Radiation-Induced Tissue Damage: Clinical Consequences and Current Treatment Options

Hillary Nepon, MD[1] Tyler Safran, MD[2] Edward M. Reece, MD, MBA, FACS[3] Amanda M. Murphy, MD, MSc[2] Joshua Vorstenbosch, MD, PhD, FRCSC[2] Peter G. Davison, MD, SM Epi, FRCSC[2]

[1] Division of Experimental Surgery, McGill University, Montreal, Quebec, Canada
[2] Division of Plastic Surgery, McGill University, Montreal, Quebec, Canada
[3] Michael E. DeBakey Department of Surgery, Division of Plastic Surgery, Baylor College of Medicine, Houston, Texas

Address for correspondence Peter G. Davison, MD, SM Epi, Division of Plastic Surgery, McGill University, Royal Victoria Hospital, 1001 Boul Decarie, Room D02.7007, Montreal, Quebec, H4A 3J1, Canada (e-mail: peter.davison@mcgill.ca).

Semin Plast Surg 2021;35:181–188.

Abstract

Radiation therapy is a valuable tool in the treatment of numerous malignancies but, in certain cases, can also causes significant acute and chronic damage to noncancerous neighboring tissues. This review focuses on the pathophysiology of radiation-induced damage and the clinical implications it has for plastic surgeons across breast reconstruction, osteoradionecrosis, radiation-induced skin cancers, and wound healing. The current understanding of treatment modalities presented here include hyperbaric oxygen therapy, autologous fat grafting and stem cells, and pharmaceutical agents.

Keywords
- radiation therapy
- fibrosis
- radiation damage

Nearly 20 million new cases of cancer are diagnosed each year.[1] Radiation therapy (RT) is one of the most significant evidence-based advancements of modern cancer care, decreasing local tumor recurrence and increasing overall survival rates for a variety of malignancies. It is estimated that around 50% of cancer patients receive RT.[1,2]

Despite the efficacy of RT from an oncological perspective, RT also comes with negative consequences. A major area of concern is the damaging effect of RT on normal neighboring tissues. RT causes acute and chronic tissue damage in noncancerous tissues with subsequent long-term clinical consequences that range from mild to life-threatening. As cancer survival rates continue to improve, increasing numbers of patients will live with the long-term effects of RT.[3] Understanding the pathophysiology of radiation-induced tissue damage, the long-term clinical consequences and current treatments are essential. The aim of this paper is to review the literature on radiation-induced tissue damage and its clinical implications.

Radiation

RT uses ionizing radiation energy which detaches electrons from other atoms to destroy cancer cells. RT can be administered in different ways. External beam radiation (EBT) delivers radiation from outside the patient's body and will be the main focus of the current review.[4,5] Once RT is administered, powerful energy is deposited within cells, damaging DNA, and ultimately causing cancer cell death.[5] DNA damage can occur directly or indirectly through generation of reactive oxygen species (ROS). Direct and indirect DNA damages cause single- and double-strand breaks in DNA, the latter accounting for the majority of cell death.[5]

The goal is to maximize the radiation dose to cancer cells and minimize the dose to surrounding normal healthy cells. Compared with normal cells, cancer cells are more sensitive to radiation and cannot repair as efficiently, allowing for specificity in cancer cell targeting.[6] Still, radiation inevitably damages healthy cells.

Pathophysiology of Tissue Injury

Radiation evokes a dynamic and complex series of events characterized by (1) ROS production, (2) vascular injury and chronic hypoxia, (3) chronic inflammatory response, and 4) myofibroblast activation and fibrosis.[7]

Reactive Oxygen Species Production

ROS production is attributed with mediating a major component of the cell and tissue damage induced by radiation.[8–10] ROS are highly unstable and reactive

Issue Theme Healing, Inflammation, and Fibrosis; Guest Editor: Joshua Vorstenbosch, MD, PhD, FRCSC

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0041-1731464.
ISSN 1535-2188.

molecules that are formed when radiation interacts with intracellular water molecules. ROS react with cellular components including lipids, proteins and DNA, and cause severe intracellular damage.[11] A key feature of ROS-induced damage is that, it amplifies the damage from radiation and can continue for a long period of time.[8]

Vascular Injury and Hypoxia

Vascular injury is intimately involved in the pathogenesis of radiation injury on both micro- and macroscopic levels.[9] Macroscopically, radiation induces coagulation pathways within vessels triggering vascular occlusion, tissue ischemia, and ultimately chronic hypoxia.[10] A low oxygen state perpetuates the production of ROS, leading to further cellular damage. Microscopically, the endothelial barrier is disrupted, increasing vascular permeability and allowing for release of proinflammatory chemokines and cytokines and immune cell migration.[7]

Inflammation

Damaged cells release endogenous danger signals known as damage-associated molecular patterns (DAMPs) which attract innate and adaptive immune cells.[7] Neutrophils arrive in the acute phase of inflammation and secrete proinflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, further triggering ROS. Lymphocytes and monocytes arrive during the chronic inflammatory phase and interact to promote monocyte differentiation into two subtypes of macrophages. M1 macrophages secrete further inflammatory factors, while M2 macrophages attract fibroblasts, stimulate fibroblast differentiation into myofibroblasts, and release transforming growth factor β (TGF-β), a potent profibrotic factor.[11]

Myofibroblasts and Fibrosis

Fibrosis is a dose-limiting complication of radiation, driven by inflammation and largely mediated by TGF-β. TGF-β works through multiple signaling pathways, resulting in activation of a profibrotic genetic program. TGF-β converts fibroblasts and other cell types into myofibroblasts. Myofibroblasts have contractile proprieties and are the main source of extracellular matrix (ECM) proteins responsible for fibrosis. The overall result is excess accumulation of collagen and ECM proteins[12] which underlies the pathology of radiation-induced tissue damage.

Tissues that were not exposed to radiation are likewise affected by signals from nearby radiated cells by a phenomenon known as the bystander effect.[13] These mechanisms persist for many years after the initial radiation exposure driving profound changes at the cellular and molecular level. The overall result of radiation damage to tissue is the profound alteration tissue structure and function.

