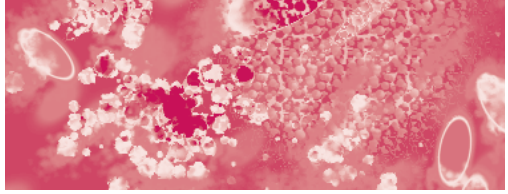

Effects of radiation on normal tissue: consequences and mechanisms

Helen B Stone, C Norman Coleman, Mitchell S Anscher, and William H McBride

The use of radiation therapy to treat cancer inevitably involves exposure of normal tissues. As a result, patients may experience symptoms associated with damage to normal tissue during the course of therapy for a few weeks after therapy or months or years later. Symptoms may be due to cell death or wound healing initiated within irradiated tissue, and may be precipitated by exposure to further injury or trauma. Many factors contribute to risk and severity of normal tissue reactions; these factors are site specific and vary with time after treatment. Treatments that reduce the risk or severity of damage to normal tissue or that facilitate the healing of radiation injury are being developed. These could greatly improve the quality of life of patients treated for cancer.

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When designing radiation therapy fields for the treatment of cancer, the radiation oncologist must take into account several important biological and technical factors (figure 1). These include: likely patterns of regional tumour spread, to ensure coverage of local tumour extensions not detectable with current imaging techniques; uncertainties in positioning the patient for each treatment; and tumour and organ movement during and between treatments. To achieve these aims, normal tissues surrounding the tumour are irradiated, which may result in symptomatic injury. The tolerance of these normal tissues to radiation dictates the dose that is prescribed in the treatment of most malignant diseases.

In contrast to chemotherapy, few prospective dose-escalation studies have been done to determine the maximum tolerated dose of radiation at any given site. Such studies are difficult to carry out because radiation dose is usually limited by late normal tissue effects and not by acute effects. Consequently, the commonly accepted tolerable doses have largely been derived empirically during the history of radiation therapy, and are based on limited retrospective data and unpublished clinical observations and teachings. Although the radiation tolerance of most organs is not precisely known, published guidelines serve as reasonable estimates.[1] A major factor affecting tolerable doses is the type of tissue exposed. In some tissues, quite a lot of damage after irradiation may be acceptable, especially if there is a reasonable probability of tumour control. For example, in the lung, a small amount of fibrosis is well tolerated and is commonly present after radiotherapy. However, in the central nervous system, the consequences can be severe and the dose must be tailored to minimise the likelihood of serious injury.

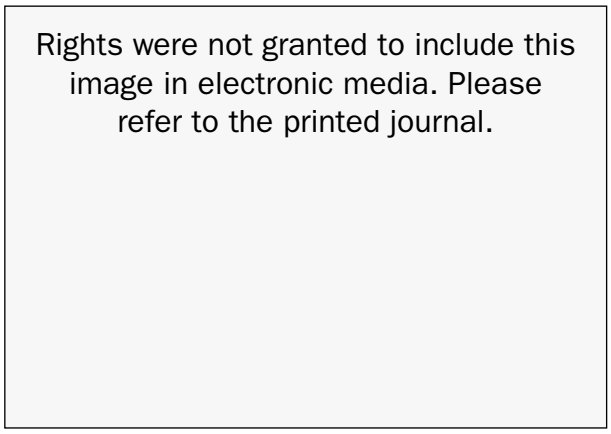

Figure 1. Patient undergoing radiotherapy. The illuminated discs over the patient's chest indicate the areas which are to receive radiation.

