STAT PEARL

Hyperbaric Treatment Of Delayed Radiation Injury

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Last Update: August 30, 2022.

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Continuing Education Activity

There will be 1.2 million cases of invasive cancer diagnosed in the United States this year. Half of those patients will receive radiation therapy as part of their treatment program. Serious radiation complications will occur in 5% of patients receiving radiation therapy. This represents about 30,000 cases per year.Often, delayed effects of radiation are diagnosed when an additional insult to the tissue such as surgery or trauma occurs. This activity explains how to properly evaluate radiation induced injury and highlights the role of the interprofessional team in caring for patients with this condition.

Objectives:

- Describe the pathophysiology of radiation induced tissue injury.
- Review the presentation of patients with radiation induced tissue injury.
- Summarize the treatment options for radiation induced tissue injury.
- Outline the importance of enhancing care coordination among the interprofessional team to ensure proper evaluation and management of radiation induced tissue injury.

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Introduction

There will be 1.2 million cases of invasive cancer diagnosed in the United States this year. Half of those patients will receive radiation therapy as part of their treatment program. Serious radiation complications will occur in 5% of patients receiving radiation therapy. This represents about 30,000 cases per year.

Radiation is dosed in Rads and Grays:

1 rad = 1 centigray (cGy) = 100 ergs of energy per gm of tissue

Often, delayed effects of radiation are diagnosed when an additional insult to the tissue such as surgery or trauma occurs.

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Etiology

The biological effect of radiation on the tissues includes DNA damage, lipid peroxidation, and protein denaturation. The cellular consequences include cell death and dysfunction. In virtually all tissues that demonstrate late effects of radiation, there is a characteristic obliterative endarteritis. Current research into the etiology of delayed radiation injury has shown that the process of radiation injury begins during the time of radiation treatment and involves the elaboration of many bioactive substances, especially fibrogenic cytokines. TGF-beta is the most commonly studied cytokine associated with late effects of radiation as well as several other cytokines.[1][2]

Acute/Subacute radiation patterns usually develop after 5000 centigray (cGy).

Occurs acutely (near immediate) and the result of cellular toxicity by free radical damage to cellular DNA.

Subacute injuries (2 to 3 months post radiation) usually involve the lung.[3]

Delayed injuries occur more than 6 months to years after completion of radiation treatment. These are precipitated by further injuries in the previously irradiated field such as surgery or trauma. Delayed radiation injury often develops after 6500 centigray (cGy).[4]

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Epidemiology

Approximately one-third of patients in the United States who received hyperbaric oxygen therapy is being treated for late effects of radiation therapy (LERT). Major advances have been made in the past 50 years in the treatment and prognosis of many cancers. Many cancers which were once considered to be universally terminal, are now routinely survivable. Unfortunately, ionizing radiation when used to treat cancer is a double-edged sword. It is highly effective at killing the malignancy and curing cancer. However, it is indiscriminate, and despite best efforts and intentions, there is no way to protect nonmalignant tissues from being irreparably damaged by the ionizing radiation. Thus the patient is fortunate to be cured of cancer, but may be faced with delayed radiation injury months or even decades after the treatment is complete.[5][3]

Many times, delayed radiation injuries are precipitated by an additional tissue insult such as trauma or surgery.[6]

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Pathophysiology

Diffuse injury pattern related to the isodosing concept. The tumor is treated as a spheroidal mass with the most number of target cells at the center. A boost dose is given to the center of the tumor. At incremental distances from the center of the tumor, the mass is less; therefore, the delivered dose is less. However, the patient develops an additional diffuse area of injury from beam divergence. Radiation wounds demonstrate a progressive, proliferative endarteritis. This is an obliterative process

that destroys the tissue blood supply. The tissue ends up chronically hypoxic, fibrotic, and with a dearth of blood vessels.[7]

There is no satisfactory treatment of radiation necrosis using conventional therapy. It is difficult if not impossible to provide adequate nutrients and oxygen to the devascularized tissues. Surgical reconstruction of previously irradiated tissue has a very high failure rate due to poor healing.

The 3 Hs of previously irradiated tissue[8][9]

- Hypoxia
- Hypovascularity
- Hypocellularity

Delayed radiation injury is a problem of impaired and inadequate tissue turnover and wound healing.