Radiodermatitis- and Chronic Radiation-Induced Fibrosis

Acute radiation damage, also known as radiodermatitis, occurs within 90 days of treatment. Signs include erythema, edema, desquamation, and ulceration. These acute symptoms can often improve with conservative treatment.[14]

Chronic damage, known as chronic radiation-induced fibrosis (RIF), presents 4 to 6 months after RT and continues to develop for years. Skin becomes thin, dry, and semitranslucent. Hair follicles and sebaceous glands are often lost. Subcutaneous tissue is replaced by dense fibrous tissue that causes induration and limited range of motion. Ischemia caused by vessel occlusion and changes in vasculature, including telangiectasia, deprive tissue of oxygen and nutrients, predisposing skin to breakdown, and ulcer formation. Skin is injured from light trauma and ulcers persist for years due to impaired healing capabilities and increased susceptibility to infection. For patients, chronic RIF can be extremely painful and for the most part, is irreversible.[8,15] Current areas in which RIF presents challenging clinical problems and patient morbidity includes breast reconstruction, osteoradionecrosis (ORN) of the jaw, secondary skin malignancies, and wound healing issues.

Clinical Challenges of Chronic Radiation-Induced Fibrosis

Breast Reconstruction

RT significantly reduces local recurrence and mortality of breast cancer.[16] Postoperative radiation is required for almost all breast-conserving therapy and is used postmastectomy in a variety of clinical situations.[17] The structural and functional changes in irradiated breasts include skin retraction, discoloration, induration, and pain and tightness in the surrounding chest, shoulders, and neck.[18] RIF significantly impacts both implant-based and autologous reconstructive outcomes.

Implant-Based Reconstruction

Implant-based reconstruction is currently the most popular reconstruction technique.[19] However, implant-based reconstructions in irradiated patients have higher complication rates compared with nonirradiated patients, including capsular contracture (CC), infection, implant loss, and reconstructive failure.[20–27] Patient-reported outcomes also tend to be inferior among radiated patients including for aesthetic outcomes, satisfaction, and quality of life.[28,29]

Two-Stage Implant-Based Reconstruction

A recent meta-analysis estimates overall implant-based reconstructive failure in irradiated breasts is 17.6%.[30] In this study, tissue expander (TE) reconstruction was associated with higher reconstructive failure rates compared with single-stage direct-to-implant (DTI) reconstruction. Similarly, Naoum et al found that TE reconstruction had significantly increased complication rates compared with DTI, including infection, skin necrosis, implant exposure, CC, and failure.[31] Higher rates of complications and failures in TE reconstruction compared with DTI have been further supported by other recent data.[32] Lin et al[33] retrospectively reviewed 256 radiated patients and found the TE patients had more complications, skin necrosis, wound breakdown, infections, and explantations compared

with DTI.[34] These results are in line with previous literature.[32,34,35]

Inferior surgical outcomes associated with two-stage TE reconstruction may be related to the fact that the second operation is performed on radiated tissue, given the diminished capacity for tissue healing. This is supported by evidence that 75% of complications within TE patients occur following exchange surgery.[31] While radiation is a risk factor for complications and reconstructive failure in TE-based reconstruction,[36] it allows for a second-stage surgery to correct some of the structural changes that occurred with Post-Mastectomy Radiation therapy (PMRT).

Single-Stage Implant-Based Reconstruction

DTI reconstruction has advantages of immediate psychological and physical benefits from immediate restoration of breast volume and shape, shorter procedure time, hospital stay, and recovery.[37,38] There is also the benefit of a single surgery. Nonetheless, RT increases the risk of developing minor and major complications including cellulitis, delayed wound healing, and dehiscence.[39] Another potential issue is that any early complications following DTI surgery can delay the initiation of adjuvant RT. A recent analysis determined that while there is an increased risk of delay, the time period is not long enough to impact survival outcomes.[40]

The prepectoral surgical plane has gained popularity in recent years for DTI reconstruction.[39,41] A benefit of the prepectoral plane is that it avoids pectoralis muscle fibrosis and shortening caused by radiation. In the irradiated submuscular plane, the implant can be disrupted by these muscle tissue changes.[42] The prepectoral plane is associated with reduced pain, elimination of animation deformity, and high patient satisfaction.[43,44] Avoiding irradiation of the pectoralis muscle minimizes associated issues.[45]

Capsular Contracture

Considering the capacity of radiation to induce fibrosis, it is unsurprising that radiation is also a risk factor for developing CC. The same TGF-β pathways that underlie RIF may also be associated with the pathogenesis of CC.[46] It is estimated that CC effects 10% of patients and 40 to 50% of patients with history of radiation.[30,47] CC causes significant patient morbidity including pain, poor aesthetic outcomes and has been attributed with being a primary cause of failure in implant-based reconstruction of radiated patients.[48]

Research on acellular dermal matrix (ADM) has shown growing evidence that it may reduce the risk of radiation-induced CC.[49,50] While initially intended to provide support and cover the lower breast pole, there is also increasing scientific evidence in support of the reduced clinical risk of CC.[51,52] This effect may be related to decreased inflammation, fibroblast activity, and collagen deposition that can be seen with capsule samples from patients that have been reconstructed with ADM.[53]

Secondary procedures for managing radiation associated CC can be successful. A recent study demonstrated that implant exchange with capsule release successfully treated over 70% of cases, while fat grafting elevated success rates up to 86%.[48] While fat grafting shows promise in the treatment of RIF, it has not demonstrated the ability to influence the occurrence or severity of CC alone.[54]

Autologous Reconstruction

Autologous flaps still represent the gold standard of reconstruction in irradiated fields, as it allows for the transfer of health nonirradiated tissue to be brought into the radiation field. Compared with implant-based reconstruction, autologous reconstruction is associated with decreased complications and failures, greater patient satisfaction, and improved quality of life.[52,53,55] However, radiation of an autologous breast reconstruction is still prone to complications, particularly RIF, contracture, fat necrosis, volume loss, and distortion of breast shape.[56,57]