General principles of normal tissue injury

The pathological processes of radiation injury begin immediately after radiation exposure, but the clinical and histological features may not become apparent for weeks, months, or even years after treatment. In the lung, for example, changes detected 6 weeks after irradiation are mild even after a high dose but by 6 months there is widespread fibrosis (figure 2). Radiation injury is commonly classified as acute, consequential, or late effects,according to the time before appearance of symptoms. Acute (early) effects are those that are observed during the course of treatment or within a few weeks after treatment. Consequential effects (sometimes called consequential late effects) appear later, and are caused by persistent acute damage.[2] Late effects emerge months to years after radiation exposure. The terms acute and late have been used for convenience in radiation therapy, but because the underlying molecular and cellular processes are complex and lead to a range of events, the definitions may be more operational than mechanistic.[3] Early symptoms may not be apparent in some organs that

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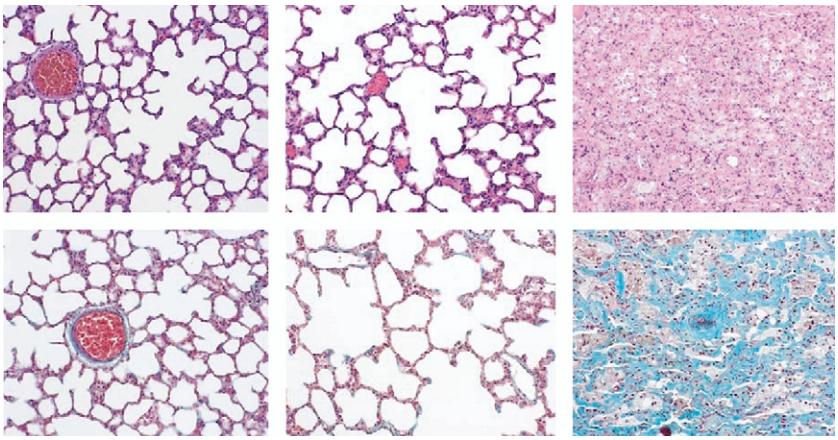

Figure 2. Radiation-induced pulmonary injury at 6 weeks (middle panels) and 6 months (right panels) after radiation exposure. At 6 weeks the changes are mild. There is a thickening of the alveolar septae due to the presence of inflammatory cells. Exudative material is present in some alveoli, but the architecture is preserved and there is nofibrosis. At 6 months, however, there is replacement of the normal alveolar architecture with widespread fibrosis. Far left panels show control tissues.

develop late injury, such as the kidney, and trauma or surgery months or years after irradiation can precipitate acute breakdown of tissue that had been functioning normally.

Acute effects

Acute radiation damage is most prominent in tissues with rapidly proliferating cells, such as in epithelial surfaces of the skin or alimentary tract. Symptoms develop when functional cells are lost as part of normal tissue turnover and are not replaced because of damage to the stem-cell compartment. In tissues such as the skin and gut, there is compensatory proliferation within the stem cells, which are more tolerant to radiation than other types of cells, followed by replacement of functional cells and recovery. Symptoms therefore generally subside, often during the course of radiotherapy.

The ionisation events and free radicals produced by radiation cause damage to vital cellular components. DNA damage from radiation commonly leads to death of cells in the first cell division after irradiation or within the first few divisions.[4] Cell death during mitosis (mitotic death) is generally caused by unrepaired or improperly repaired chromosomal damage.[5] Cell death may also occur by apoptosis. Certain cell types, especially lymphocytes, spermatogonia, and serous cells in the salivary gland undergo apoptosis during interphase after irradiation.[6,7] This type of death is rapid and is often associated with cells in specific locations within tissues, for example, in proliferative cells of intestinal crypts.[8] The clinical significance of apoptosis is not always evident. Cells may also leave the reproductive pool by differentiation rather than proliferation.[9] This senescence may be a particularly important response of fibroblasts, resulting in excess collagen deposition and fibrosis.

Some acute responses, such as erythema in the skin and increased intracranial pressure in the central nervous system, probably involve mechanisms other than cell death.[10,11] Radiation activates various cellular signalling pathways[12] that lead to expression and activation of proinflammatory and profibrotic cytokines,[13–15] vascular injury,[16] and activation of the coagulation cascade.[17] These changes may be involved in the development of oedema, inflammatory responses, and the initiation of wound-healing processes. The cytokines induced by radiation are, in many cases, tissue specific.

