Esophagus

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Contents

Abstract

- The esophagus is exposed to high radiation doses during thoracic RT, and acute esophagitis is a frequent dose-limiting toxicity of concurrent chemoradiotherapy regimens.
- Acute esophageal effects are related to damage of the basal epithelial layer, while late esophageal effects appear to be largely related to damage of the muscular wall.
- Animal models demonstrate necrosis of the muscular esophageal wall as the relevant pathway to late effects of RT on the esophagus, and associated molecular changes include oxidative stress and elevated levels of TGF-β and inflammatory cytokines.
- Esophageal peristalsis is an essential normal organ function. Disruption of esophageal motility is common after RT, as visualized by esophagograms or manometry.
- Severity of acute esophageal toxicity from RT is associated with an increased risk of late esophageal injury, suggesting a partial consequential relationship between acute and late injury.
- Late manifestations of RT-induced esophageal damage include dysphagia, dysmotility, stricture, ulceration, and fistula. The most common presentation of late esophagitis is dysphagia to solids due to focal stricture.
- The current standard instrument for scoring both acute and chronic esophagitis is the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0, which relies strongly upon patient-reported symptoms.
- Clinical parameters associated with increased risk of late esophageal injury may include concurrent chemotherapy, hyperfractionated RT, presence of dysphagia prior to RT, severity of acute esophagitis, and the addition of intraluminal brachytherapy.
- Emami et al. provided the first dose-volume recommendations for esophagitis, using the clinical endpoint of clinical stricture or perforation at 5 years, based upon expert consensus.

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- In the era of three-dimensional treatment planning, dosimetric factors that have been associated with late esophagitis include: volume and surface area exposed to >50 Gy, length of full-circumference dose >50 Gy, maximum full-circumference dose >80 Gy.
- Although data are limited, hypofractionated RT regimens for lung cancer would be expected to result in higher rates of late toxicity, based upon classic radiobiology principles.
- Recommended guideline for esophageal dose constraints in RT planning include: (1), avoiding "hot spots" above the prescription dose; (2), limiting the amount of esophagus exposed to 50–55 Gy or more; and (3), minimizing full-circumference doses to less than 80 Gy.
- Optimization of RT techniques, including intensity-modulated RT, may prevent esophagitis by reducing esophageal exposure. Radioprotective agents, such as amifostine and glutamine have been evaluated for the reduction of RT-induced esophagitis, though their clinical utility has not been clearly established.
- Preventive medical management strategies for acute esophagitis during RT have been suggested to include implementation of a bland diet, pain relief, antifungal medication, and suppression of gastric acid production, but these interventions are not evidence-based.
- Endoscopic dilatation is the primary treatment for late esophageal stricture after RT. Medical management of esophageal dysmotility involves antispasmodic therapy and metoclopramide to reduce gastro-esophageal reflux.
- Future directions to prevent late esophageal injury include a better understanding of relevant dosimetric parameters, more sophisticated techniques for RT delivery, and the development of effective radioprotective agents.

Abbreviations

AJCC	American Joint Committee on Cancer
CRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
EG junction	Esophagogastric
EB	External beam
RT	Radiation therapy
FSUs	Functional subunits
HDR	High-dose rate
LENT	Late Effects of Normal Tissues
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic body RT
SOMA	Subjective Objective Management and Analytic
UNC	University of North Carolina

1 Introduction

The esophagus is a muscular, tubular structure in the alimentary tract that functions to transport food from the pharynx to the stomach. It is lined with squamous epithelium and composed of mucosa, submucosa, and a muscular layer. The esophagus is exposed to high radiation doses during therapeutic strategies that incorporate irradiation or chemo-irradiation in the management of many thoracic malignancies. Acute esophagitis is a frequent source of morbidity and potential treatment breaks for patients receiving thoracic RT. Although most of the available literature regarding radiation therapy (RT)-related esophageal injury is based upon the treatment of carcinomas of the lung or esophagus, esophagitis is also observed in patients undergoing RT for thymic neoplasms, lymphoma, or vertebral body metastases. Although late effects of esophageal injury are less frequently observed than acute esophagitis, the impact of delayed toxicity may be severe. Late manifestations of RT-induced esophageal injury include dysphagia, dysmotility, stricture, ulceration, and fistula formation (Coia et al. 1995) (Fig. 1).

The clinical effects of external beam (EB) radiation therapy (RT) on the esophagus were described prior to the 1960s (Seaman and Ackerman 1957; Engelstad 1934). As trends in therapeutic approaches for non-small cell lung cancer (NSCLC) led toward more intensive therapeutic regimens of RT and chemotherapy, rates of treatment-related acute esophagitis increased. Whereas the rate of grade 3 or higher acute esophagitis was approximately 1 % with sequential chemoradiotherapy (CRT), the rates of esophagitis are higher, around 27–40 %, with concurrent CRT (Byhardt et al. 1998; Dillman et al. 1990; Curran W Jr et al. 2000; Ball et al. 1995; Umsawasdi et al. 1985; Gagel et al. 2007). Higher rates of severe acute esophagitis have been associated with increased incidence of late esophagitis (Ahn et al. 2005), but late manifestations of esophageal injury remain less common than acute toxicity in the era of CRT. In recent reports, death due to late esophageal injury occurs in only 0.4–1 % of patients treated for NSCLC (Qiao et al. 2005; Singh et al. 2003). It is anticipated, however, that the burgeoning role of hypofractionated RT in NSCLC may result in higher rates of late esophagitis due to the administration of higher doses per fraction, based upon accepted principles of radiobiology (Onimaru et al. 2003; Timmerman et al. 2006).

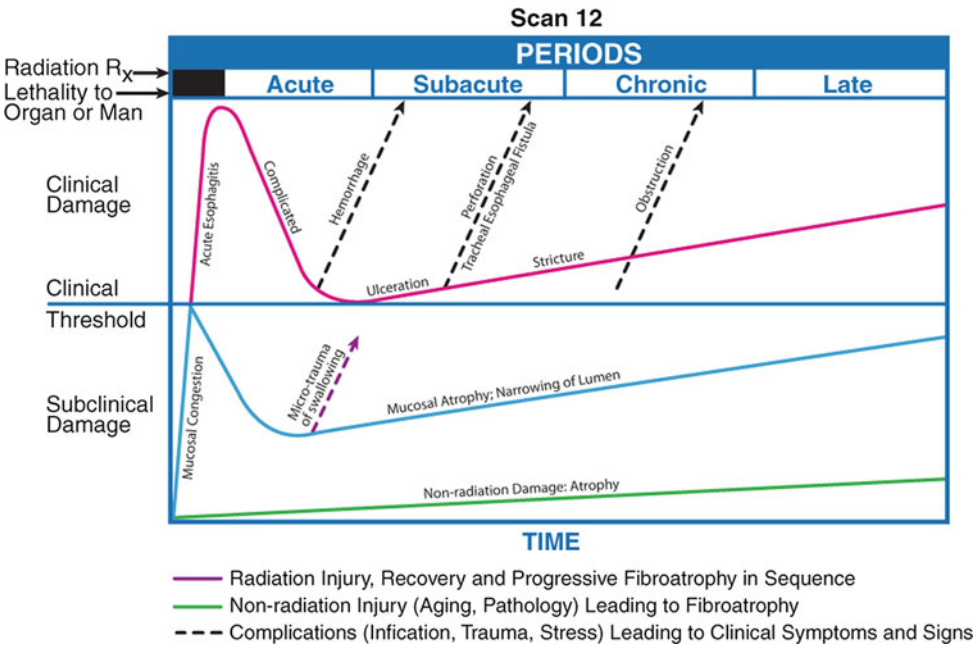

Fig. 1 Biocontinuum of adverse early and late effects of the esophagus (with permissions from Rubin and Casarett 1968)

A variety of treatment-related factors may influence the development of late effects of the esophagus after RT. An understanding of these variables will provide a foundation for efforts to limit the incidence of and to manage the symptoms of late RT-induced esophageal injury. In this chapter, we review the current understanding of RT-induced esophagitis, provide dose-volume recommendations for the clinical radiation oncologist, and describe recommendations for future directions. Bio-continuum of adverse early and late effects is shown in Fig. 1.

2 Anatomy and Histology

2.1 Gross Anatomy

The esophagus is a muscular, tubular structure that measures approximately 25 cm in length at extends from the cricoid cartilage, at the level C6 vertebral body level, to the esophagogastric (EG) junction, at the level of the T11 vertebral body level. It is located posterior to the trachea and bronchi in the posterior mediastinum. The esophagus is anterior to the spinal cord and the separation between the esophagus and spinal cord increases toward its gastric interface. The presence of an extensive network of submucosal lymphatics permits the spread of esophageal cancer several centimeters beyond the gross tumor, which is a relatively common event (Czito et al. 2008; Bradley and Mutic 2006). Sakata first demonstrated in 1903 that the submucosal lymphatics drain longitudinally, rather than in a segmental fashion (Sakata 1903). The network of lymphatics within the esophagus results in erratic spread of lymphatic metastases with frequent skip metastases to lymph nodes (van de Ven et al. 1999). Immunohistochemical analyses of surgical specimens for resected esophageal cancers have revealed a 66 % rate of skip metastases (Hosch et al. 2001). It is due to this potential for longitudinal spread that the length of longitudinal surgical margin is a predictor of outcomes after resection of esophageal cancer and that a longitudinal resection margin of 5 cm is recommended (Barbour et al. 2007) (Fig. 2).

