Chapter IX. Acute Radiation Effects: Organ Specific Radiation Dose and Species Differences:

Section E: Oral/Oropharynx/Esophagus

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Introduction:

Radiation damage to the esophagus presents as two pathophysiological syndromes: acute radiation esophagitis (1-2) and chronic radiation stricture (3). Radiation damage to the oral cavity/oropharynx also displays the two stages of pathologic findings. This chapter will deal with the esophagus first, and then the oral cavity/oropharynx. Acute esophagitis is commonly seen in clinical radiation oncology patients, who receive fractionated irradiation for the treatment of lung cancer (29) or esophagus cancer (20). In the 1960s and 1970s, when Hodgkin's Disease patients were commonly treated with mantle/thoracic irradiation, esophagitis was also seen in these patients, particularly those who were receiving combination chemotherapy at the same time as their radiotherapy. Acute esophagitis is characterized clinically by dysphagia (difficulty swallowing). Often patients report feeling a "lump" in their throat when they try to swallow in the absence of pain, and there is an exacerbation of esophageal reflux symptoms (heartburn) in many patients. The first symptoms of esophagitis may appear in any one of these categories, but clearly pain on swallowing is the most common.

As with many other clinical radiotherapy side effects, the symptoms appear in a direct dose response relationship to total radiotherapy dose, length of the esophagus being treated (volume of tissue treated), and fraction size. Those patients treated to a significant length of the esophagus (20 – 30 cm. in length), who were receiving 1.8 Gy per day by multifield conformal treatment or Intensity Modulated Radiotherapy will usually develop esophagitis later, perhaps 3 – 5 weeks into a 6 week treatment course compared to those patients, who would be treated with a 2.5 Gy per day fraction size (20).

The histopathologic appearance of radiation esophagitis is very similar to that seen in oral cavity and oropharyngeal mucositis with a couple of exceptions (1-5). The esophagus is unique in the gastrointestinal system, because it does not have a serosa fibrous outer layer. The esophageal mucosa, which is squamous epithelium in the adult, then is distally seen to abut both circumferential and longitudinal muscle layers, which are responsible for the swallowing effect of movement of boluses of food or liquid into the stomach. In the human fetus, the esophageal epithelium is glandular until the third trimester of development. For this reason, esophageal tissue stem cells have a multipotential differentiation capacity with ability to form glandular tissue, as well as keratinizing squamous epithelium. The multilineage differentiation capacity of esophageal stem cells (6-7, 9, 11) may in part explain the development of adenocarcinomas of the esophagus at the esophageal gastric junction since eroding of the esophageal squamous epithelium by acid reflux (heartburn) can lead to regeneration based on distal esophageal stem cells, which have capacity for glandular differentiation.

One theory of the etiology of glandular esophageal adenocarcinomas is that the differentiating esophageal stem cells in the setting of injury from acid reflux, respond to the acid environment by producing glandular tissue including cells capable of secreting mucin and other protective factors to neutralize acid reflux (9). The mechanism of esophageal adenocarcinoma formation is not directly related to this differentiation process, and squamous cell carcinomas of the esophagus are still detected, although with lower frequency. The mechanisms currently being studied to explain esophageal carcinogenesis, which is increasing in frequency in the United States have been attributed to increasing use of proton pump inhibitors, and other acid

neutralizing medications, which facilitate a change in the acid environment of the stomach. Accordingly, gastrin production in response to the decreased acid available in the stomach has been suggested to be a co-carcinogen. Other potential etiologies have involved migration into the stomach of distal intestinal microbes, which can proliferate in the low acid environment. Research is also continuing on mechanisms of dietary change, the role of obesity, and physical acid reflux with repeated trauma to the distal esophagus.

Of relevance to this chapter, it is important to note that acid reflux can exacerbate and contribute to the early onset of radiation esophagitis. These issues are separate, but may be related to the question of the etiology of esophageal carcinogens.

Therapies for Radiation Esophagitis

Several treatments have been tested in a clinical setting in Radiation Oncology departments. Most of these treatments have been designed to ameliorate the symptoms of esophagitis. Carafate, and orally administered Benadryl elixir (Benadryl/Milk of Magnesia/Xylocaine) has been used as a first therapy to decrease the pain from esophagitis. Roxicet, as well as Opioid-based analgesia often follows, and in some cases, patients must be treated with systemic opioids to ameliorate the pain. Most radiation oncologists will give patients a treatment break and cease radiotherapy to allow patients time for the esophagus to heal. Dietary modifications to minimize esophagitis are recommended, including: maintenance of room temperature diet including liquids, temporary elimination of solid foods that require a bolus volume swallowed amounts that will stretch the esophageal muscles and exacerbate the microulceration in the setting of esophagitis.