Similar to implant-based reconstruction, the optimal timing of reconstruction in relation to radiation is an active area of discussion. The options are to perform autologous tissue transfer at the time of mastectomy, before radiation is administered or to perform tissue transfer in a delayed fashion after radiation treatment has been completed. Emerging evidence tends to be in support of delayed autologous reconstruction; however, the ideal time period is still unknown. Delayed reconstruction avoids the exposure of flap tissue to radiation. Many studies show decreased complications, wound contracture, volume loss, fat necrosis, and need for revision surgery,[58–61] although delayed reconstruction comes with the disadvantage of requiring the patient to have an unreconstructed mastectomy defect for some time. Several studies support safe and acceptable outcomes for immediate autologous reconstruction, and it should be considered an optimal option for selected patients.[62–64]

Osteoradionecrosis

Radiation damage also has implications for head and neck cancer (HNC) patients. ORN is a significant and morbid complication associated with poor cosmetic and functional outcomes that affects 7% of radiated HNC patients.[65] By definition, ORN is a necrotic process of the bone resulting from RT that persists for greater than 3 months and is unrelated to neoplastic disease or recurrence.[66] The mandible is most often the site of pathology and symptoms usually present within the first year of RT.[67] ORN typically presents as painful denuded bone and can include purulent drainage and fistula formation. In advanced stages, necrosis can progress through the full thickness of bone and lead to pathologic fractures.[68,69]

Treatment of ORN correlates with severity of disease, ranging from conservative management to surgical resection and free flap reconstruction. Basic management approaches involve optimization of oral health. Poor periodontal health hygiene is not only a significant risk factor for ORN, but dental extractions are the most common initiating factor.[68,70] Other risk factors include a high radiation dose (>60 Gy), as well as alcohol and tobacco abuse.[70] Management of risk factors, local irrigation, and antibiotic therapy for acute infections results in resolution in up to one-third of cases for patients with mild disease.[70–72]

Surgical treatment options include wound debridement, sequestrectomy (removal of isolated islands of necrotic bone), and mandibulectomy for advanced disease. Advanced ORN includes those with fractures and fistulas. Risk of flap failure and postoperative complications are significantly higher compared with in nonradiated HNC patients.[73] The fibular free flap remains the gold standard for advanced ORN reconstruction.[74]

Radiation-Induced Skin Malignancy

Nonmelanoma Skin Cancer

RT increases life-time risk of developing precancerous lesions and nonmelanoma skin cancer (NMSC) within the radiation field.[14,75] The mechanism may be linked to the reduction of tumor suppressor genes and activation of oncogenes induced by RT.[8] Most cases of radiation-induced NMSC are connected with head and neck radiation.[76] There is an established association between RT and basal cell carcinoma (BCC), with an estimated incidence of 2%.[76] Evidence for squamous cell carcinoma (SCC) and melanoma are weaker.[77,78]

Merkel's Cell Carcinoma

Merkel's cell carcinoma (MCC) is another rare and aggressive cancer that may be induced by RT. MCC is a cutaneous neuroendocrine tumor that usually presents in the elderly and is linked to immunosuppression, chronic ultraviolet radiation exposure, and Merkel's cell polyomavirus.[79]

Wound Healing

The damage induced by radiation fundamentally impairs normal skin function and wound healing processes.[15,80,81] Normal wound healing relies on inflammation, proliferation, and remodeling phases. Inflammation is hindered from disrupted cytokine and chemokines involved in normal wound healing. Proliferation is impacted by endothelial damage, the resulting vasculopathy, and impaired neovascularization. Lastly, damaged fibroblasts produce dysfunctional collagen and impaired wound strength. Together, the effects manifest as poorly healing skin.[82]

However, performing surgery on irradiated tissues is sometimes unavoidable. Soft tissue sarcoma's resection often presents this clinical situation. Sarcomas are relatively rare malignant tumors that affect 1% of the population, often presenting on the extremities.[83] Historically, sarcomas were treated with limb amputation. Similar to breast-conserving therapy, limb-preserving therapy is reliant on RT and surgical tumor resection.[84,85] Major wound complications following sarcoma resection and radiation treatment are estimated at 30 to 46%.[86,87]

Timing of radiation significantly affects wound healing. Patients who receive radiation prior to surgery experience more wound healing difficulties, infection, seroma, hematoma, and dehiscence.[86,88] Other risk factors for wound complications in irradiated sarcoma patients are diabetes, older age, obesity, smoking, acute radiation dermatitis, and tumor size >10 cm.[86,89]

Radiation-Induced Fibrosis Treatment Options

Hyperbaric Oxygen Therapy

Hyperbaric oxygen (HBO) therapy involves inhalation of pure oxygen in a closed chamber. HBO was used for decades as adjuvant treatment of ORN and has been applied to radiation-induced tissue complications of the head, neck, and breast.[90] HBO creates an oxygen gradient across hypoxic tissue, stimulates anigiogenesis, and reduces necrosis.[91] Other benefits include decreased production of inflammatory cytokines and inhibition of fibroblast activity.[92,93] HBO is used for postradiation soft tissue necrosis both pre- and postoperatively.[94] Recently, debate of the efficacy of HBO therapy for ORN has grown after studies provided underwhelming evidence of clear benefits.[91,95,96] However, more robust prospective multicenter randomized controlled trials are underway.[97] A recent case series of breast cancer patients showed promising results of HBO treatment for radiation tissue injury including decrease in pain, fibrosis, edema, and increased shoulder movement.[98]

Autologous Fat Grafting and Adipose-Derived Stem Cells

Autologous fat grafting (AFG) is a promising, minimally invasive therapeutic approach for improving side effects of radiation. AFG was originally used to restore volume deficits but is gaining attention in its ability to restore damaged tissue.[99] AFG has been shown to reduce pathologic dermal thickness, collagen production, and increase healthy vascularity in irradiated tissue,[100] and the clinical result is improved symptoms in RIF patients.[98] In breast cancer patients, AFG has been used to treat radiation-induced wounds[101] and has been shown to improve esthetic outcomes, such as skin quality in reconstructed patients.[102–104]