The esophagus is generally divided into the cervical, upper thoracic, mid-thoracic, and lower thoracic regions. In the American Joint Committee on Cancer (AJCC) Staging Manual, these regions are defined as: cervical (extending from the inferior border of cricoid to thoracic inlet, at approximately18 cm from upper incisors on endoscopy), upper thoracic (extending from the thoracic inlet to level of the carina, approximately 24 cm from upper incisors), mid-thoracic (extending from the level of the carina to just superior to the EG junction, 32 cm from incisors); and lower thoracic/abdominal, the abdominal portion of the esophagus and the EG junction (40 cm from incisors) (American Joint Committee on Cancer 2002). See Fig. 2 for esophageal anatomy and index distances from upper incisors on endoscopy (Czito et al. 2008). For RT planning, the external border of the esophagus may be defined manually on axial computed tomography (CT) images. In order to obtain an accurate and informative dose-volume histogram, the esophagus should be segmented from its origin at the cricopharyngeus muscle to its termination at the gastroesophageal junction. One recent report suggests that a "correction method" for esophageal segmentation on CT images, based upon physiological principles of the normal

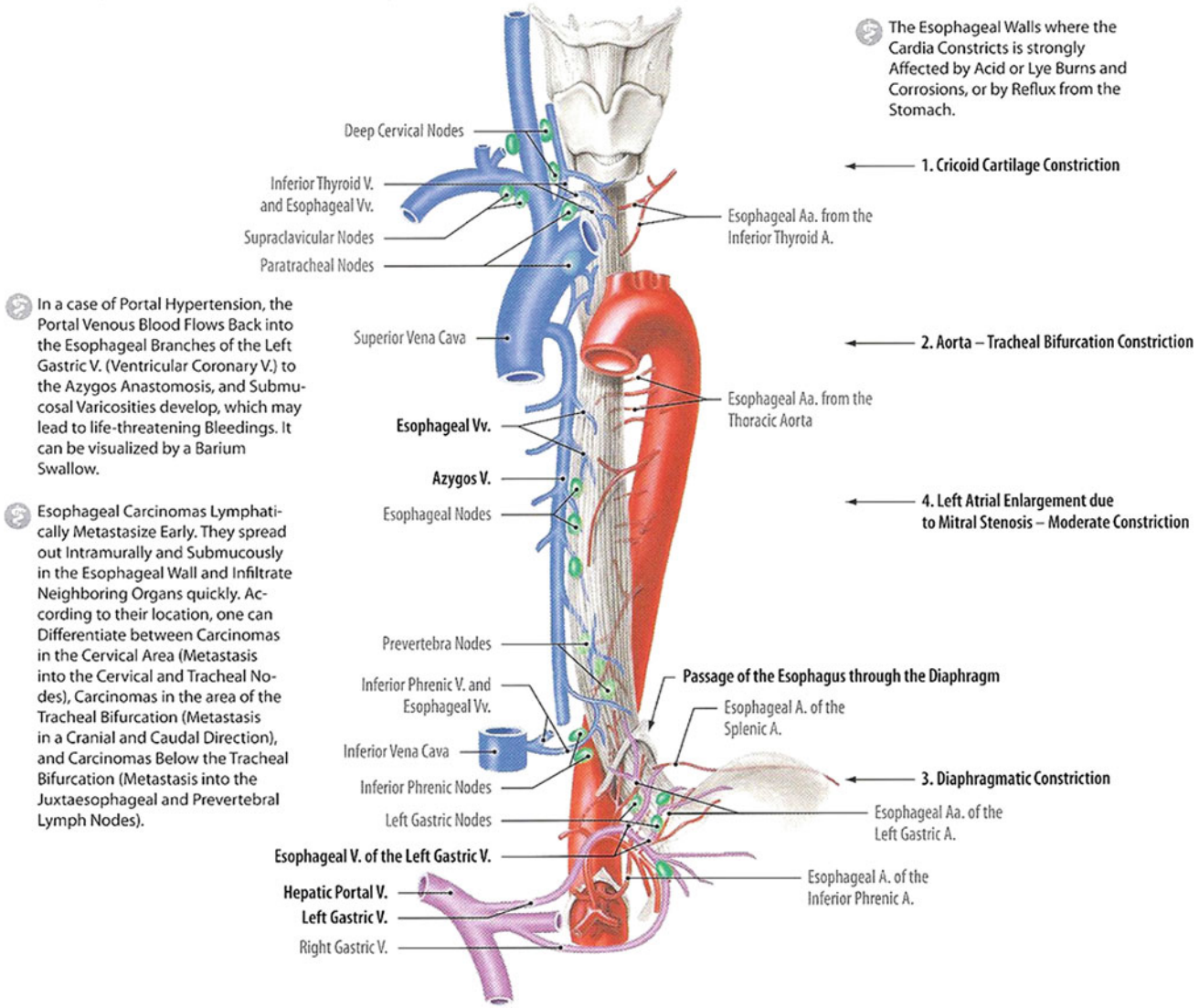

Fig. 2 Anatomy: Esophagus, Blood Supply, Lymphatic and Esophageal Sphincters: ventral view (with permission from Tillman 2007)

esophageal circumference, may improve dosimetric predictions of clinical toxicity outcomes after RT for lung cancer (Kahn et al. 2005), emphasizing the relevance of esophageal anatomy to RT planning.

2.2 Histology and the Functional Subunit

The esophageal wall contains the basic histological architecture characteristic of the gastrointestinal tract: mucosa, submucosa, two muscular layers (inner circular layer and outer longitudinal layer), and adventitia (Fig. 3a) (Rubin and Casarett 1968; Junqueira et al. 1094). It lacks serosa, a deficiency that is thought to increase the opportunity for radial extension of tumor from the esophageal wall into the periesophageal tissues. The clinical relevance, however, of the lack of serosal coverage is unclear; it is not known how much a thin serosa would protect against extramural extension for a tumor that has invaded through the muscular wall. The esophageal mucosa is composed of non-keratinized stratified squamous epithelium (Squier and Kremer 2001). The components of the esophagus may be characterized using Rubin and Casarett's classification of radiosensitivity, which is based on cellular reproductive and functional characteristics (Rubin and Casarett 1968). According to the Rubin and Casarett system, the inner germinal stratum of the esophageal epithelium contains vegetative (Group I) and differentiating (Group II) intermitotic cells, which are considered radiosensitive. The outer germinal stratum, adjacent to the esophageal lumen, is composed of fixed postmitotic cells (Group IV), which do not multiply and are considered radioresistant (Rubin and