Late effects

Late effects develop months or years after treatment. The symptoms may be mild or severe, self-limiting, or progressive, and may develop gradually or suddenly. Some studies have reported progression of late effects for 20–34 years after therapy.[18,19] Late effects tend to occur in tissues with a slow turnover of cells, such as subcutaneous tissue, fatty tissue, muscle, brain, kidney, and liver, and in sites of slow turnover within tissues that contain rapidly-proliferating cells, such as the wall of the intestine. The lesions are diverse pathologically, but include fibrosis, necrosis, atrophy, and vascular damage. Carcinogenesis is an important consequence of radiation exposure, but is not considered in this review.

Late effects develop through complex interacting processes that are not yet well understood, particularly with respect to the importance of cell death during proliferation. Cells exist within a complex community whose members depend on each other and contribute individually to the welfare of the whole tissue. Irradiation of tissue activates a rapid molecular response. Part of this response is the production of cytokines, which leads to an adaptive response in the surrounding tissue and cellular infiltration (figure 3). Damage to the vasculature and release of vasoactive cytokines enables fibrin to leak into the tissues, which promotes collagen deposition. Overall, the response has the features of wound healing; waves of cytokines are produced in an attempt to heal the injury.[14,20] Leukocyte adhesion to endothelia cells and thrombi can block the vascular lumen, as can growth of endothelial-cell colonies during vascular regeneration, which may lead to loss of cells dependent on those vessels.[21–23] Conversely, death of parenchymal cells can lead to atrophy of the vasculature supplying them.[24] The response may be perpetuated by cell loss, dysregulated interactions between cell populations, or hypoxia.[25] In tissues such as the lung, accelerated senescence of stromal cells and their infiltration into sites of damage results in further fibrotic consolidation in susceptible tissues.[26] In other tissues, such as the brain, necrosis is the most serious complication.

Consequential late effects

In some patients, acute reactions fail to heal completely and persist into the late period. The resulting chronic lesions, termed consequential late effects, add to the overall damage.[2] Consequential late effects are increasingly being observed because of the introduction of new aggressive treatment regimens with combined modalities, such as radiotherapy plus chemotherapy protocols. The urinary and intestinal systems, mucosa, and skin are most susceptible.

Treatment-related factors

The risk, severity, and nature of early, consequential, and late reactions in a patient depend on several factors. Radiation-related treatment factors include the total dose, the dose per fraction, and schedule of treatment (ie, one versus two or three treatments per day). The current practice of fractionating radiotherapy treatments arose from observations that late effects were less severe and better local tumour control rates could be achieved with multiple, small radiation fractions than with one or a few large fractions. Late effects are generally more sensitive to changes in fraction size,[27] and less sensitive to changes in overall treatment time[28] than early responses. The use of chemotherapy can exacerbate the reactions.[29] The volume of normal tissue receiving high doses of radiation is also important, with larger volumes carrying higher risk of organ-function impairment.[30] The tolerance of normal tissue may depend upon its functional reserve and its structural organisation.[31] For example, the lung is able to tolerate a high dose in a small volume, but is less able to tolerate a low dose to the whole lung. Conversely, a high dose to a small volume in the spinal cord could be hazardous, but a low dose to a large area would be innocuous.

Patient-related factors

Patient-related factors include trauma or surgery in an irradiated site and co-morbidities, particularly those involving impaired vascularity, such as diabetes and hypertension.[32,33] Age may be a factor, but age by itself must not be considered a reason for avoiding the use of a curative regimen.

Some groups of patients may have a genetic susceptibility to the development of radiation injury. For example, patients with genetic abnormalities such as ataxia telangiectasia develop severe radiation reactions because of defects in the repair of DNA after radiation damage.[34,35] Differences in radiation sensitivity of various strains of mice suggest that other genetic factors contribute to individual differences in radiosensitivity,[36] but determination of the radiosensitivity of cells isolated from patients has not yet proved to be a reliable predictor for clinical use, except in rare cases of extreme radiosensitivity.[37]

Studies of the comparison of early and late responses in individual patients have shown that patients who have severe acute responses do not necessarily or predictably develop significant late reactions.[38] This finding may be a reflection of differences in underlying mechanisms involved in the development of these types of injury.