The mechanism in which AFG induces tissue regeneration is debated. It is believed that adipose-derived stem cells (ADSC) are responsible; however, this has not yet been definitively proven.[105] Adipose tissue contains ADSC, which produce angiogenic and antiapoptotic paracrine signaling factors,[106] and have the ability to differentiate into multiple mesenchymal cell lineages,[107] including endothelial cells that incorporate into vessels and promote new vessel growth.[108] However, the quantity of ADSC in lipoaspirate is thought to be insufficient to be responsible for the regenerative affects. ADSCs can be concentrated through cell-assisted lipotransfer which involves enzymatically digesting the lipoaspirate with collagenase and subsequently centrifuging it to extract the stromal vascular fraction.[109,110] However, cell-assisted lipotransfer is considered stem-cell therapy by the U.S. Food and Drug Administration and use is currently limited to clinical trials overseen by the organization. One of the reasons for strict regulation is that the concern over the ability of stem cells to promote malignancy and metastases, especially in cancer patients.[111,112] In contrast, traditional fat grafting indicated for breast reconstruction and esthetics is considered safe in breast cancer patients from an oncological perspective.[113–115]

Pharmaceutical Agents

Anti-inflammatory and Antioxidant Treatment

A common pharmaceutical therapy for radiation fibrosis is combined treatment with pentoxifylline and α-tocopherol (vitamin E).[40] Pentoxifylline is a methylxanthine derivative that induces vasodilation, increases erythrocyte membrane flexibility, and decreases platelet aggregation to enhance blood flow. Vitamin E has antioxidant properties that can limit free radical damage and is also proposed to inhibit TGF-β, collagen, and fibronectin production.[116] The combination of both agents' works through multiple mechanisms to reduce subcutaneous fibrosis. It is commonly used in HNC patients and has recently been introduced to breast cancer patients.[117–121] Currently, data are limited but small clinical studies suggest pentoxifylline and vitamin E therapy can treat and prevent RIF with low rates of side effects.[122]

Fibrosis Inhibitors

Due to its crucial role in the pathogenesis of fibrosis, TGF-β and its associated signaling molecules have been examined as therapeutic targets. For example, the small molecule inhibitor, LY2109761, and a natural derivative (halofuginone) have all been used to target various components of the TGF-β pathway to mitigate inflammation, matrix deposition, and fibrosis. These agents are currently in animal model stages[123–125] but preclinical data are promising. Efficacy in humans has not yet been shown.[126]

Deferoxime

Deferoxime (DFO) is a well-studied iron chelator drug commonly used to treat iron overload.[127] Over the past years, attention has shifted to the therapeutic ability of DFO in the treatment of wounds by reducing iron-catalyzed ROS production and improving tissue vascularization through the activation of proangiogenic genes.[128] Previous animal models demonstrated the ability of DFO to improve tissue hypoxia in skin flaps and irradiated bone and to prevent diabetic ulcer formation.[129–131] The potential role of DFO in the treatment of RIF was demonstrated recently with evidence that radiated mice treated with transdermal DFO had significantly improved skin perfusion and reduced dermal thickness akin to nonirradiated tissue.[132]

Conclusion

In conclusion, RT has tremendous implications on wound healing and surgical outcomes. As surgeons, it is important to understand the pathophysiology of this changes, as well as the surgical scenarios most effected by RIF. Future studies will help hopefully elicit and demonstrate the effectiveness of new therapeutics in the fight against radiation-induced tissue changes.

Conflict of Interest
None declared.

References

1 Mattiuzzi C, Lippi G. Current cancer epidemiology. J Epidemiol Glob Health 2019;9(04):217–222
2 Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005;104(06):1129–1137
3 Cho H, Mariotto AB, Schwartz LM, Luo J, Woloshin S. When do changes in cancer survival mean progress? The insight from population incidence and mortality. J Natl Cancer Inst Monogr 2014;2014(49):187–197
4 Jaffray DA, Gospodarowicz MK. Radiation therapy for cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, eds. Cancer: Disease Control Priorities, Third ed. Vol. 3. Washington (DC): The International Bank for Reconstruction and Development/The World Bank; 2015
5 Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. Int J Med Sci 2012;9(03): 193–199
6 Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer 2011;11(04):239–253
7 Wang B, Wei J, Meng L, et al. Advances in pathogenic mechanisms and management of radiation-induced fibrosis. Biomed Pharmacother 2020;121:109560
8 Najafi M, Motevaseli E, Shirazi A, et al. Mechanisms of inflammatory responses to radiation and normal tissues toxicity: clinical implications. Int J Radiat Biol 2018;94(04):335–356
9 Paris F, Fuks Z, Kang A, et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. Science 2001;293(5528):293–297
10 Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y, Thomas SM. Radiation-induced fibrosis: mechanisms and implications for therapy. J Cancer Res Clin Oncol 2015;141(11):1985–1994
11 Zhang H, Han G, Liu H, et al. The development of classically and alternatively activated macrophages has different effects on the varied stages of radiation-induced pulmonary injury in mice. J Radiat Res (Tokyo) 2011;52(06):717–726
12 Yarnold J, Brotons MC. Pathogenetic mechanisms in radiation fibrosis. Radiother Oncol 2010;97(01):149–161
13 Najafi M, Fardid R, Hadadi G, Fardid M. The mechanisms of radiation-induced bystander effect. J Biomed Phys Eng 2014;4 (04):163–172
14 Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. J Am Acad Dermatol 2006;54(01):28–46
15 Mendelsohn FA, Divino CM, Reis ED, Kerstein MD. Wound care after radiation therapy. Adv Skin Wound Care 2002;15(05): 216–224
16 Castaneda SA, Strasser J. Updates in the treatment of breast cancer with radiotherapy. Surg Oncol Clin N Am 2017;26(03): 371–382
17 Recht A, Gray R, Davidson NE, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. J Clin Oncol 1999;17(06):1689–1700
18 Coles CE, Moody AM, Wilson CB, Burnet NG. Reduction of radiotherapy-induced late complications in early breast cancer: the role of intensity-modulated radiation therapy and partial breast irradiation. Part I–normal tissue complications. Clin Oncol (R Coll Radiol) 2005;17(01):16–24
19 Agarwal S, Kidwell KM, Farberg A, Kozlow JH, Chung KC, Momoh AO. Immediate reconstruction of the radiated breast: recent trends contrary to traditional standards. Ann Surg Oncol 2015; 22(08):2551–2559
20 See MS, Farhadi J. Radiation therapy and immediate breast reconstruction: novel approaches and evidence base for radiation effects on the reconstructed breast. Clin Plast Surg 2018;45(01):13–24