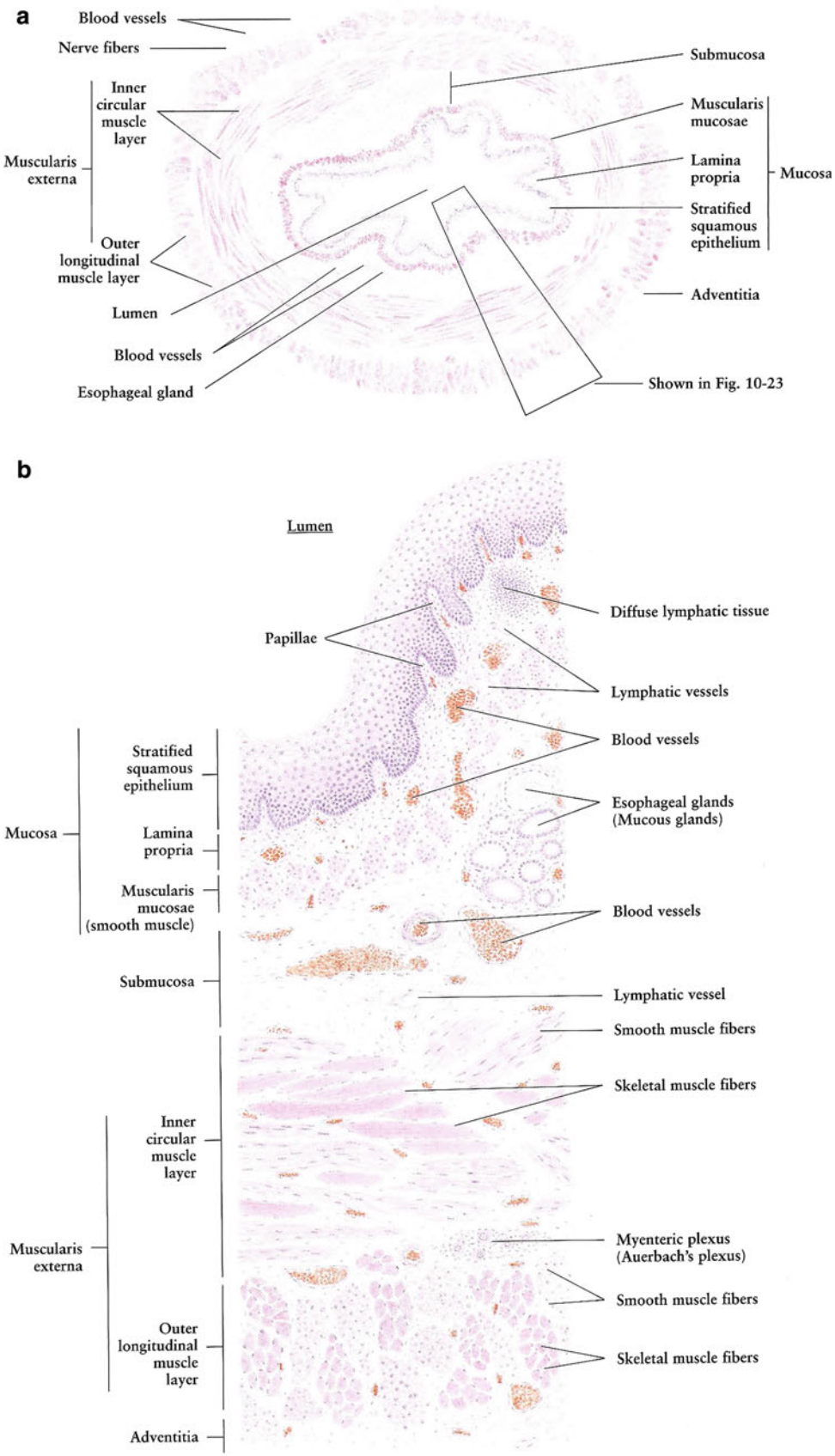

Fig. 3 **a** Histology: Esophagus cross section, very low magnification. **b** Histology: Esophagus cross section, low magnification (with permissions from Zhang 1999)

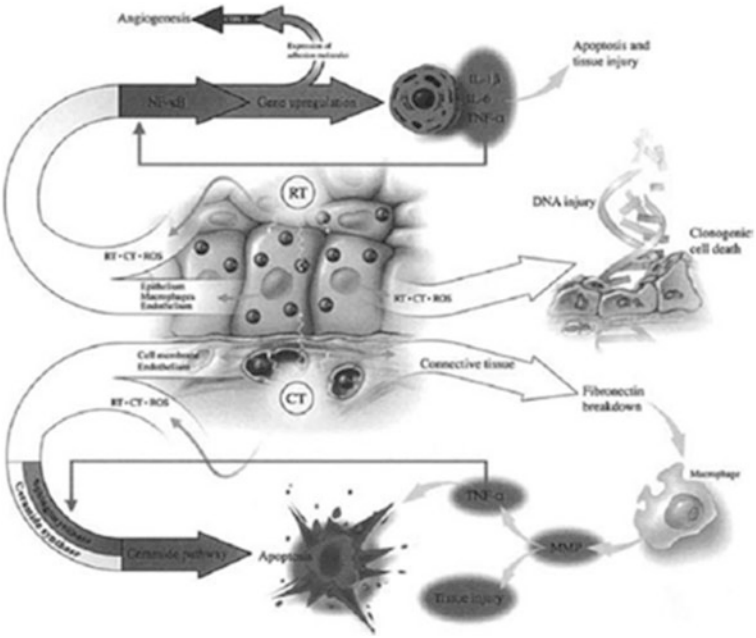

Fig. 4 Radiotherapy (RT) and chemotherapy (CT) generate ROS resulting in direct DNA injury as well as stimulation of secondary mediators leading to apoptosis. Other genes are also up regulated leading to angiogenesis. (Reprinted from Sonis ST et al. 2004; with permission)

Casarett 1968; Hall and Giaccia 2006). Although the mucosal epithelium is avascular, it receives nutrients by diffusion from capillaries contained in the lamina propria, which is also the site of venous and lymphatic drainage (Rubin and Casarett 1968). Small mucous glands, whose functions are to protect mucosa and facilitate food transport, are present within the submucosa throughout the esophagus ("esophageal glands") and within the lamina propria in the distal esophagus near the stomach ("esophageal cardiac glands") (Junqueira et al. 1094). The muscular components of the esophageal wall, governed by both reflexive and autonomic nervous system mechanisms, are responsible for the peristalsis and sphincter regulation necessary for food transport. When considered as an organ using the Michalowski classification, the esophageal radiosensitivity is in agreement with hierarchical (H-type) tissues, which are early-responding cell lines (Michalowski and Hornsey 1986; Wheldon et al. 1982). The esophagus is comprised of structurally undefined functional subunits (FSUs), in contrast to the lung, which implies that repopulation after RT may result from the migration of clonogenic cells from one FSU to another (Hall and Giaccia 2006) (Fig. 3a, b).

3 Physiology, Biology, and Pathophysiology

A series of molecular mechanisms (Fig. 4) lead to the clinical RT-induced esophageal injury that has been often divided into two phases: the acute phase, associated with mucosal damage, and the late phase, associated with harm to the muscular wall (Fig. 5a, b). There is significant overlap between the two phases, and the strong predictive association between the severity of acute esophagitis and the development of late toxicity (Fig. 5c) (Ahn et al. 2005) suggests a causative relationship. In their 1968 text, Rubin and Casarett wrote, "The radiation-induced responses and lesions in the esophagus and stomach are basically similar in principle and mechanism to those which have been described for the skin and oropharyngeal mucosa" (Rubin and Casarett 1968). This early statement has been confirmed by subsequent literature describing the pathophysiology of the acute and late effects of esophageal irradiation, both in animal models and in humans (Seaman and Ackerman 1957; Engelstad 1934; Rubin and Casarett 1968; Northway et al. 1979; Phillips and Margolis 1972; Phillips and Ross 1974; Novak et al. 1979; Gilette et al. 1998) (Figs. 4 and 5a, b, c).

3.1 Physiology

The principal function of the esophagus is to deliver food from the pharynx to the stomach, and this rapid transfer requires complex coordination to ensure proper timing and anterograde direction. Although swallowing is initiated voluntarily, esophageal motility is largely under automatic control that consists of input from the brainstem and involvement of vagal parasympathetic, efferent nerve fibers and the enteric nervous system. The upper and lower esophageal sphincters must be relaxed at the appropriate time during swallowing, as these structures are closed at rest in order to prevent retrograde movement of digestive contents. Esophageal peristalsis is activated by the stimulatory effects of distention on mechanoreceptors, triggering a

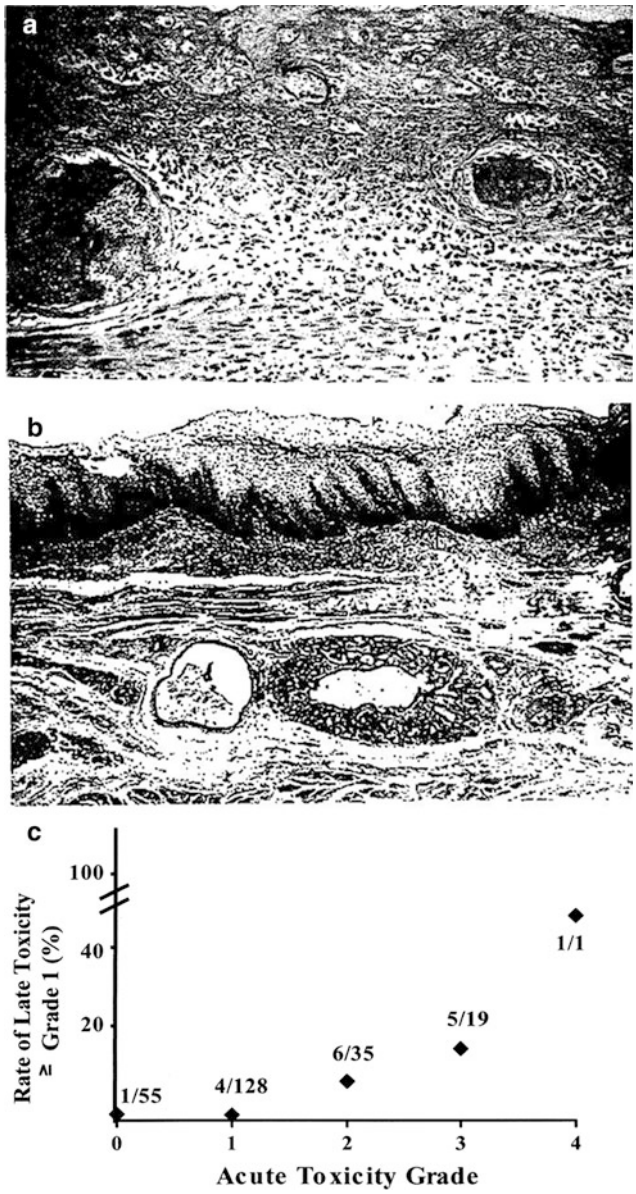

Fig. 5 **a** Acute: One-year earlier, this patients received 30 Gy to the esophagus for metastatic bone malignancy from breast carcinoma, and 20 days before death she received 30 Gy for sternal and cervical spine metastases. This photomicrograph shows acute necrosis of the esophageal mucosa (*upper*) and intense submucosal inflammation in which two thin-walled vessels are seen containing fibrin thrombi. High power. **b** Fibrosis: Postradiation esophageal squamous epithelial hyperplasia and parakeratosis are seen over submucosal fibrosis, distorted and atrophic esophageal mucosal glands, and several small blood vessels with fibrosed walls and narrow lumens. Low power. (with permission from Fajardo 2001). **c** The severity of acute esophagitis is associated with incidence of late esophageal toxicity for NSCLC patients receiving RT *With permission* (Ahn et al. 2005)

vagovagal reflex that is responsive to food bolus volume and temperature (Barrett 2307). The delivery of a food bolus from the oropharynx to the stomach is a complex, coordinated process dependent upon adequate function of multiple autonomic and reflexive processes.

