molteni A, Moulder JE, Cohen EP, et al: Prevention of radiation-induced nephropathy and fibrosis in a model of bone marrow transplant by an angiotensin II receptor blocker. Exp Biol Med (Maywood) 226:1016-1023, 2001
63. Marx RE: A new concept in the treatment of osteoradionecrosis. J Oral Maxillofac Surg 41:351-357, 1983
64. Marx RE, Johnson RP, Kline SN: Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin. J Am Dent Assoc 111:49-54, 1985
65. David LA, Sandor GK, Evans AW, et al: Hyperbaric oxygen therapy and mandibular osteoradionecrosis: A retrospective study and analysis of treatment outcomes. J Can Dent Assoc 67:384, 2001
66. Feldmeier JJ, Heimbach RD, Davolt DA, et al: Hyperbaric oxygen in the treatment of delayed radiation injuries of the extremities. Undersea Hyperb Med 27:15-19, 2000
67. Feldmeier JJ, Heimbach RD, Davolt DA, et al: Hyperbaric oxygen as an adjunctive treatment for severe laryngeal necrosis: A report of nine consecutive cases. Undersea Hyperb Med 20:329-335, 1993
68. Feldmeier JJ, Heimbach RD, Davolt DA, et al: Hyperbaric oxygen an adjunctive treatment for delayed radiation injuries of the abdomen and pelvis. Undersea Hyperb Med 23:205-213, 1996
69. Mayer R, Klemen H, Quehenberger F, et al: Hyperbaric oxygen—An effective tool to treat radiation morbidity in prostate cancer. Radiother Oncol 61:151-156, 2001
70. Plafki C, Carl UM, Glag M, et al: The treatment of late radiation effects with hyperbaric oxygenation (HBO). Strahlenther Onkol 174:66-68, 1998 (suppl 3)
71. van den Blink B, van der Kleij AJ, Versteeg HH, et al: Immunomodulatory effect of oxygen and pressure. Comp Biochem Physiol A Mol Integr Physiol 132:193-197, 2002
72. Carl UM, Feldmeier JJ, Schmitt G, et al: Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery. Int J Radiat Oncol Biol Phys 49:1029-1031, 2001
73. Pritchard J, Anand P, Broome J, et al: Double-blind randomized phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. Radiother Oncol 58:279-286, 2001
74. Box RC, Reul-Hirche HM, Bullock-Saxton JE, et al: Shoulder movement after breast cancer surgery: Results of a randomised controlled study of postoperative physiotherapy. Breast Cancer Res Treat 75:35-50, 2002
75. Box RC, Reul-Hirche HM, Bullock-Saxton JE, et al: Physiotherapy after breast cancer surgery: Results of a randomised controlled study to minimise lymphoedema. Breast Cancer Res Treat 75:51-64, 2002
76. Lennox AJ, Shafer JP, Hatcher M, et al: Pilot study of impedance-controlled microcurrent therapy for managing radiation-induced fibrosis in head-and-neck cancer patients. Int J Radiat Oncol Biol Phys 54:23-34, 2002
77. Dubrawsky C, Dubravsky NB, Withers HR: The effect of colchicine on the accumulation of hydroxyproline and on lung compliance after irradiation. Radiat Res 73:111-120, 1978
78. Grossman HJ, White D, Grossman VL, et al: Effect of interferon gamma on intrahepatic haemodynamics of the cirrhotic rat liver. J Gastroenterol Hepatol 13:1058-1060, 1998
79. Cales P: Apoptosis and liver fibrosis: Antifibrotic strategies. Biomed Pharmacother 52:259-263, 1998
80. Peter RU, Gottlober P, Nadeshina N, et al: Interferon gamma in survivors of the Chernobyl power plant accident: New therapeutic option for radiation-induced fibrosis. Int J Radiat Oncol Biol Phys 45:147-152, 1999
81. Moreno MG, Muriel P: Remission of liver fibrosis by interferon-alpha 2b. Biochem Pharmacol 50:515-520, 1995
82. Tredget EE, Shankowsky HA, Pannu R, et al: Transforming growth factor-beta in thermally injured patients with hypertrophic scars: Effects of interferon alpha-2b. Plast Reconstr Surg 102:1317-1328, 1998
83. Dufour JF, DeLellis R, Kaplan MM: Regression of hepatic fibrosis in hepatitis C with long-term interferon treatment. Dig Dis Sci 43:2573-2576, 1998
84. Cutroneo KR, Rokowski R, Counts DF: Glucocorticoids and collagen synthesis: comparison of in vivo and cell culture studies. Coll Relat Res 1:557-568, 1981
85. Hopewell JW, van den Aardweg GJ, Morris GM, et al: Amelioration of both early and late radiation-induced damage to pig skin by essential fatty acids. Int J Radiat Oncol Biol Phys 30:1119-1125, 1994
86. Baillet F: Alpha-tocopherol treatment of radiation fibrosis post-brachytherapy for breast cancer. Radiother Oncol 97:S3, 1997 (suppl 43)
87. Piguet PF, Rosen H, Vesin C, et al: Effective treatment of the pulmonary fibrosis elicited in mice by bleomycin or silica with anti-CD-11 antibodies. Am Rev Respir Dis 147:435-441, 1993
88. Piguet PF, Vesin C: Treatment by human recombinant soluble TNF receptor of pulmonary fibrosis induced by bleomycin or silica in mice. Eur Respir J 7:515-518, 1994
89. Delanian S: Striking regression of radiation-induced fibrosis by a combination of pentoxifylline and tocopherol. Br J Radiol 71:892-894, 1998