21 Classen J, Nitzsche S, Wallwiener D, et al. Fibrotic changes after postmastectomy radiotherapy and reconstructive surgery in breast cancer. A retrospective analysis in 109 patients. Strahlenther Onkol 2010;186(11):630–636

22 Ho AL, Bovill ES, Macadam SA, Tyldesley S, Giang J, Lennox PA. Postmastectomy radiation therapy after immediate two-stage tissue expander/implant breast reconstruction: a University of British Columbia perspective. Plast Reconstr Surg 2014;134(01): 1e–10e

23 Ho AY, Patel N, Ohri N, et al. Bilateral implant reconstruction does not affect the quality of postmastectomy radiation therapy. Med Dosim 2014;39(01):18–22

24 Alderman AK, Wilkins EG, Kim HM, Lowery JC. Complications in postmastectomy breast reconstruction: two-year results of the Michigan Breast Reconstruction Outcome Study. Plast Reconstr Surg 2002;109(07):2265–2274

25 Krueger EA, Wilkins EG, Strawderman M, et al. Complications and patient satisfaction following expander/implant breast reconstruction with and without radiotherapy. Int J Radiat Oncol Biol Phys 2001;49(03):713–721

26 Cordeiro PG, Snell L, Heerdt A, McCarthy C. Immediate tissue expander/implast breast reconstruction after salvage mastectomy for cancer recurrence following lumpectomy/irradiation. Plast Reconstr Surg 2012;129(02):341–350

27 Tallet AV, Salem N, Moutardier V, et al. Radiotherapy and immediate two-stage breast reconstruction with a tissue expander and implant: complications and esthetic results. Int J Radiat Oncol Biol Phys 2003;57(01):136–142

28 Cowen D, Gross E, Rouannet P, et al. Immediate post-mastectomy breast reconstruction followed by radiotherapy: risk factors for complications. Breast Cancer Res Treat 2010;121(03):627–634

29 Eriksson M, Anveden L, Celebioglu F, et al. Radiotherapy in implant-based immediate breast reconstruction: risk factors, surgical outcomes, and patient-reported outcome measures in a large Swedish multicenter cohort. Breast Cancer Res Treat 2013;142(03):591–601

30 Ricci JA, Epstein S, Momoh AO, Lin SJ, Singhal D, Lee BT. A meta-analysis of implant-based breast reconstruction and timing of adjuvant radiation therapy. J Surg Res 2017;218:108–116

31 Naoum GE, Salama L, Niemierko A, et al. Single stage direct-to-implant breast reconstruction has lower complication rates than tissue expander and implant and comparable rates to autologous reconstruction in patients receiving postmastectomy radiation. Int J Radiat Oncol Biol Phys 2020;106(03):514–524

32 Nava MB, Pennati AE, Lozza L, Spano A, Zambetti M, Catanuto G. Outcome of different timings of radiotherapy in implant-based breast reconstructions. Plast Reconstr Surg 2011;128(02):353–359

33 Lin AM, Christensen JM, et al. Postmastectomy Radiation Therapy on permanent implants or tissue expanders: which is better? Ann Surg. 2019; Doi: 10.1097/SLA.0000000000003670

34 Cordeiro PG, Albornoz CR, McCormick B, et al. What is the optimum timing of postmastectomy radiotherapy in two-stage prosthetic reconstruction: radiation to the tissue expander or permanent implant? Plast Reconstr Surg 2015;135(06): 1509–1517

35 Lentz R, Ng R, Higgins SA, Fusi S, Matthew M, Kwei SL. Radiation therapy and expander-implant breast reconstruction: an analysis of timing and comparison of complications. Ann Plast Surg 2013;71(03):269–273

36 Hoejvig JH, Pedersen NJ, Gramkow CS, Bredgaard R, Kroman N, Bonde CT. Delayed two-stage breast reconstruction: the impact of radiotherapy. J Plast Reconstr Aesthet Surg 2019;72(11): 1763–1768

37 Kim SW, Lee HK, Kang SM, et al. Short-term outcomes of immediate breast reconstruction using an implant or tissue expander after mastectomy in breast cancer patients. Breast Cancer 2016;23(02):279–285

38 Roostaeian J, Sanchez I, Vardanian A, et al. Comparison of immediate implant placement versus the staged tissue expander technique in breast reconstruction. Plast Reconstr Surg 2012; 129(06):909e–918e

39 Safran T, Al-Halabi B, Viezel-Mathieu A, Boileau JF, Dionisopoulos T. Direct-to-implant, prepectoral breast reconstruction: a single-surgeon experience with 201 consecutive patients. Plast Reconstr Surg 2020;145(04):686e–696e

40 Shammas RL, Ren Y, Thomas SM, Hollenbeck ST, Greenup RA, Blitzblau RC. Immediate breast reconstruction allows for the timely initiation of postmastectomy radiation therapy. Plast Reconstr Surg 2019;144(03):347e–357e

41 Sbitany H, Gomez-Sanchez C, Piper M, Lentz R. Prepectoral breast reconstruction in the setting of postmastectomy radiation therapy: an assessment of clinical outcomes and benefits. Plast Reconstr Surg 2019;143(01):10–20

42 Sigalove S. Prepectoral breast reconstruction and radiotherapy-a closer look. Gland Surg 2019;8(01):67–74

43 Huang TT. Breast and subscapular pain following submuscular placement of breast prostheses. Plast Reconstr Surg 1990;86 (02):275–280

44 Pittman TA, Abbate OA, Economides JM. The P1 method: prepectoral breast reconstruction to minimize the palpable implant edge and upper pole rippling. Ann Plast Surg 2018;80(05): 487–492