Disruption of esophageal motility is a frequent occurrence after RT. Goldstein et al. used esophagograms to study RT-induced changes. They found motility disorders to be the most common RT-induced problem and reported loss of peristalsis in the irradiation portion of the esophagus, with adjacent areas of rhythmic, but uncoordinated, contraction after an average 50 Gy of RT (Goldstein et al. 1975). Lepke and Libshitz observed similar dysmotility after RT, which they described as developing 4–12 weeks after RT (Lepke and Libshitz 1983). Technetium scintigraphy has also been used to visualize temporarily prolonged esophageal transit times in most patients after RT doses higher than 40 Gy (Lamanna et al. 1985). Impaired esophageal motility may also be observed by manometry (Kaplinsky et al. 1991). The impaired motility may be related to neuronal and/or muscular injury (Coia et al. 1995; Kaplinsky et al. 1991). Due to the tubular geometry of the esophagus, the development of mural thickening or stricture may severely impair the transit of food (Coia et al. 1995; Fajardo et al. 2001). Esophageal dysmotility and stricture is a serious late morbidity for patients after RT.

3.2 Biology (Molecular Mechanisms of RT-Induced Esophageal Injury)

Although the pathologic response of the esophagus to radiation injury has been characterized (Rubin and Casarett 1968), the molecular events responsible for the late effects of radiotherapy are complex and not resolved fully (Stone et al. 2003; Brush et al. 2007; Denham and Hauer-Jensen 2002). The response of normal tissue to RT involves a sequence of steps intended to promote healing, including inflammation, epithelial proliferation, collagen deposition, and remodeling (Denham and Hauer-Jensen 2002). When compared to wound healing after non-RT tissue damage, the injury response is often dysregulated after RT. Whereas the tissue-damage response functions to promote successful wound healing in response to other insults, this response contributes to chronic damage after RT. It is possible that cytokine-mediated damage in response to RT is due to changes in the microenvironment, the influence of cell death on nearby tissues, or DNA damage (Brush et al. 2007). Pro-inflammatory mediators, such as chemokines and cytokines, are expressed in tissues, including the esophagus after RT (Vujaskovic et al. 2007; Brush et al. 2007). The significance of oxidative stress and integrin $\alpha v6\beta$-mediated stimulation of TGF-β is supported by preclinical work with amifostine in a rat model. Vujaskovic et al. showed that amifostine reduced acute and late pathologic changes after RT with associated decreases in oxidative stress and levels of integrin$\alpha v6\beta$ and TGF-β (Vujaskovic et al. 2007). It has been shown that manganese superoxide dismutase gene therapy

can ameliorate acute and late esophageal injury via modulation of RT-induced elevation of inflammatory cytokines (Epperly et al. 2001). These animal model studies of radioprotective agents for esophageal injury emphasize the relevance of pro-inflammatory mechanisms in the development of late effects after irradiation of the esophagus. In summary, the late clinical effects of esophageal irradiation appear to be initiated by oxidative stress, mediated by cytokines, and guided by end-pathway damage to the muscle wall and submucosal thickening (Fig. 4).

3.3 Pathophysiology (The Radiation Response of the Esophagus)

3.3.1 Pathologic Response to Radiation Therapy

The acute effects of RT on the esophagus are related primarily to damage of the basal epithelial layer (Phillips and Ross 1974), and late effects are associated with RT-induced changes in the submucosa and muscular tissue of the esophageal wall (Northway et al. 1979; Fajardo et al. 2001). The pathologic changes observed during RT-induced acute esophagitis are similar to findings in acute dermatitis or mucositis (Rubin and Casarett 1968; Fajardo et al. 2001). During the course of therapy, RT limits the proliferation of the basal cell layer, with degenerative changes and failure of cellular renewal. Characteristic morphologic changes include epithelial swelling, focal necrosis of the basal cell layer, and nuclear hyperchromasia. The basal cell layer may be considered the target for acute RT-induced esophagitis, as this is the region of rapid mitosis and multiplication (Fajardo et al. 2001). Dilatation of capillaries is also observed early in the course, with erythema and increased interstitial edema. The destruction of the basal cell layer results in mucosal thinning or ulceration and may culminate in esophageal mucosal denudation (Rubin and Casarett 1968; Squier and Kremer 2001; Fajardo et al. 2001) (Fig. 5a, b and c).

Although regeneration of the esophageal mucosal epithelium starts during RT, this period may also include the start of progression toward fibrosis of the esophageal wall. During the subacute period after RT, subepithelial fibrosis may become apparent. The chronic period may be viewed as a continual progression of pathologic changes observed during the subacute period, with increased thickening of the esophageal wall (Rubin and Casarett 1968; Fajardo L-G 1982). Stricture is the most common delayed sequela of esophageal irradiation (Coia et al. 1995; Fajardo et al. 2001; Fajardo L-G 1982). Morphologic findings at the stricture site include severe submucosal fibrosis, atrophic epithelial layer, and telangiectatic vessels within the lamina propria (Fajardo et al. 2001). Esophageal ulcers may develop as a delayed toxicity after RT and are usually solitary, round lesions with well-defined, raised borders. Ulceration typically involves the lamina propria and/or submucosa, but the muscularis propria is occasionally eroded. Microscopically, late esophageal ulcers characteristically contain a base of necrotic tissue with acute granulation tissue underneath, as well as chronic granulation tissue below. Chronic ulceration is associated with extensive fibrosis, and esophageal ulcers are often thought to be due to RT-induced vascular insufficiency (Fajardo et al. 2001).

Esophageal motility disorders are a significant feature of late esophagitis. Dysmotility after RT has also been attributed to neuronal injury, based upon findings of manometry and dynamic isotope studies (Kaplinsky et al. 1991). However, morphologic evidence of neuronal damage is *not* commonly found in pathologic specimens after RT (Fajardo et al. 2001), thus suggesting an alternative mechanism. Nevertheless, it is possible that there are neuronal effects that without detectable abnormalities being seen on light microscopy (Fajardo et al. 2001). It has also been suggested that motility changes after RT may be related to muscularis propria damage (Seaman and Ackerman 1957).

3.3.2 Insights from Animal Models

Animal models of esophageal injury after RT have provided important clues to the pathogenesis of acute and chronic esophagitis, beginning in 1921 with the experiments by Lacassagne involving radium exposure of the rabbit esophagus (Lacassagne 1921). After a single, large-dose RT fraction, characteristic pathologic changes in the mucosa occur that correspond to acute effects (Engelstad 1934; Phillips and Ross 1974; Lacassagne 1921). Phillips et al., using a mouse model, observed vacuolization and absence of mitoses within the basal level and thinning of the squamous surface by the third day after RT, followed by areas of basal cell proliferation during the second week, and regeneration of the mucosal lining by the end of the third week (Phillips and Ross 1974). These findings have been confirmed by pathologic studies of acute esophagitis in humans (Seaman and Ackerman 1957; Mascarenhas et al. 1989). In a more recent study, designed to evaluate amifostine in a rat model of RT injury, Vujaskovic et al. administered a single fraction of 9 Gy and observed increased esophageal mucosal thickness within 5 days of irradiation. They reported decreased acute pathologic radiation response in rats receiving amifostine (Vujaskovic et al. 2007).

Animal models have also contributed to our understanding of late pathologic changes of the esophagus after RT. Because the opossum esophagus is comprised of a muscular wall with architecture similar to the human esophagus, this has been used as a model of late RT-induced pathologic change. After a single dose of 22.5 Gy to the opossum, Northway et al. reported necrosis of the muscularis propria

and deep musculature, as well as the presence of inflammatory cells surrounding the mesenteric plexus (Northway et al. 1979). These findings have been confirmed in humans (Fajardo et al. 2001; Fajardo L-G 1982; Papazian et al. 1983) and implicate the muscular component of the esophagus as the relevant target for late esophageal injury after RT. Northway et al. also observed peristalsis abnormalities and impaired esophageal sphincter function in opossum 1–8 months after RT (Northway et al. 1979).