Clinicians must not assume that a patient's problem is due to radiation without consideration of the differential diagnosis and a thorough assessment. For example, rectal bleeding after pelvic irradiation may also be a result of haemorrhoids, anal fissures, or undiagnosed colorectal cancer. Radiation injury often mimics recurrence of the original tumour, even on imaging. This is a common problem with tumours prone to local recurrence, such as glioblastoma and non-small-cell lung cancer. Finally, overt injury generally develops within the radiation field, so that clinicians must be careful when attributing tissue injury to radiation therapy if it falls outside the irradiated volume. It is crucial to remember that diagnosis of radiation injury is a diagnosis of exclusion.

The role of the tumour

In addition to the contribution of radiation itself, the presence of the tumour may predispose the surrounding normal tissue to injury. Tumours change their surroundings in several ways. They physically distort normal tissue architecture[39,40] resulting in defects that can add to damage produced by therapy.[41] Tumours also release proteolytic enzymes that facilitate invasion and metastasis.[42] Tumour vessels leak fibrinogen, which is converted to fibrin, resulting in collagen deposition and fibrosis.[43,44] Loss of heterozygosity in genes—possibly affecting bioavailability of proinflammatory and profibrotic cytokines—has been observed in patients with lung cancer[45] and in tissues adjacent to breast and bladder tumours.[46]

Common clinical manifestations of radiation injury

Radiation injury varies from organ to organ, thus a comprehensive discussion is beyond the scope of this review, but is covered in other papers.[5,26,47–49] For each area discussed here—the thorax (lung and breast tumours), head and neck, and pelvis (prostate and cervical tumours)—we describe symptoms, the histopathology underlying the symptoms, medical management of the symptoms, and future prospects for preventing or treating radiation toxicity.

Thorax

The lung is one of the most radiosensitive organs, yet is frequently irradiated as part of treatment programmes for

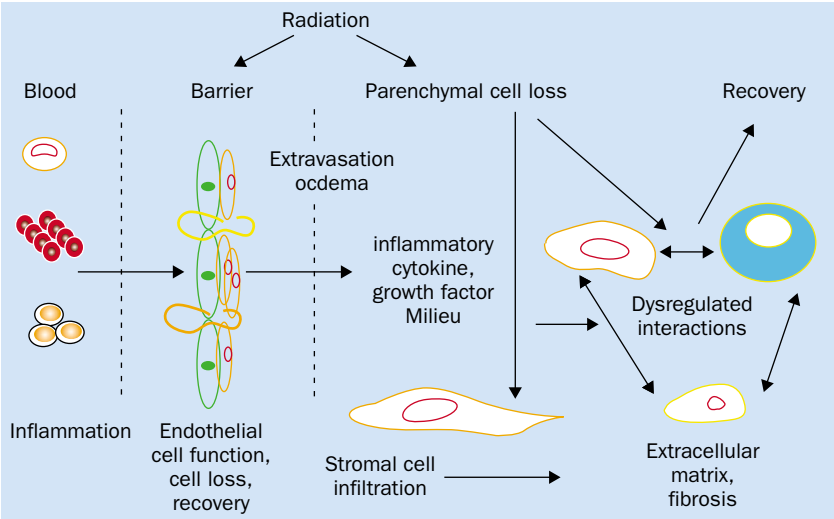

Figure 3. Tissues are composed of various interacting cellular systems. Radiation produces the release of cytokines and growth factors with cellular infiltrates reminiscent of wound healing This is perpetuated by radiation-induced cell death and loss, dysregulated interactions between surviving cells, and hypoxia due to vascular damage.