45 Sinnott CJ, Persing SM, Pronovost M, Hodyl C, McConnell D, Ott Young A. Impact of postmastectomy radiation therapy in prepectoral versus subpectoral implant-based breast reconstruction. Ann Surg Oncol 2018;25(10):2899–2908

46 Katzel EB, Koltz PF, Tierney R, et al. The impact of Smad3 loss of function on TGF-β signaling and radiation-induced capsular contracture. Plast Reconstr Surg 2011;127(06):2263–2269

47 Headon H, Kasem A, Mokbel K. Capsular contracture after breast augmentation: an update for clinical practice. Arch Plast Surg 2015;42(05):532–543

48 Haran O, Bracha G, Tiosano A, et al. Postirradiation capsular contracture in implant-based breast reconstruction: management and outcome. Plast Reconstr Surg 2021;147(01):11–19

49 Lardi AM, Ho-Asjoe M, Junge K, Farhadi J. Capsular contracture in implant based breast reconstruction-the effect of porcine acellular dermal matrix. Gland Surg 2017;6(01):49–56

50 Spear SL, Seruya M, Clemens MW, Teitelbaum S, Nahabedian MY. Acellular dermal matrix for the treatment and prevention of implant-associated breast deformities. Plast Surg Nurs 2017;37 (02):76–87

51 Moyer HR, Pinell-White X, Losken A. The effect of radiation on acellular dermal matrix and capsule formation in breast reconstruction: clinical outcomes and histologic analysis. Plast Reconstr Surg 2014;133(02):214–221

52 Salzberg CA, Ashikari AY, Berry C, Hunsicker LM. Acellular dermal matrix-assisted direct-to-implant breast reconstruction and capsular contracture: a 13-year experience. Plast Reconstr Surg 2016;138(02):329–337

53 Basu CB, Leong M, Hicks MJ. Acellular cadaveric dermis decreases the inflammatory response in capsule formation in reconstructive breast surgery. Plast Reconstr Surg 2010;126(06): 1842–1847

54 Martin S, Cai L, Beniwal A, Tevlin R, Lee G, Nazerali RS. Autologous fat grafting and the occurrence of radiation-induced capsular contracture. Ann Plast Surg 2021;86(5S, suppl 3): S414–S417

55 El-Sabawi B, Sosin M, Carey JN, Nahabedian MY, Patel KM. Breast reconstruction and adjuvant therapy: a systematic review of surgical outcomes. J Surg Oncol 2015;112(05):458–464

56 Rogers NE, Allen RJ. Radiation effects on breast reconstruction with the deep inferior epigastric perforator flap. Plast Reconstr Surg 2002;109(06):1919–1924, discussion 1925–1926