Michalowski and Hornsey demonstrated a dose/length effect for ulcerative esophagitis after RT, reporting that the mean effective dose for single-fraction RT decreased only slightly, from 24.5 to 22 Gy, when length of irradiated esophagus was doubled in a mouse model (Michalowski and Hornsey 1986). This weak volume effect suggests that the esophagus is a "parallel" organ. In a recent study of RT-induced esophageal injury in rodents, a single fraction of 9 Gy resulted in damage to the tunica muscularis, higher submucosal deposition of collagen, and increased presence of macrophages. These findings were associated with oxidative stress and elevation of TGF-β levels (Vujaskovic et al. 2007).

4 Clinical Syndromes (Endpoints)

For patients receiving RT for thoracic malignancies, acute esophagitis is a common treatment-related toxicity. After 2 weeks of daily standard irradiation to portals that encompass the esophagus, dysphagia, and odynophagia are commonly reported. Morbidity may be severe enough to create treatment interruptions due to consequential dehydration and weight loss. Rates of severe ($\geq$ grade 3) acute esophagitis increased from 1 % with sequential chemotherapy and RT for NSCLC (Byhardt et al. 1998; Dillman et al. 1990) to 15–46 % with concurrent chemoradiation treatment strategies (Byhardt et al. 1998; Curran et al. 2000; Choy et al. 1998) (Fig. 6, Tables 1 and 2).

Late esophagitis, which is less commonly observed than acute esophagitis, develops in <10 % of NSCLC patients receiving contemporary chemoradiotherapy (Byhardt et al. 1998). It is possible that late esophagitis will increase in frequency as hypofractionated RT becomes more prevalent for NSCLC treatment (Onimaru et al. 2003; Timmerman et al. 2006). Rates of late esophagitis are high among patients who receive large fractions of intraluminal brachytherapy in addition to external beam RT and chemotherapy, with a 12–17 % rate of fistulas and 24 % rate of strictures (Gaspar et al. 1997; Sharma et al. 2000). The late effects of RT on the esophagus generally manifest as dysphagia and odynophagia, which may be associated with stricture formation due to fibrosis of the muscular wall. Defects in esophageal motility are characteristic of late RT

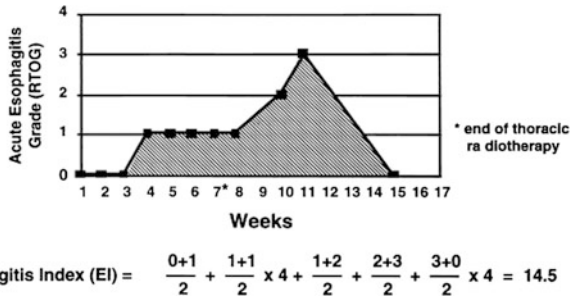

Fig. 6 Esophagitis Index is a measure of toxicity that uses an area-under-the-curve calculation to quantify the esophagitis grade over time (with permission from Werner-Wasik et al. 2000, 2002)

damage and may be observed on barium swallow (Lepke and Libshitz 1983; Goldstein et al. 1975), scintigraphy (Lamanna et al. 1985), or manometry (Coia et al. 1995; Kaplinsky et al. 1991). Strictures may develop 3 or more months after RT, with a median time of $\approx$6 months (O'Rourke et al. 1988). Barium swallow may demonstrate esophageal stricture, and endoscopy allows both visualization and potential for dilatation (Wax et al. 1997; Swaroop et al. 1994; Siersema 2008). In order to evaluate treatment-related esophagitis, several approaches have been utilized for standardized assessment of both acute and late findings.

The RTOG/EORTC developed the Subjective Objective Management and Analytic (SOMA) scale was published in 1995, as a product of the Late Effects of Normal Tissues (LENT) Conference, and provides a standard, consensus-based instrument for scoring late esophagitis (No Authors Listed 1995) (Table 1a and b).

The current version of the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) for Adverse Events (AE), CTC version 4.0 (CTCAEv4.0), and the immediately prior version (CTCAEv3.0), differ from previous versions by relying more strongly upon patient symptoms. Prior criteria, including the RTOG scale and the CTCv2.0, were based more strongly upon the clinician's assessment of the patient's symptoms, dietary changes, analgesic requirement, weight loss, and need for IV fluids and/or non-oral nutritional supplementation. The CTCAE v4.0 criteria, which are designed for both acute and late effects can be found online. Late effects of esophageal RT may also be scored using the CTCAEv4.0 GI stricture criteria. The CTCAEv4.0 is currently considered the standard instrument for evaluating both acute and chronic esophagitis. The scale is meant to incorporate symptoms due to gastroesophageal reflux, but esophagitis symptoms attributable to infection (most commonly candidiasis) must be excluded when determining a score. Toxicity scores apply to only one point in time, without information regarding the duration of suffering. For patients receiving CRT for thoracic malignancies, symptoms of acute esophagitis develop after the second week of RT

Table 1 Late effect of normal tissues for the esophagus. LENT SOMA

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Dysphagia	Difficulty eating solid foods	Difficulty eating soft foods	Can take liquids only	Totally unable to swallow
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Objective				
Weight loss from time of treatment	≥5–10 %	>10–20 %	>20–30 %	>30 %
Stricture	>2/3 normal diameter with dilatation	>1/3–2/3 normal diameter with dilatation	<1/3 normal diameter	Complete obstruction
Ulceration	Superficial ≤1 cm^2	Superficial >1 cm^2	Deep ulcer	Perforation, fistulae
Bleeding (melena or hematemesis)	Occult	Occasional, normal Hb	Intermittent, 10–20 % decrease in Hb	Persistent, >20 % decrease in Hb
Anemia		Fatigue	Exhaustion	
Management				
Dysphagia/Stricture	Diet modification or antacids	Diet modification and occasional dilatation	Temporary NG tube or regular dilatation	Parenteral feeding, prosthesis, gastrostomy or permanent NG tube
Weight loss	Diet modification	Nutritional supplements	Tube feeding	Surgical bypass, PEG
Pain/Ulceration	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention
Analytic				
Barium esophagram	Assessment of esophageal lumen, stricture, dilatation			
Endoscopy	Assessment of esophageal lumen, mucosal integrity, ulceration			
CT	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
MRI	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
Ultrasonography	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
Mobility esophagram	Assessment of motility of bolus and peristalsis			
Electromyogram	Assessment of motility of bolus and peristalsis			

and increase to peak severity during the treatment course (Wei et al. 2006). Acute esophagitis symptoms commonly resolve within 2–3 weeks after RT, but late symptoms of esophageal damage may develop 3–8 months afterwards. The most common presentation of late esophagitis is solid food dysphagia due to focal esophageal stricture. In the study by Ahn et al., the median time to onset of late esophageal toxicity was 5 months (maximum, 40 months) (Ahn et al. 2005). In addition to stricture formation, deficits in esophageal motility are also observed frequently, with occurrence typically within 1–3 months after RT alone or within 1 week from the start of concurrent CRT (Coia et al. 1995; Goldstein et al. 1975).

It is challenging to score the severity of acute esophagitis as the severity of symptoms varies over time. Is 1 day of severe symptoms 'better or worse' than a week of moderate symptoms? The Esophagitis Index has been suggested as a reasonable manner to generate a single quantity (area under the curve) to reflect the severity and duration of symptoms (Fig. 6) (Werner-Wasik et al. 2000, 2002). The potential advantage of this approach is that it quantifies the degree of toxicity over time, but its calculation requires the collection of toxicity scores at specific points in time (Werner-Wasik et al. 2000).

A variety of endpoints that can be used to describe late esophageal injury are presented in Table 2.

4.1 Detection: Endoscopy

In the assessment of RT-induced esophagitis, endoscopy, and imaging studies provide important information. During the acute phase, endoscopic findings of esophagitis include mucosal erythema, erosion or ulceration (Mascarenhas et al.

Table 2 Endpoints for late esophageal toxicity may be broadly divided into categories of subclinical versus clinical, and focal versus global, with corresponding examples as shown

	Focal	Global
Subclinical	1. Endoscopically detected mucosal changes (e.g., telangiectasias, ulcer, bleeding)	1. Asymptomatic dysmotility on swallowing study
	2. CT-defined thickening	2. Weight loss
	3. Stricture observed on endoscopy or swallowing study	
Clinical	1. Bleeding/ulceration	1. Dysphagia
	2. Stricture	2. Weight loss

1989; Hirota et al. 2001). Hirota et al. performed endoscopic examination during or soon after RT for patients with NSCLC, most treated with concurrent chemoradiotherapy, and found a good correlation between endoscopy-measured esophagitis grade and RTOG toxicity score (rank correlation coefficient = 0.428, $p < 0.0001$) (Hirota et al. 2001). Endoscopic findings of acute esophagitis from Hirota et al., along with the accompanying score, are displayed in Fig. 7a (Hirota et al. 2001). The agreement between endoscopic appearance of the esophagus during the acute phase and the reported RTOG toxicity score is supportive of the scoring system's validity (Werner-Wasik et al. 2004). In some instances, however, endoscopic findings of esophagitis may not be confirmed by histology when biopsied (Mascarenhas et al. 1989), producing some false-positive results. Although endoscopy may be useful in the management of esophagitis, endoscopic findings are not a primary determinant of toxicity grade in standard practice. The current CTCAE criteria emphasize patient symptoms of esophagitis, but the description of CTCAEv4.0 Grade 1 esophagitis does include asymptomatic findings on endoscopy or radiography.