cancers of the lung, oesophagus, breast, and lymphatic system. The early clinical phase of radiation effects in the lung becomes apparent at about 1–3 months after radiotherapy, with congestion, cough, dyspnoea, fever, and chest pain caused by pneumonitis (pneumopathy). Tissue histology during the early phase shows an increase in type II pneumocytes and a decrease in parenchymal cells and surfactant concentrations. Oedema and inflammatory cells are present in the tissues and alveolar macrophages are prominent. Haematogenous exudates fill the alveoli, and hyaline membranes composed of fibrin develop.[22] Radiographic studies usually reveal an infiltrate within the irradiated field. This syndrome can also be caused by systemic or inhaled toxins, various drugs, infections, and tumour recurrence.[22] It is a common complication in patients who have been irradiated before bone-marrow transplantation.[50] The dyspnoea can be mild or severe. In severe cases, hypoxaemia and signs of right-sided heart failure may be present. Partial lung irradiation occasionally induces a bilateral, immunologically-mediated pneumonitis that generally resolves without treatment.[51]

Pneumonitis generally subsides after several weeks and is followed by a phase of chronic inflammation and fibrosis that develops months or years after irradiation. In this phase, vascular damage and collagen deposition become apparent.[22,44,52] If the volume affected is small, the patient may not experience symptoms and the scarring may be detected only radiographically. If a larger volume has been irradiated, the patient may have a cough, shortness of breath, and chest discomfort from a major reduction in diffusion capacity and respiratory volume due to significant scarring and tissue retraction.[52] A PET scan may help to distinguish radiation injury from tumour recurrence because the latter will appear much more hypermetabolic.

The association between pneumonitis and the development of fibrosis is still uncertain. Data from animal and human studies indicate that vascular injury and the coagulation cascade, cellular adhesion molecules, proinflammatory and profibrotic cytokines, and oxidative stress all seem to have vital roles in the development of radiation pneumonitis.[13] Mice that lack the gene for the endothelial cell adhesion molecule ICAM1 do not develop pneumonitis or show infiltration of inflammatory cells after irradiation.[53] The mice without *ICAM* develop fibrosis, but only at high radiation doses, suggesting that an inflammatory response is not the sole factor underlying the development of radiation fibrosis. Patients who have high plasma concentrations of the proinflammatory cytokine interleukin 1, or the profibrotic cytokines interleukin 6 and TGFβ, before or during radiotherapy have a higher risk of developing pneumonitis.[13,54] Patients with increased concentrations of TGFβ at the end of radiotherapy have a higher risk of symptomatic radiation-induced lung injury 6 months to 2 years after radiotherapy.[15] In a fibrosis-prone strain of mice given a single dose of 20 Gy to the thorax, increases in interleukin 1 were observed during the early postirradiation period and were associated with pneumonitis, whereas increases in TNFα, TGFβ1, and TGFβ2 occurred later and were associated with the development of fibrosis.[55] Fibrosis-prone mice express more and different chemokines and chemokine receptors 6 months after irradiation than fibrosis-resistant mice.[56] This finding implicates the recruitment and activation of monocytes, macrophages, and lymphocytes in the development of fibrosis in irradiated lung tissue. Gene therapy with manganese superoxide dismutase (MnSOD) reduces fibrosis in these mice,[57] suggesting a role of oxidative stress in the development of injury. The antifibrotic action of the related compound copper and zinc-containing superoxide dismutase (Cu/ZnSOD) may be mediated by reduction in the expression of TGFβ in myofibroblasts involved in scarring.[58] The renin–angiotensin system, which is associated with the development of radiation nephropathy, is also involved in the development of pulmonary injury after irradiation. Although blockage of this system with angiotensin-converting enzyme inhibitors or an angiotensin receptor blocker protected rat lungs from both pneumonitis and fibrosis after radiation exposure,[59] patients who were taking these types of drugs for management of hypertension did not have a reduced incidence of pneumonitis.[60]