57 Spear SL, Ducic I, Low M, Cuoco F. The effect of radiation on pedicled TRAM flap breast reconstruction: outcomes and implications. Plast Reconstr Surg 2005;115(01):84–95
58 Tran NV, Chang DW, Gupta A, Kroll SS, Robb GL. Comparison of immediate and delayed free TRAM flap breast reconstruction in patients receiving postmastectomy radiation therapy. Plast Reconstr Surg 2001;108(01):78–82
59 Carlson GW, Page AL, Peters K, Ashinoff R, Schaefer T, Losken A. Effects of radiation therapy on pedicled transverse rectus abdominis myocutaneous flap breast reconstruction. Ann Plast Surg 2008;60(05):568–572
60 Patel KM, Albino F, Fan KL, Liao E, Nahabedian MY. Microvascular autologous breast reconstruction in the context of radiation therapy: comparing two reconstructive algorithms. Plast Reconstr Surg 2013;132(02):251–257
61 Yun JH, Diaz R, Orman AG. Breast reconstruction and radiation therapy. Cancer Contr 2018;25(01):1073274818795489
62 Chatterjee JS, Lee A, Anderson W, et al. Effect of postoperative radiotherapy on autologous deep inferior epigastric perforator flap volume after immediate breast reconstruction. Br J Surg 2009;96(10):1135–1140
63 Mirzabeigi MN, Smartt JM, Nelson JA, Fosnot J, Serletti JM, Wu LC. An assessment of the risks and benefits of immediate autologous breast reconstruction in patients undergoing postmastectomy radiation therapy. Ann Plast Surg 2013;71(02):149–155
64 Billig J, Jagsi R, Qi J, et al. should immediate autologous breast reconstruction be considered in women who require postmastectomy radiation therapy? A prospective analysis of outcomes. Plast Reconstr Surg 2017;139(06):1279–1288
65 Wang TH, Liu CJ, Chao TF, Chen TJ, Hu YW. Risk factors for and the role of dental extractions in osteoradionecrosis of the jaws: a national-based cohort study. Head Neck 2017;39(07): 1313–1321
66 Buglione M, Cavagnini R, Di Rosario F, et al. Oral toxicity management in head and neck cancer patients treated with chemotherapy and radiation: xerostomia and trismus (part 2). Literature review and consensus statement. Crit Rev Oncol Hematol 2016;102:47–54
67 Moon DH, Moon SH, Wang K, et al. Incidence of, and risk factors for, mandibular osteoradionecrosis in patients with oral cavity and oropharynx cancers. Oral Oncol 2017;72:98–103
68 Rivero JA, Shamji O, Kolokythas A. Osteoradionecrosis: a review of pathophysiology, prevention and pharmacologic management using pentoxifylline, α-tocopherol, and clodronate. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124(05):464–471
69 Frankart AJ, Frankart MJ, Cervenka B, Tang AL, Krishnan DG, Takiar V. Osteoradionecrosis: exposing the evidence not the bone. Int J Radiat Oncol Biol Phys 2021;109(05):1206–1218
70 Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. Int J Oral Maxillofac Surg 2011;40(03):229–243
71 Owosho AA, Tsai CJ, Lee RS, et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): the Memorial Sloan Kettering Cancer Center experience. Oral Oncol 2017;64:44–51
72 Oh HK, Chambers MS, Martin JW, Lim HJ, Park HJ. Osteoradionecrosis of the mandible: treatment outcomes and factors influencing the progress of osteoradionecrosis. J Oral Maxillofac Surg 2009;67(07):1378–1386
73 Lee M, Chin RY, Eslick GD, Sritharan N, Paramaesvaran S. Outcomes of microvascular free flap reconstruction for mandibular osteoradionecrosis: a systematic review. J Craniomaxillofac Surg 2015;43(10):2026–2033
74 Kim JW, Hwang JH, Ahn KM. Fibular flap for mandible reconstruction in osteoradionecrosis of the jaw: selection criteria of fibula flap. Maxillofac Plast Reconstr Surg 2016; 38(01):46
75 Milam EC, Rangel LK, Pomeranz MK. Dermatologic sequelae of breast cancer: From disease, surgery, and radiation. Int J Dermatol 2021;60(04):394–406
76 Cuperus E, Leguit R, Albregts M, Toonstra J. Post radiation skin tumors: basal cell carcinomas, squamous cell carcinomas and angiosarcomas. A review of this late effect of radiotherapy. Eur J Dermatol 2013;23(06):749–757
77 Shore RE. Radiation-induced skin cancer in humans. Med Pediatr Oncol 2001;36(05):549–554
78 Karagas MR, McDonald JA, Greenberg ER, et al; For The Skin Cancer Prevention Study Group. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. J Natl Cancer Inst 1996;88(24):1848–1853
79 Walsh NM, Cerroni L. Merkel cell carcinoma: a review. J Cutan Pathol 2021;48(03):411–421
80 Harper JL, Franklin LE, Jenrette JM, Aguero EG. Skin toxicity during breast irradiation: pathophysiology and management. South Med J 2004;97(10):989–993
81 Denham JW, Hauer-Jensen M. The radiotherapeutic injury–a complex 'wound'. Radiother Oncol 2002;63(02):129–145
82 Johnson MB, Pang B, Gardner DJ, et al. Topical fibronectin improves wound healing of irradiated skin. Sci Rep 2017;7 (01):3876
83 Lehnhardt M, Daigeler A, Hauser J, et al. The value of expert second opinion in diagnosis of soft tissue sarcomas. J Surg Oncol 2008;97(01):40–43
84 Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. 1980. Clin Orthop Relat Res 2003;(415):4–18
85 Chao AH, Mayerson JL, Chandawarkar R, Scharschmidt TJ. Surgical management of soft tissue sarcomas: extremity sarcomas. J Surg Oncol 2015;111(05):540–545
86 Slump J, Bastiaannet E, Halka A, et al. Risk factors for postoperative wound complications after extremity soft tissue sarcoma resection: a systematic review and meta-analyses. J Plast Reconstr Aesthet Surg 2019;72(09):1449–1464
87 Sanniec KJ, Swanson S, Casey WJ III, Schwartz A, Bryant L, Rebecca AM. Predictive factors of wound complications after sarcoma resection requiring plastic surgeon involvement. Ann Plast Surg 2013;71(03):283–285
88 Abouarab MH, Salem IL, Degheidy MM, et al. Therapeutic options and postoperative wound complications after extremity soft tissue sarcoma resection and postoperative external beam radiotherapy. Int Wound J 2018;15(01):148–158
89 LeBrun DG, Guttmann DM, Shabason JE, Levin WP, Kovach SJ, Weber KL. Predictors of wound complications following radiation and surgical resection of soft tissue sarcomas. Sarcoma 2017;2017:5465130
90 Kirby JP. Hyperbaric oxygen therapy and radiation-induced injuries. Mo Med 2019;116(03):198–200
91 Bennett MH, Feldmeier J, Hampson NB, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst Rev 2016;4:CD005005
92 Oscarsson N, Ny L, Mölne J, et al. Hyperbaric oxygen treatment reverses radiation induced pro-fibrotic and oxidative stress responses in a rat model. Free Radic Biol Med 2017;103:248–255
93 Romero-Valdovinos M, Cárdenas-Mejía A, Gutiérrez-Gómez C, Flisser A, Kawa-Karasik S, Ortiz-Monasterio F. Keloid skin scars: the influence of hyperbaric oxygenation on fibroblast growth and on the expression of messenger RNA for insulin like growth factor and for transforming growth factor. In Vitro Cell Dev Biol Anim 2011;47(07):421–424
94 Cooper JS, Hanley ME, Hendriksen S, Robins M. Hyperbaric Treatment of Delayed Radiation Injury. Treasure Island (FL): StatPearls; 2021
95 Rice N, Polyzois I, Ekanayake K, Omer O, Stassen LF. The management of osteoradionecrosis of the jaws–a review. Surgeon 2015; 13(02):101–109