Although most endoscopic findings of acute esophagitis resolve without the development of chronic effects, some damage that is evident during the acute period may progress to late esophagitis (Hirota et al. 2001). Endoscopy permits the visualization of strictures that occur as a late effect after RT (Fig. 7b) and provides an opportunity for dilatation by bougie or balloon, the standard therapeutic approach for post-RT benign esophageal stricture (Siersema 2008; Raymondi et al. 2008). Many strictures require more than one dilatation, with a reported median number of 2.5 dilatations delivered after a median time of 5 months between procedures (O'Rourke et al. 1988). The likelihood of requiring more than one dilatation for esophageal stricture is higher for complex versus simple strictures, which may be

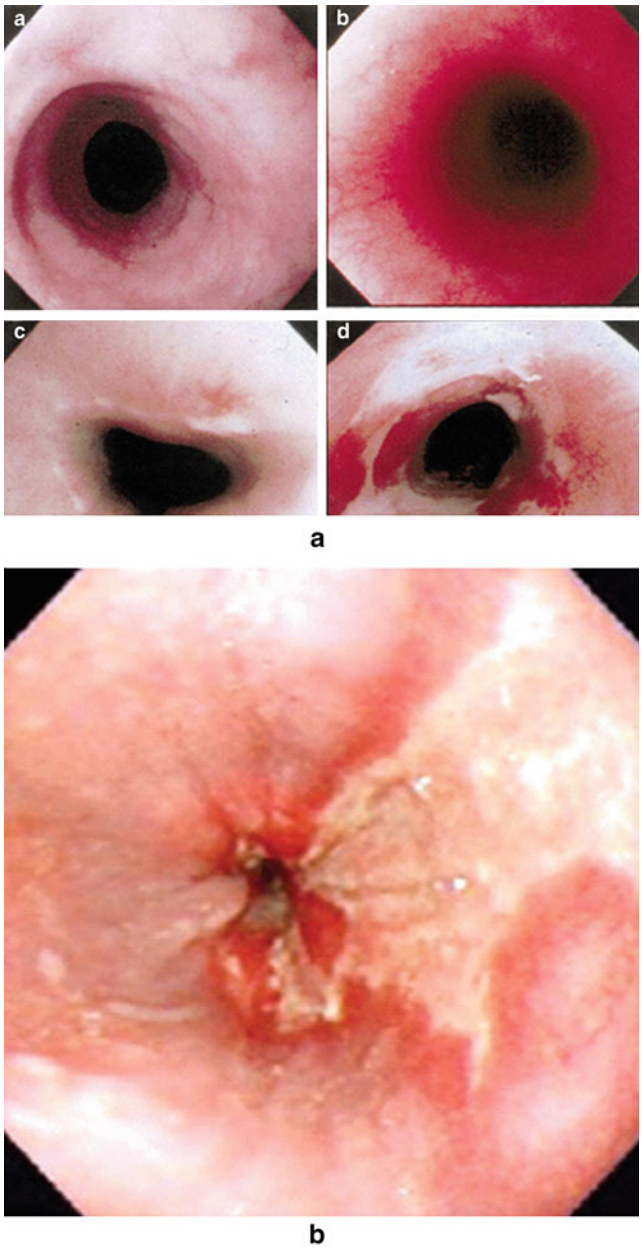

Fig. 7 Endoscopically assessed score used by Hirota et al. 2001 **a** Grade 0 for normal mucosa. **b** Grade 1 for mucosa with erythema. **c** Grade 2 for mucosa with erosion. **d** Grade 3 for mucosa with thickly-coated ulcer *Adapted with permission.* Endoscopic appearance of esophageal stricture as a late effect after RT *With permission*

determined by endoscopy. Simple strictures are short, straight, and wide enough to permit passage of a standard-diameter endoscope. Longer (>2 cm), tortuous strictures, through which a standard endoscope may not be advanced, are categorized as complex and are a challenge for endoscopic visualization and dilatation (Siersema 2008; Giever et al. 2008; Lew and Kochman 2002). Endoscopic dilatation

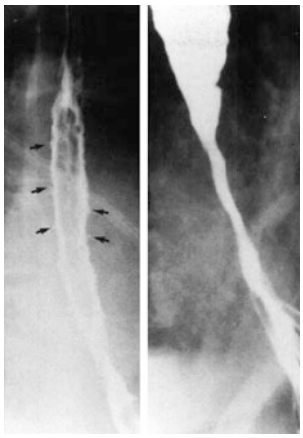

Fig. 8 Double-contrast esophagograms show the presence of multiple, small ulcers in the acute period (*left*) and the development of stricture at the site of radiation injury as a late effect (*right*). *With permission* (Collazzo et al. 1997)

is discussed in further detail below in Sect. 8.2 along with other aspects of management of RT-related esophagitis.

4.2 Diagnosis: Imaging (Radiology)

Radiological studies may complement endoscopy and clinical evaluation in the assessment of esophagitis after RT. The esophagogram may be used to demonstrate esophageal stricture and dysmotility after RT (Lepke and Libshitz 1983; Goldstein et al. 1975; Ellenhorn et al. 1993). Goldstein et al. observed deficiencies in peristaltic waves on esophagograms in patients who received mediastinal RT (Goldstein et al. 1975). Double-contrast esophagograms may demonstrate the presence of multiple ulcers or granular mucosa as an acute effect of RT, as well as stricture as a late effect after RT, as shown in Fig. 8 (Collazzo et al. 1997). Manometry and technetium transit scintigraphy may also be used to demonstrate abnormal esophageal motility after RT (Kaplinsky et al. 1991; Lamanna et al. 1985). Findings on esophageal manometry after RT that support the diagnosis of esophagitis include low-amplitude, weakened or absent peristaltic contractions (Collazzo et al. 1997). Among 25 patients who received RT, Lamanna et al. observed protracted transit times using technetium transit scintigraphy in nearly all patients after more than 40 Gy, and some patients displayed transit abnormalities at >2 months after RT (Lamanna et al. 1985). During the initial evaluation of esophageal stricture after RT, esophagography may be helpful in defining the location and extent of stricture. Other modalities, such as manometry or scintigraphy, may provide complementary information regarding esophageal motility. In appropriate cases, endoscopy would then be performed, with biopsy or dilatation as appropriate. In summary, radiography can demonstrate RT-induced esophageal injury and complements endoscopy in the evaluation of acute and late esophagitis.

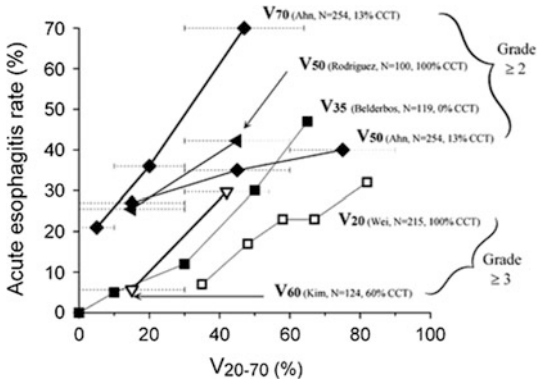

Fig. 9 The QUANTEC review analyzed the associations among dose-volume parameters and risk of acute toxicity. Incidence of acute esophagitis (y-axis) versus Vx (volume receiving more than x Gy). x-Axis values estimated according to range of doses reported. Each curve annotated as follows: Vdose (investigator, number of patients, percentage with concurrent chemotherapy (CCT). Dashed horizontal lines reflect dose ranges ascribed to each data point. Upper x-axis range of greatest data point for V50, are indefinite according to data (*light-gray dotted bars*). Solid and open symbols represent reported rates of Grade 2 or greater acute esophagitis and Grade 3 or greater acute esophagitis, respectively. Thicker and thinner solid lines represent higher and lower doses of Vx, respectively (i.e., thicker line for V70 and thinner line for V20) *Reproduced with permission* (Werner-Wasik et al. 2010)

5 Radiation Tolerance (Predicting Radiation-Induced Esophageal Injury)

Rates of late esophageal complications after RT have been associated with RT dose, with evidence of a relatively-steep dose–response curve (Morichau-Beauchant et al. 1983; Phillips and Margolis 1972). Analyses of associations between dosimetric parameters and late esophagitis have provided insight into dose-volume aspects of delayed esophageal injury after RT (Ahn et al. 2005; Qiao et al. 2005; Kahn et al. 2005; Maguire et al. 1999; Rose et al. 2008). In their seminal publication of estimated normal tissue dose limits, Rubin and Emami, Lymen, et al. suggested that the doses for whole-esophagus RT that result in a 5 and a 50 % rate of stricture or perforation at 5 years are 55 and 68 Gy, respectively, in standard fractionation (Emami et al. 1991). In the following section, we review factors associated with risk of radiation-induced esophageal injury (Fig. 9, Tables 3 and 4).