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Histopathology

Two mechanisms of injury have been proposed and supported by animal and in vitro studies. The first postulates direct damage to small vessel endothelium, being a tissue that exhibits rapid turnover, through interaction with the radiation-induced reactive oxidative species. The resulting debris interrupts the vascular flow, a process known as endarteritis obliterans. The other model describes a delayed process initiated at the

time of radiation with the release of bioactive, fibrogenic cytokines inhibiting parenchymal and stem cells and causing the extensive fibrosis seen in several damaged irradiated tissue. This is known as the fibro-atrophic effect.[10][11]

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Toxicokinetics

The effects of ionizing radiation on soft tissues are permanent and ever-changing. Patients treated with radiation therapy for prostate cancer can develop post radiation cystitis and hematuria even 20 years after the completion of the radiation therapy. Patients treated for prostate and colon cancers can develop proctitis as well as cystitis due to late effects of ionizing radiation.[12][13][14][15]

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History and Physical

Patients who develop delayed effects of radiation present most commonly with radiation cystitis, radiation proctitis, vaginal radionecrosis, soft tissue radionecrosis, or laryngeal radionecrosis.[16][17]

Patients who have undergone radiation to the head and neck for soft tissue and palate or bone cancers may develop osteoradionecrosis of the jaw. This can be manifested by exposed bone (usually the maxilla or mandible) in previously irradiated tissue that has

failed to close spontaneously or with treatment for at least six months. These patients may also develop chronic draining sinus tracts and fistulae from the bone.[18][8][19]

It is important to document when the radiation treatment was completed and what the total dose was given.

Total doses of more than 6500 cGy are associated with the development of osteoradionecrosis and soft tissue radionecrosis.

Note if the patient has undergone recent bone biopsies, salvage surgery, trauma due to an oral or dental prosthesis, dental or periodontal disease, or extraction.[20][21][7][22]

Often, women who have received radiation for breast cancer develop post-radiation tissue fibrosis and hypovascularity of the chest-wall tissue which can make successful reconstruction and healing difficult, if not impossible.[23][24]

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Evaluation

Patients presenting for hyperbaric oxygen treatment for late or delayed effects of radiation should have a formal consultation with the hyperbaric physician and treatment team. Information needed to determine the diagnosis and develop a treatment plan include:

- Radiation therapy record: Specifically the total dose received and the dates the therapy was given
- Any history of chemotherapy and agents used
- Recent imaging results such as PET, CT, or MRI scans to document that the patient is currently cancer-free
- Reports and records from the referring physician requesting the hyperbaric medicine consultation.[25]

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Treatment / Management

Treatment protocols vary depending on the treated tissue.

Robert Marx, DDS did most of the work elucidating the benefit of hyperbaric oxygen for treatment of osteoradionecrosis of the mandible in patients who received head and neck radiation. Osteoradionecrosis of the jaw is the result of an aseptic, avascular necrosis of the bone. Marx showed that for hyperbaric oxygen to be consistently successful, it must be combined with surgery and antibiotic therapy. The major principals elucidated by Marx in the treatment and prevention of ORN include an emphasis on pre-surgical hyperbaric oxygen to improve tolerance to surgical wounding. These patients typically receive 20 pre-extraction treatments followed by ten post-extraction hyperbaric oxygen treatments.[26][27]

Laryngeal necrosis and other soft tissue necrosis of the head and neck due to late effects of radiation therapy have been successfully treated with hyperbaric oxygen to improve tissue quality both preoperatively and postoperatively and to improve survival of surgical flaps in previously irradiated head and neck tissues.[28]

A growing body of literature supports the use of hyperbaric oxygen therapy in the prevention of radiation injury. This is usually in the setting of proposed surgery within a previously irradiated field where the likelihood of complications and difficult wound healing is high.[29]

At present, a reasonable approach is to provide adjunctive hyperbaric oxygen treatments when surgery in heavily irradiated tissue bed is planned.[30][31]

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Differential Diagnosis

- Bowen’s disease
- Burns
- Basal carcinoma
- Cold injuries
- Early diabetes
- Marjolin’s ulcer
- Obesity
- Polyarteritis nodosa
- Systemic lupus erythematosus
- Venous stasis

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Enhancing Healthcare Team Outcomes

Delayed radiation injuries (soft tissue and bony necrosis) is a CMS-approved diagnosis for hyperbaric oxygen therapy. Depending on the individual patient diagnosis and the proposed surgery, the patient may receive from 20 to 60 hyperbaric oxygen treatments to treat and mitigate the symptoms of LERT. An interprofessional team of specialty trained hyperbaric nurse and clinician should monitor the patient during treatment. [Level V]

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