96 Annane D, Depondt J, Aubert P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. J Clin Oncol 2004;22(24):4893–4900
97 Shaw R, Forner L, Butterworth C, et al. Randomised controlled trials in HBO: "a call to arms" for HOPON & DAHANCA-21. Br J Oral Maxillofac Surg 2011;49(01):76–77
98 Spruijt NE, van den Berg R. The effect of hyperbaric oxygen treatment on late radiation tissue injury after breast cancer: a case-series of 67 patients. Diving Hyperb Med 2020;50(03):
99 Rigotti G, Marchi A, Galiè M, et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. Plast Reconstr Surg 2007;119(05):1409–1422
100 Garza RM, Paik KJ, Chung MT, et al. Studies in fat grafting: Part III. Fat grafting irradiated tissue–improved skin quality and decreased fat graft retention. Plast Reconstr Surg 2014;134(02): 249–257
101 Fukuba M, Uozaki H, Komuro Y. Effectiveness of the combination of fat grafting and injection on radiation ulcer healing. J Plast Surg Hand Surg 2020;54(01):24–28
102 Panettiere P, Marchetti L, Accorsi D. The serial free fat transfer in irradiated prosthetic breast reconstructions. Aesthetic Plast Surg 2009;33(05):695–700
103 Salgarello M, Visconti G, Barone-Adesi L. Fat grafting and breast reconstruction with implant: another option for irradiated breast cancer patients. Plast Reconstr Surg 2012;129(02):317–329
104 Serra-Renom JM, Muñoz-Olmo JL, Serra-Mestre JM. Fat grafting in postmastectomy breast reconstruction with expanders and prostheses in patients who have received radiotherapy: formation of new subcutaneous tissue. Plast Reconstr Surg 2010;125(01):12–18
105 Rinker BD, Vyas KS. Do stem cells have an effect when we fat graft? Ann Plast Surg 2016;76(Suppl 4):S359–S363
106 Coleman SR. Structural fat grafting: more than a permanent filler. Plast Reconstr Surg 2006;118(3, suppl)108S–120S
107 Conci C, Bennati L, Bregoli C, et al. Tissue engineering and regenerative medicine strategies for the female breast. J Tissue Eng Regen Med 2020;14(02):369–387
108 Cao Y, Sun Z, Liao L, Meng Y, Han Q, Zhao RC. Human adipose tissue-derived stem cells differentiate into endothelial cells in vitro and improve postnatal neovascularization in vivo. Biochem Biophys Res Commun 2005;332(02):370–379
109 Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng 2001;7(02):211–228
110 Arshad Z, Halioua-Haubold CL, Roberts M, et al. Adipose-derived stem cells in aesthetic surgery: a mixed methods evaluation of the current clinical trial, intellectual property, and regulatory landscape. Aesthet Surg J 2018;38(02):199–210
111 Rowan BG, Gimble JM, Sheng M, et al. Human adipose tissue-derived stromal/stem cells promote migration and early metastasis of triple negative breast cancer xenografts. PLoS One 2014;9 (02):e89595
112 Eterno V, Zambelli A, Pavesi L, et al. Adipose-derived mesenchymal stem cells (ASCs) may favour breast cancer recurrence via HGF/c-Met signaling. Oncotarget 2014;5(03):613–633
113 Mestak O, Hromadkova V, Fajfrova M, Molitor M, Mestak J. Evaluation of oncological safety of fat grafting after breast-conserving therapy: a prospective study. Ann Surg Oncol 2016;23(03):776–781
114 Petit JY, Maisonneuve P, Rotmensz N, et al. Safety of lipofilling in patients with breast cancer. Clin Plast Surg 2015;42(03):339–344
115 Kronowitz SJ, Mandujano CC, Liu J, et al. Lipofilling of the breast does not increase the risk of recurrence of breast cancer: a matched controlled study. Plast Reconstr Surg 2016;137(02): 385–393
116 Delanian S, Porcher R, Balla-Mekias S, Lefaix JL. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. J Clin Oncol 2003;21(13):2545–2550
117 Patel S, Patel N, Sassoon I, Patel V. The use of pentoxifylline, tocopherol and clodronate in the management of osteoradionecrosis of the jaws. Radiother Oncol 2021;156:209–216
118 Patel V, Gadiwalla Y, Sassoon I, Sproat C, Kwok J, McGurk M. Prophylactic use of pentoxifylline and tocopherol in patients who require dental extractions after radiotherapy for cancer of the head and neck. Br J Oral Maxillofac Surg 2016;54(05): 547–550
119 Patel V, Gadiwalla Y, Sassoon I, Sproat C, Kwok J, McGurk M. Use of pentoxifylline and tocopherol in the management of osteoradionecrosis. Br J Oral Maxillofac Surg 2016;54(03):342–345
120 Patel V, McGurk M. Use of pentoxifylline and tocopherol in radiation-induced fibrosis and fibroatrophy. Br J Oral Maxillofac Surg 2017;55(03):235–241
121 Jacobson G, Bhatia S, Smith BJ, Button AM, Bodeker K, Buatti J. Randomized trial of pentoxifylline and vitamin E vs standard follow-up after breast irradiation to prevent breast fibrosis, evaluated by tissue compliance meter. Int J Radiat Oncol Biol Phys 2013;85(03):604–608
122 Kaidar-Person O, Marks LB, Jones EL. Pentoxifylline and vitamin E for treatment or prevention of radiation-induced fibrosis in patients with breast cancer. Breast J 2018;24(05):816–819
123 Lee JW, Tutela JP, Zoumalan RA, et al. Inhibition of Smad3 expression in radiation-induced fibrosis using a novel method for topical transcutaneous gene therapy. Arch Otolaryngol Head Neck Surg 2010;136(07):714–719
124 Flechsig P, Dadrich M, Bickelhaupt S, et al. LY2109761 attenuates radiation-induced pulmonary murine fibrosis via reversal of TGF-β and BMP-associated proinflammatory and proangiogenic signals. Clin Cancer Res 2012;18(13):3616–3627
125 Xavier S, Piek E, Fujii M, et al. Amelioration of radiation-induced fibrosis: inhibition of transforming growth factor-beta signaling by halofuginone. J Biol Chem 2004;279(15):15167–15176
126 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 2000;47(02):277–290
127 Wright JA, Richards T, Srai SK. The role of iron in the skin and cutaneous wound healing. Front Pharmacol 2014;5:156
128 Shen X, Wan C, Ramaswamy G, et al. Prolyl hydroxylase inhibitors increase neoangiogenesis and callus formation following femur fracture in mice. J Orthop Res 2009;27(10):1298–1305
129 Donneys A, Deshpande SS, Tchanque-Fossuo CN, et al. Deferoxamine expedites consolidation during mandibular distraction osteogenesis. Bone 2013;55(02):384–390
130 Farberg AS, Jing XL, Monson LA, et al. Deferoxamine reverses radiation induced hypovascularity during bone regeneration and repair in the murine mandible. Bone 2012;50(05):1184–1187
131 Mericli AF, Das A, Best R, Rodeheaver P, Rodeheaver G, Lin KY. Deferoxamine mitigates radiation-induced tissue injury in a rat irradiated TRAM flap model. Plast Reconstr Surg 2015;135(01): 124e–134e
132 Shen AH, Borrelli MR, Adem S, et al. Prophylactic treatment with transdermal deferoxamine mitigates radiation-induced skin fibrosis. Sci Rep 2020;10(01):12346