5.1 Dose Time Fractionation (Dosimetric Parameters)

Although threshold doses for RT-induced esophageal injury had been described earlier (Roswit 1974), Emami et al.

Table 3 Normal tissue tolerance estimates for esophagus, proposed by Emami et al. based upon clinical experience and review of the literature. TD5/5 and TD50/5 represent the dose that results in 5 risk and 50 % risk, respectively, for the selected endpoint of clinical esophageal stricture or perforation at 5 years

Risk	Estimated tolerance doses for esophageal irradiation			Endpoint
	1/3 Volume	2/3 Volume	3/3 Volume	
TD5/5	6000	5800	5500	Clinical stricture/perforation
TD50/5	7200	7000	6800	Clinical stricture/perforation

From Emami et al. (1991) with permission

Table 4 Example dosimetric factors that have been associated with late esophagitis in the medical literature

Author	Years	N	Dosimetric parameter
Maguire et al. (1999)	1999	91	Volume tx >50 Gy
			Surface area tx >50 Gy
			Length of 100 % circumference tx >50 Gy
			Length of 100 % circumference tx >60 Gy
			Maximum % circumference tx >80 Gy
Ahn et al. (2005)	2005	196	Length of 75 % circumference tx ≥70 Gy
			Length of 100 % circumference tx ≥50 Gy
			Length of 100 % circumference tx ≥55 Gy
			Maximal percentage of circumference tx ≥70 Gy
Kahn et al. (2005)	2005	236	Volume tx ≥60 Gy
Qiao et al. (2005)	2005	208	Mean esophageal dose ≥40 Gy
			Maximal dose point ≥60 Gy

provided the first dose-volume recommendations for esophagitis, using the endpoint of clinical stricture or perforation at 5 years, based upon the authors' clinical experience and review of the literature (Emami et al. 1991) (Table 3). Subsequently, the widespread availability of three-dimensional RT planning has provided informative data for the prediction of esophagitis. The length of irradiated esophagus has been reported to impact esophagitis, as suggested by animal studies that demonstrated that increasing the length of irradiated esophagus lowers the mean effective dose for ulcerative esophagitis (Michalowski and Hornsey 1986). However, findings in clinical studies are contradictory and do not confirm the presence of such a relationship between length or irradiation esophagus and esophagitis in NSCLC patients (Ball et al. 1995; Werner-Wasik et al. 2000; Werner-Wasik et al. 2004; Choy et al. 1999; Langer 1999). Dosimetric parameters have been associated with both acute and late esophagitis in published reports, and are reviewed below (see Tables 3, 4 and 5).

Direct associations between dosimetric factors and chronic esophagitis after RT have been described by several groups (Ahn et al. 2005; Qiao et al. 2005; Kahn et al. 2005; Maguire et al. 1999). Qiao et al. evaluated the influence of clinical and dosimetric factors upon the occurrence of esophageal injury, combining acute and late esophagitis in their analysis. In their cohort of 208 consecutive patients who received RT for NSCLC, only concurrent chemotherapy and maximal organ point dose ≥60 Gy were significant predictors of esophagitis (acute or chronic) in multivariate analysis. Late esophagitis was not evaluated separately in this paper to determine its association with the parameters studied (Qiao et al. 2005).

Investigators from the Duke University Medical Center have provided insight into the associations among clinical and dosimetric parameters and the incidence of late esophageal toxicity after RT. They also tried to consider the spatial distribution of dose to the esophagus (i.e., its longitudinal and circumferential character). The following three studies summarize their findings (Ahn et al. 2005; Kahn et al. 2005; Maguire et al. 1999). Maguire et al. evaluated the associations among incidence of late toxicity with the esophageal volume or surface area exposed to RT doses above 50, 60, and 70 Gy. In their series of NSCLC patients published in 1999, both the volume and the surface area of esophagus receiving >50 Gy (but not >60 or >70 Gy) were significant predictors of late esophageal toxicity. RT plans that delivered 50 Gy or higher to more than 32 % of the esophageal volume or surface area resulted in a threefold higher rate of late esophagitis (Maguire et al. 1999). The length of full-circumference esophageal irradiation was a significant predictor of late toxicity at a threshold dose of 50 Gy. Lengths >3.2 cm of full-circumference irradiated to beyond 50 Gy were associated with a

Table 5 Summary of large published series investigating treatment-related esophagitis in patients with non-small cell lung cancer *Reproduced with permission* (Werner-Wasik et al. 2010)

Series Institution (Author, Year)	Patient number	Prescription dose range [Median][a] in Gy (special fractionations)	% with CCT	Endpoint[b] (rate)	Univariate significant factors	Multivariate significant factors:
Duke (Maguire et al. 1999)	91	64-86 (Collazzo et al. 1997)[d] (64 % BID, 1.25−1.6 Gy/fx)	47	Acute grade ≥3 (Gr 3: 11 % Gr 4 and 5: 0 %)	None	None
				Any late:[d]18 % (Gr 1: 9 % Gr 2: 6 % Gr 3: 3 %)	V50; A50; Length of 100 % circumference >50 Gy	Gender; pre-RT dysphagia; V50; maximum % of circumference >80 Gy
Thomas Jefferson (Werner-Wasik et al. 2000)[d]	105	45–70 (Barrett 2307) (7 % BID)[f, g]	55	Acute Grade ≥3 (Gr 3: 12 % Gr 4: 1 %)	CCT; BID treatment; female gender	CCT; BID treatment
Wash Univ (Singh et al. 2003)	207	60–74 (Wei et al. 2006)[n]	25.6	Acute Grade ≥3 (Gr 3: 4.3 % Gr 4: 0.5 %)	CCT; Dmax ≥58 Gy; Mean Dose >34 Gy; Subcarinal nodes; Race	CCT; Dmax ≥58 Gy
				AND/OR[i]		
				Late Grade ≥3 (Gr 3: 4.8 % Gr 4: 0.5 % Gr 5: 0.5 %)[j]		
Wash Univ (Bradley et al. 2004)[k]	166	60–74 (Wei et al. 2006)[k]	24.7	Acute Grade ≥2 (Gr 2: 22.3 % Gr 3: 4.2 % Gr 4: 0.6 %)	CCT; aA range (aA5-aA70); aA55[m]; aV range (aV5-aV70); aV60[m]	CCT and aV60; CCT and aV60 and aV80; CCT and aA55; CCT and aA55 and aA80 "volume and area equally predictive"
Duke (Ahn et al. 2005)[n]	254	30–86 (Wax et al. 1997)[l] (39 % BID, 1.25−1.6 Gy/fx))	12.6	Acute Grade ≥3 (Gr 3: 8.7 % Gr 4: 0.4 %)	BID; nodal stage; pre-treatment dysphagia; Dmax; Mean dose; V50 Length of 50 %, 75 % or 100 % circumference ≥50 Gy; Max % circumference. ≥50, 60, 70 Gy	BID RT; nodal stage; pre-treatment dysphagia
				Any late[d] (Gr 2: 2 % Gr 3: 2 % Gr 4: 1 %)	Length with 75 % circ ≥70 Gy; Length with 100 % circ. ≥50, 55 Gy; Max % circ. ≥60−80 Gy	Prior acute toxicity dominates all dosimetric factors
NKI (Belderbos et al. 2005)	156	Group 1 (88 pts) 50−95 at 2.25/fx[o, g,o] Group 2 (68 pts) 66 at 2.75/fx [o, g]	23.7[q]	Acute Grade ≥2 (Gr 2: 20 % Gr 3: 6 % Gr 4: 0.6 %)	Lyman NTCP[r],V range (V20-V60); 35[m] % Length 100 % circumference ≥40 Gy or ≥66 Gy; Treatment group (column 3 of table); CCT worse than sequential C/RT or RT only; Sequential C/RT worse than RT alone; T Stage and Nodal stage; Age[s]	V35; CCT
Univ Michigan (Chapet et al. 2005)	101	65–103[o,g,p]	0	Acute Grade ≥2 (Gr 2: 13 % Gr 3: 3 %)	Nodal stage; V range (V40-V70); Dose- % volume range (D5-D60), D30[m];D1 cc, 2.5 cc, 5 cc	Lyman model NTCP with study-specific parameters
Goyang (Kim et al. 2005)	124	54−66 (Barrett 2307) [o,g]	60	Acute Grade ≥3–4 (G3: 12 % G4: 0.8 %)	CCT; V range (V58-V63); Dmax Lyman Model NTCP (Burman (24) parameters)	CCT; V60 (in pts with CCT)

(continued)

Table 5 (continued)