Esophagoscopy observations in patients with radiation esophagitis showed denudation of the esophageal mucosa, ulceration, and in some cases, hemorrhage. In severe cases, esophageal perforation may occur, particularly in patients with severe radiation esophagitis, who take adequate analgesics, and continue to stretch the esophageal injured tissues. Perforation of the esophagus requires emergency surgical evaluation and in some cases, surgical repair of the damage.

More recent approaches to treat radiation esophagitis have included application of agents that can prevent damage rather than treat the symptoms. These have included a gene therapy approach with swallowed Manganese Superoxide Dismutase (MnSOD) plasmid liposomes (1-5, 8, 10, 13, 15, 16), which if delivered prior to each radiation fraction can decrease irradiation-induced DNA double strand breaks, and decrease radiation apoptosis. Gene therapy using a transgene for Catalase has also been used in gene therapy approaches (12). Administration of SOD mimic molecules including: GS-nitroxide (a CMCR radiation mitigator drug) have proven effective in mouse models of radiation esophagitis (17-19, 21).

What Are the Methodologies for Studying and Quantitating Radiation Esophagitis?

The models of radiation esophagitis have included primarily rodent models in mice and rats, and esophageal length studies have been carried out in rabbits. Studies of precursor lesions of early esophageal carcinoma (Barrett's esophagus) have been carried out in pig models, and

photodynamic therapy approaches to treating localized lesions in the distal esophagus have been tested and validated in a pig model (22). Each of these animal model systems quantitation of esophageal damage is carried out using means of clinical observation and histopathology. Weight loss is the most easily measured parameter to quantitate the severity of damage to the esophagus, because dysphagia in animal models results in decreased eating. Weight loss of greater than 30% for rodent models is usually associated with termination of the experiment due to Institutional IACUC regulations (1). Listlessness of animals associated with dehydration, water bottle measured consumption should be measured daily, as a quantitation of potential dehydration effects of painful esophagitis. Experiments terminated even before the 30% weight loss in situations, where fluid consumption is decreased. The mainstay of quantitation of acute esophagitis is the histopathologic evaluation.

Removal of the animal (rodent) esophagus and opening the tube longitudinally allows quantitation of ulcerated areas. Using iodine staining or other colorimetric dye for gross pathologic evaluation can allow experimenters to place the rodent esophagus under a dissecting microscope and quantitate the number of ulcerated lesions seen in the 1st cm. length of esophagus. Microscopic histopathology is the best for quantitation of esophagitis. The ulcerated lesions are visible as disruptions in the squamous epithelium, and vascular swelling, interstitial edema, and in some cases, damage to the muscle layer. These histopathologic figures and photos have been published (1). Irradiation damage to the esophagus can be quantitated by counting the number of apoptotic cells seen in the epithelium and muscle layers (1).

The apotag assay is a valuable method for quantitating death of individual cells in the esophagus prior to the appearance of ulceration. The earliest biomarkers of esophageal radiation damage are those detectable by either real time preliminary change reaction to quantitate mRNA levels (28), or Luminex assay for proteins (30). Radiation damage associated proteins in the esophagus are common to those used for measurement of damage in other tissues including: lung, oral cavity, bone marrow, and in total body irradiation. Increase in markers for inflammatory cytokines including: TGF-β, IL-1, TNF-α, and others have published as early biomarkers of esophageal damage (3). The delivery of swallowed agents to ameliorate irradiation damage has been associated with a decrease in these biomarkers. The appearance of RNA and protein for inflammatory biomarkers may precede detection of physical ulceration and other histopathologic features making these assays more sensitive. In particular, the assays have been used to quantitate the effect of drugs being tested to decrease radiation esophagitis (1). Radiation esophagitis is a major complication of thoracic radiotherapy in the Modern era, and the development of new agents to prevent lesions rather than to palliate the symptoms is a subject of intense investigation. One of the main reasons for prevention of the lesions of acute radiation esophagitis is that these have been associated with the appearance of late esophageal fibrosis causing esophageal stricture.