Current treatment approaches for severe acute radiation pneumonitis—after appropriate assessment of the patient to rule out other causes of acute respiratory distress—include the use of systemic corticosteroids, which can be tapered gradually.[52] Supplemental oxygen, and even mechanical ventilation, may be necessary. It may soon be possible to identify patients at high or low risk by measuring profibrotic or proinflammatory cytokines (or both) in the circulation, thereby enabling individualisation of treatment fields and dose on the basis of a risk profile for normal tissue injury.[61]

Prevention of this problem is more effective than its treatment. Recent improvements in imaging and computer technology have contributed to the development of 3-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT), which enable more precise sculpting of the dose distribution to the tumour, with deliberate avoidance of sensitive normal tissues.[62] The normal tissue within the treatment field should be able to tolerate these higher doses because of the smaller volumes involved. In the case of thoracic tumours, gating techniques are being used to minimise or accommodate tumour movement during breathing.[63] With IMRT, however, larger volumes of tissue are exposed to moderate doses because these techniques use longer "beam-on" time and many more beam angles than conventional radiotherapy—even 360° sweeps.[64] When beam energies greater than 10 MV are used, neutrons are produced that expose large volumes outside the treatment field to low or moderate doses.[64] The long-term consequences are not known.

Head and neck

Skin, mucosa, subcutaneous tissues, bone, and salivary glands are often affected when radiotherapy is given for head and neck cancer. In the skin, early responses include erythema and dry or moist desquamation from depletion of

rapidly proliferating cells and failure to replace functional cells.[65] The response is possibly exacerbated by inflammatory and cytokine-mediated responses. These reactions may be accompanied by pruritis, hypersensitivity, or pain. Symptoms usually develop during a course of treatment, and may reach a peak and start to subside before the end of treatment as a result of stimulation of proliferation. However, dermatitis may not begin to resolve until weeks after the completion of treatment.

Mucositis, as with dermatitis, results from loss of functional cells and temporary lack of replacement from the pools of rapidly proliferating cells.[66] Mucositis and dermatitis may begin to heal toward the end of treatment, or may not begin to resolve until days or weeks after the completion of therapy; thus, acute reactions may become progressive consequential reactions. If mucositis is severe, the patient may have difficulty eating and a feeding tube may be necessary to provide adequate nutrition, especially with very intensive combined modality treatment or multiple daily fractions. A temporary interruption in treatment may be required.

Under microscopic examination, the skin and mucosa show hyperaemia, vascular congestion, vasodilation, and plasma leakage, with denudation of the epithelia. Late effects in the skin include alopecia, pigmentation changes, telangiectasia, atrophy, retraction, fibrosis, and ulceration. Although acute effects occur mostly in rapidly proliferating cells of the epidermis and mucosa, the fibrosis, retraction, oedema, lymphoedema, and atrophy that develop later largely reflect damage to the vascular and connective tissues. The microscopic picture is of atrophy, atypical cells, vascular lesions, and fibrin exudates leading to collagen deposition.[22] Patients with high concentrations of salivary epidermal growth factor before and during radiotherapy have less oral mucositis, but further study is needed to determine whether this could be exploited for therapy.[67]

The salivary glands, particularly the parotid glands, are frequently irradiated during treatment of tumours of the head and neck. The parotid glands contain serous cells that are radiosensitive and die by apoptosis.[7] The more resistant submandibular and sublingual glands contain mucous and serous cells. Damage occurs primarily in the parenchyma of the salivary gland, rather than in the ducts, but inflammation, vascular changes, and oedema contribute to the damage.[68] Functional impairment increases with the volume exposed and the radiation dose.[69] Swelling and tenderness can develop after the first treatment, possibly because of apoptosis, but generally subside within a few days. Xerostomia is the primary symptom because saliva becomes scant, sticky, and viscous as a result of changes in its composition during a course of radiotherapy. It makes eating, speech, and wearing dentures difficult. Recovery, if it occurs at all, may take months or years.[68]