Late Radiation Damage to the Esophagus is Radiation Fibrosis and Esophageal Stricture

Clinical Radiotherapy, Local Control of Cancers in the Thoracic Cavity by Chemoradiotherapy has resulted in large numbers of patients enjoying cancer free survival for several years after completion of radiotherapy. Unfortunately, radiation fibrosis, a histopathologic sequellae of radiotherapy in many organs is expressed in esophagus as esophageal stricture. Esophageal

strictures can occur in any region of the esophagus including cervical esophagus, mid-thoracic esophagus, and gastroesophageal junction, and is radiation dose dependent. Radiation doses of 40 – 50 Gy, currently a commonly used dose range for both pre-operative chemoradiotherapy of esophagus cancer and a definitive radiotherapy for inoperable patients can be associated with late esophageal stricture, particularly in the setting of concomitant chemotherapy. Many chemotherapy drugs exacerbate radiation damage to the esophagus and a 40 – 50 Gy dose delivered in fraction sizes of 1.8 to 2.5 Gy can be biologically equivalent to much higher doses if patients receive Taxol, Carboplatinum, and other analog drugs (20). Radiation dose range utilized at present is based on several studies showing that higher radiation doses increase the toxicity without improving local control or survival.

Patients with recurrent esophageal cancer in the local environment at a resection margin, at an anastomosis line in the setting of esophagectomy followed by "pull-through" and position of the stomach into the thoracic cavity with anastomosis to cervical esophagus, in the case of mid-thoracic or distal esophageal cancers, may require localized high doses of radiotherapy to allow local control. Recurrent esophageal cancer often requires higher radiotherapy doses, because secondary surgery is not possible, either because of the toxicity of prior pre-operative chemoradiotherapy, or because further resection is not feasible due to the absence of adequate esophagus for a secondary anastomosis. In these patients, the incidence of esophageal stricture is much higher.

What is Esophageal Stricture?

Patients will report difficulty swallowing, belching, often gagging and vomiting, associated with the inability of food to pass through a narrowing of the esophageal lumen (5-9). The narrowing is caused by proliferation of fibroblasts in the high dose irradiated area. Radiation fibrosis is the main late complication of radiotherapy of any tissues. The mechanism by which fibroblast proliferation occurs 6 months to 2 years after completion of high dose radiotherapy (equivalent to around 100 days after thoracic irradiation in a mouse model) is unknown, but recent research indicate contribution of fibroblast progenitor cells migrating into the site of fibrosis from the bone marrow (7). Some patients will develop radiation fibrosis, while others will not. This genetic contribution to the radiation late effect is partially elucidated in mouse models, in which some genetically inbred mouse strains (C57BL/6) develop radiation fibrosis, while others (C3H/HEJ) do not. Radiation fibrosis appears to be related to overall radioresistance of a particular mouse strain (C57BL/6J mice have the LD 50/30 of 9.25 – 9.75 Gy, while C3H/HEJ mice have an LD 50/30 of around 8 Gy). Readers should refer to the Chapter VIII on total body radiation effects to understand the LD 50/30 (total body dose for radiation, which is responsible for the death of 50% of animals at 30 days, and is associated with depletion of the bone marrow and the hematopoietic syndrome).

The mechanism by which acute radiation esophagitis subsides followed by a latent period, followed by the re-emergence of upregulated mRNA and proteins for inflammatory cytokines is unknown (3, 30). The hypothesis that a slowly proliferating cell population with a delayed doubling time, is responsible for the initiation of late radiation effects has been disputed by mouse labeling techniques, searching for delayed cell doubling (7). Recent data have demonstrated the continued upregulation of inflammatory cytokines in endothelial cells during

the “latent period” between acute radiation injury and fibrosis. Endothelial cells may retain molecular mechanisms of irradiation injury and accumulated expression of proteins associated with this prolonged injury response may be responsible for the eventual induction of fibroblast migration into the injured site and/or proliferation of surviving fibroblast cells at the site. One particularly attractive hypothesis is that senescence of cells induced by irradiation (Senescent cells sit in the tissue microenvironment, do not proliferate, but produce cytokines that are deleterious to both the local and distant tissues.) may be responsible for initiating fibrosis.