Xerostomia can cause the patient to become more susceptible to fulminant dental caries. Carious teeth can result in infection of the underlying bone leading to osteoradionecrosis. This complication is more common in the jaw bone than in the upper jaw bone, because of the relatively poor blood supply of the former.[70] Osteoradionecrosis may be prevented in most patients by removing unsalvageable teeth before treatment and initiating a programme of aggressive prophylactic dental care, including daily fluoride rinses. Antibiotic therapy and resection of devitalised bone may be necessary. This complication may respond to hyperbaric oxygen treatments, but the mechanism of action is not known.[71] For xerostomia, saliva substitutes, sialogogues, water, and sugarless sweets and gum may help. The radioprotector amifostine, given before each fraction of radiotherapy, reduces the incidence of xerostomia.[72] Treatment plans using 3DCRT and IMRT can be designed to reduce the dose of radiation to the salivary glands, particularly the volume exposed to high doses (conformal avoidance).[62] Other investigators have attempted salivary gland transfer to a position outside the treatment field to protect salivary function.[73]

Pelvis

The rectum is the area most often affected by pelvic irradiation for treatment of prostate and cervical cancer. The acute symptoms are diarrhoea from loss of integrity of the epithelium and increased secretion of mucus. The tissues develop oedema and hyperaemia. The most common late effects include increased stool frequency, urgency, spotting of blood, and partial incontinence. Less common are ulceration, severe bleeding, pain, stricture, severe incontinence, and fistula.[74] Fibrosis and ischaemia in the submucosa and muscularis are largely responsible for these effects, accompanied by telangiectasia and other vascular abnormalities, mucosal congestion, collagen deposition, and abnormal fibroblasts.[75] The risk of complications depends primarily on the total dose and the amount of rectum in the treatment field. The latter depends on the radiation technique used. Brachytherapy (radioactive implants) techniques centre most of the radiation near the radioactive source, so accuracy of placement is important.[76] The volume of rectum in the high-dose region is reduced with 3DCRT and IMRT, which are being extensively studied for the treatment of prostate cancer.[77–79] Early reports indicate that escalation of dose to the tumour can be accomplished without an increase in normal tissue injury, but only limited long-term results are available.[77,80]

Molecular processes involved in the development of radiation-induced rectal injury have not been fully explored. Reduced amounts of endothelial thrombomodulin have been observed in normal rectum and tumours after irradiation, which could lead to increased fibrin deposition with upregulation and release of inflammatory and fibrogenic cytokines.[81] Increased concentrations of mRNA for TGFβ1 and TNFα have been found in colorectal tissues of fibrosis-susceptible and fibrosis-resistant strains of mice 6 months after irradiation.[82] This finding indicates that other factors contribute to the differences in response. In the ileum of rats, increases in TGFβ1, TGFβ2, and TGFβ3 were observed 2 weeks after a radiation dose of 12 or 21 Gy, but after 26 weeks, only TGFβ1 remained high.[83] TGFβ1 was particularly prominent

Search strategy and selection criteria

The references included in this review were identified by searches of PubMed, Current Contents, and citation searches on Web of Science with the search terms "IMRT", "radiation injury", "skin", "salivary gland", "lung", "breast", "cervix", "prostate", "bladder", "rectum", "inflammation", "fibrosis", "angiotensin", "TGF-beta", "interleukin", "KGF", "mechanism", "carcinogenesis", "hyperbaric oxygen treatment", and "wound healing". Reference lists in selected papers and the authors' personal collections of reprints were also searched. Owing to the extensive body of literature on normal tissue effects of radiation, not all relevant papers could be cited. Those selected were chosen as examples of the topics discussed, to provide leads to further reading, and for their quality, importance and relevance. Only papers published in English were included.

in areas with chronic fibrosis, in smooth muscle, mesothelium, endothelium, and fibroblasts. Several growth factors (eg, acidic fibroblast growth factor, basic fibroblast growth factor, and vascular endothelial growth factor) have shown protective effects against acute reactions in the small intestine,[84] but have not been evaluated in clinical trials involving radiation exposure to the rectum.

Treatments for rectal complications include: oral anti-inflammatory agents, pain management, stool softeners, intrarectal steroids, transfusions (for bleeding), and dilatation of strictures.[85] For serious or refractory complications, hyperbaric oxygen or surgical intervention with temporary or permanent colostomy may be required.[85]

Assessing normal tissue responses

When a new cancer therapy is evaluated, the toxic effects on normal tissues must be assessed and compared with standard therapy. A new scoring system has recently become available: common terminology criteria for adverse events v3.0 (CTCAE, http://ctep.cancer.gov/reporting/ctc.html). It was developed from two earlier scoring systems, the common toxicity criteria (CTC), developed by the National Cancer Institute (NCI) for evaluating acute toxicity of new chemotherapeutic agents and acute effects of radiation,[86] and the late effects normal tissue/subjective objective management analytical (LENT/SOMA) for assessing late normal tissue effects and their management.[85,87] The merged scoring system includes early and late responses, and is applicable to chemotherapy, radiotherapy, surgery, other treatment modalities, and combinations of therapies. It also includes quality-of-life measures. The new scoring system will be useful for assessing the effectiveness of new approaches for preventing or reducing injury to normal tissue.

Prospects for the future

Progress in cancer research is being made in many biological and technological areas. As cancer therapy improves and more patients survive longer, we need to direct research towards elucidating the processes that lead to complications of therapy. The NCI has identified long-term survival from cancer as one of the new areas of public health emphasis, particularly "studying adverse long-term or late effects of cancer and its treatment" (http://plan.cancer.gov/public/survivor.htm#studying).

It is important to focus research efforts on studying molecular and cellular changes in pathways leading to overt damage and to develop interventions that lessen the incidence and severity of normal tissue injury without compromising tumour control. We must learn more about the similarities and differences between injury caused by radiation and that produced by other cytotoxic agents, surgery, and trauma. Furthermore, we must also find out more about the process of wound healing if we are to prevent or repair damage from ionising radiation and other anticancer therapies. Also, research to identify molecular targets for the development of new anticancer agents must verify whether those targets exist in normal tissues as well as tumour tissue.

The NCI Radiation Research Program sponsored a workshop to survey studies of mechanisms underlying late effects of radiation and to discuss the prospects for treatment given after irradiation to help tissue healing.[88] Among the areas recommended for further study were: renin–angiotensin system inhibition (ie, use of ACE inhibitors and angiotensin II receptor antagonists), growth factors and cytokines (particularly TGFβ, basic fibroblast growth factor, and keratinocyte growth factor), proteases and their inhibitors, vitamin E and pentoxifylline, penicillamine, eicosanoids, COX2 inhibitors, Cu/ZnSOD and MnSOD, hyperbaric oxygen, and stem-cell transplants. Treatments given before irradiation such as amifostine and expanders of stem-cell populations can also protect normal tissues from acute and late effects.[89] We need to identify surrogate molecular markers, patterns of gene expression, genetic polymorphisms, and imaging patterns that will accurately predict patients at risk for normal tissue injury—such as TGFβ and pneumonitis—and to investigate appropriate timing of interventions to arrest or prevent complications. The radiation dose range in which these processes might successfully be interrupted is not known. Mechanisms of damage are likely to be tissue specific and may be under genetic control. Efforts to develop and evaluate new therapies to prevent or reduce injury to normal tissue will be facilitated by increased understanding of the mechanisms by which treatments for radiotoxicity work, and from greater knowledge of why radiation damage does or does not heal. It is also important to ensure that these treatments are effective in the clinical setting and do not protect or give a survival advantage to tumour cells.

Information from the study of damage to normal tissues caused by radiation are likely to be applicable to other cancer therapies and also to accidental or intentional radiation exposure.[88,89] As new cancer treatments are developed, it is essential to investigate their long-term consequences, because therapeutic efficacy of the cancer treatment must be considered along with quality of life. The new tools of molecular biology will give insights into how cancer treatment leads to the development of damage in normal tissues, and may lead to better ways of preventing or treating the damage.

Conflict of interest
None declared.

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