Treatment of Esophageal Stricture

Esophagoscopy using balloon expansion techniques is the usual approach toward management of patients with radiation-induced esophageal stricture. Patients may require balloon dilation frequently over years after completion of successful pre-operative chemoradiotherapy and surgery. Esophageal dilation is also frequently required in patients, who have received definitive chemoradiotherapy with no subsequent esophagectomy. Physical stretching of the constricted fibrotic area usually results in relief of symptoms, ability to maintain adequate nutrition, and freedom from symptoms of stricture (20).

Anti-fibrotic agents (drugs designed to relieve or reverse fibrosis) have been a subject of intense research. The hypothesis that the fibrotic/scarred tissue is an active tissue with depletion of cells and repopulation with other cells migrating in from non-irradiated areas or through the circulation from the bone marrow has been tested in rodent model systems. Administration of drugs designed to prevent migration of profibrotic, fibroblast precursors into the irradiated site has been tested with limited success. Delivery of drugs that inhibit fibroblast progenitor differentiation and proliferation has also been tested. At present, there is no accepted medical treatment for esophageal stricture, but rather physical stretching of the region is recommended. In some patients placement of a stent (Physical expanded cylindrical net inside the esophagus has been tested to attempt to maintain an open lumen.).

Acute Radiation Damage to the Oral Cavity and Oropharynx.

Acute radiation effects on the oral cavity and oropharynx are similar to those in the esophagus with the exception that there is a complexity associated with the presence of the bacterial microbiome involving teeth, the salivary glands, and the important role of muscles involved in vocalization and swallowing.

Radiation oncologists currently devise treatment plans for Head and Neck Cancers, which preserve salivary gland function. They use Intensity Modulated radiotherapy, 3-D conformal radiotherapy, and in some cases, radiosurgery to spare one of the parotid glands and if possible, submandibular glands. The boost (high dose) radiation volume, depending on the site of the primary tumor will dictate, which salivary glands can be spared from the (CTV) clinical target volume or field. This effort is critical to reduce the incidence and severity of xerostomia (dry mouth).

Numerous agents are available to treat xerostomia including artificial saliva, and stimulatory agents that push salivary glands to produce more saliva. Several publications using animal

models have demonstrated the effectiveness of using antioxidants to decrease radiation-induced mucositis (ulceration of the oral cavity). Initial studies with MnSOD-plasmid liposomes (MnSOD-PL), were the same as those used in esophageal radiation protection (23-26). Oral cavity radiation protection has been demonstrated in several animal models using MnSOD-PL.

SOD mimic molecules, principally GS-nitroxides, have also been used in formulations to treat the oral cavity and oropharynx, delivering the medication before each radiotherapy fraction (27-28).

The acute radiation effects on the head and neck region also involve the teeth and gums. Decreased saliva promotes dry mouth, which facilitates exacerbation of inflammation of the gums, which can lead to significant damage to the roots of teeth, increasing the likelihood of infection, and periodontitis. Poor dentition prior to radiotherapy initiation, often involves dental consult and removal of decaying or carious teeth prior to initiation of radiotherapy. The salivary gland radiation is minimized by sparing one or more of the major salivary glands. Sparing one parotid can significantly improve the production of saliva and can decrease both xerostomia and associated dental problems.

The musculature in the jaw also irradiated to significant doses can cause inflammation and pain on chewing. These radiation affects also influence late irradiation damage fibrosis in the treated volume.

Late Irradiation Damage to the Oral Cavity/Oropharynx

Late irradiation damage to the oral cavity and oropharynx is associated with fibrosis very similar to that seen in esophageal irradiation late effects (22). In contrast to late effects to the esophagus, fibrosis in the oral cavity and base of tongue region can usually be managed with physical therapy, and continued activity to facilitate recovery of the voluntary musculature. A major problem in late effects of oral cavity irradiation is trismus, which is fibrosis of the muscles surrounding one or more both sides of the jaw. Trismus can result in inability to eat due to the limited motion of the jaw and can result in painful muscle movement of the jaw during chewing due to fibrotic regions in the temporo-mandibular joint. Physical therapy techniques to stretch fibrotic tissue are applied similar to the dilation techniques used for esophageal stricture.

Readers are encouraged to contact the authors for more detailed information and more references or discussions of methods (Email addresses are listed after the authors in Table of Content).

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