Series Institution (Author, Year)	Patient number	Prescription dose range [Median][a] in Gy (special fractionations)	% with CCT	Endpoint[b] (rate)	Univariate significant factors	Multivariate significant factors:
Harbin Univ., (Qiao et al. 2005)	208	60–72 (Wei et al. 2006)[h]	26	Acute Grade ≥3 (Gr 3: 5 % Gr 4:0.5 % Gr 5: 1 %) AND/OR[i] Late Grade ≥3 (Gr 3: 5 % Gr 4: 0.5 %)	CCT; Dmax ≥60 Gy; Mean dose ≥40 Gy; Subcarinal lymph nodes	CCT; Dmax ≥60 Gy
MDACC (Wei et al. 2006)	215	60–70 (Choy et al. 1998)[n] (16 % BID, 1.2 Gy/Fx)	100	Acute Grade ≥3[t] (Gr 3: 20 % Gr 4: 0.5 %)	aV range (aV15-V45); V range (V10-V45); Mean dose ≥34.5 Gy	V20
Barcelona (Rodriguez et al. 2009)	100	55–65 (Lamanna et al. 1985)	100	Acute Grade ≥1 Gr 2: 29 %Gr 3: 4 % Esophagitis Index[u]	V50–V55	n/a

Std Fx: five-daily fractions of 1.8–2.2 Gy/fraction per week, unless otherwise noted. *BID*: two fractions/day. *CCT*: concurrent chemotherapy
Dmax: maximum dose
Vdose (e.g., V20): relative volume receiving ≥ specified dose (e.g., ≥20 Gy). *Adose*: relative surface area receiving ≥ specified dose
aVdose, aA dose: absolute volume (V) or area (A) receiving ≥ specified dose
D#: Dose encompassing hottest # % of the esophagus. *D #cc*: Dose encompassing hottest #cc of esophagus
[a] All doses at standard fractionation 1.8–2.2 Gy/day, 5 days per week unless otherwise stated
[b] Unless otherwise specified, RTOG grading was used
RTOG Grade 2: Moderate dysphagia or odynophagia, requiring narcotic agents or liquid diet
RTOG Grade 3: Severe dysphagia or odynophagia with dehydration or weight loss, requiring nasogastric feeding
[c] Clinical calculations and prescriptions done without inhomogeneity correction. Doses for the study retrospectively corrected for inhomogeneity and are tabulated above
[d] Late complications based on fraction of patients assessable for late toxicity
[e] No 3D CRT but correlation with irradiated esophagus length as inferred from length of spine in field was investigated
[f] All the BID patients also had CCT
[g] Doses are fraction-size corrected using the LQ model and $\alpha/\beta = 10$ Gy
[h] Doses reported without tissue heterogeneity correction
[i] Acute and Late complications analyzed together
[j] Percent late complications from raw numbers (e.g. 4.8 % = 10 pts/207 pts)
[k] Same patients analyzed by El Naqa et al. (2006)
[l] Various treatment techniques and fractionation schedules used. Most common was standard fractionation for 45 Gy to the CTV with cone down to 66 Gy total to the GTV. The dose range quoted above is overall dose to isocenter, corrected for tissue heterogeneity
[m] Lowest p value
[n] Some patients analyzed by Ahn et al. (2005) were also analyzed by Maguire et al. (1999)
[o] Doses are heterogeneity corrected
[p] Esophagus constraint on treatment plan
[q] All CCT patients were in the 66 Gy group, a randomized trial of concurrent versus sequential chemotherapy; they were 54 % of that group but only 23.7 % of the total
[r] Found Lyman NTCP model parameters that gave visually good fit to data; significance not stated
[s] Not specified whether toxicity is more likely at older age
[t] Grading by institutional modification of RTOG
[u] See reference 123 for definition

threefold higher risk of late esophagitis. Similar findings were not observed at the higher dose levels, >60 Gy or >70 Gy. The administration of more than 80 Gy to any portion of the full esophageal circumference was also linked to a higher incidence of late esophagitis. In their multivariate analysis of clinical and dosimetric parameters, Maguire et al. found that significant predictors of late esophagitis were volume irradiated to >50 Gy (OR 1.10, $p = 0.02$) and maximum circumference treated to >80 Gy (OR 1.09, $p = 0.02$), as well as gender and pre-RT dysphagia (Maguire et al. 1999). This study suggested that a dose-volume effect exists for late toxicity of the esophagus after RT to a modest dose, 50 Gy, but that delayed damage may also develop after full-circumference irradiation to a higher dose, 80 Gy.

In their series of 254 NSCLC patients treated at Duke, Ahn et al. found a strong relationship between the occurrence and the severity of acute esophagitis and the subsequent development of late esophageal toxicity. In multivariate analysis of a multitude of clinical parameters, only the presence of grade 2 or worse, and grade 3 or worse, acute esophagitis were associated with late esophagitis. Seven-percent of patients developed late esophageal toxicity, and the severity of acute esophagitis was a significant predictor of late effects ($p < 0.0001$). Late esophagitis was observed in 2, 3, 17, 26, and 100 % of patients with Grade 0, 1, 2, 3, and 5 acute esophageal toxicity, as measured by the RTOG scoring criteria. Dosimetric parameters that were associated with the subsequent development of late esophagitis included length of 100 % organ circumference receiving ≥50 Gy ($p = 0.05$) and ≥55 Gy ($p = 0.05$), as well as maximum percentage of organ circumference receiving ≥60 Gy ($p = 0.03$), ≥70 Gy ($p = 0.01$), and ≥80 Gy ($p = 0.02$). The strong relationship observed in this study between the severity of acute esophageal toxicity and the incidence of late esophagitis may suggest a "consequential components" of late radiation effects, as suggested by the authors (Ahn et al. 2005).

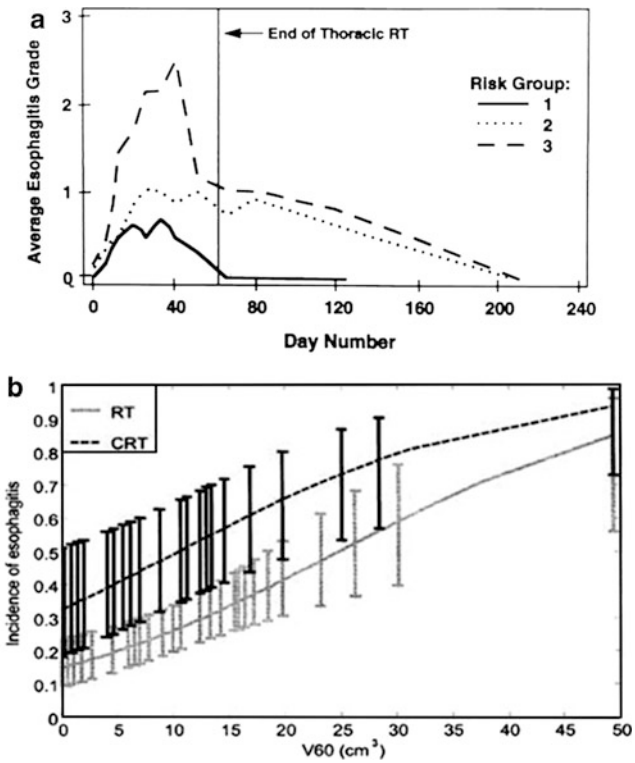

Fig. 10 The time course of acute and chronic esophagitis, as measured by the Esophagitis Index (Group 1 = standard thoracic RT alone or with induction chemotherapy. Group 2 = standard thoracic RT with concurrent chemotherapy. Group 3 = twice daily RT with concurrent chemotherapy) *With permission* (Werner-Wasik et al. 2000). Rate of ≥ grade 1 acute esophagitis as a function of the volume of esophagus receivinf ≥60 Gy (V_{60}). 95 % confidence intervels are reperesented by error bars; $p < 0.0004$ RT versus CRT. RT, radiation therapy or sequential chemotherapy followed by radiation theraphy; CRT, concurrent chemoradiation. (Reprinted from Elsiever, with permission Rubin et al. 1968)

5.2 Dose-Volume Histogram

Kahn et al. developed a "correction" method in order to produce esophageal Dose-Volume Histograms (DVHs) that reflect anatomic realities of the esophagus. That study illustrated that the circumference of the esophagus as segmented on serial axial CT images is usually variable, while the anatomic reality is that the majority of the esophagus has a fairly uniform circumference. The correction applied in that study forced a uniform "weight" to be given to each axial level in the Dose-Volume Histogram (DVH) computation. This was adopted to assess if the correlation of dosimetric factors with clinical outcomes could be improved by this "correction." It is important to emphasize that this was *not* a correction in the contouring/segmentation. Rather, it was an adjustment to the *weight* applied to each contour/segment used in computing the DVH. For 236 patients treated with RT for NSCLC, both corrected and uncorrected esophageal DVHs were analyzed with respect to both acute and late esophagitis. The correction method appeared to strengthen the associations between dosimetric parameters and the incidence of grade 1 or higher late esophagitis. Whereas the uncorrected volume of esophagus exposed to ≥60 Gy was not predictive of late esophagitis ($p = 0.091$), the correction method resulted in a significant relationship for this dosimetric factor ($p = 0.05$). A similar trend was observed for mean esophageal dose and volume receiving ≥50 Gy, but statistical significance was not observed. These findings suggest that anatomic correction of esophageal DVHs may improve the correlation between selected dosimetric parameters and observed toxicity (Kahn et al. 2005). This observation highlights a potential shortcoming of traditional DVHs, and illustrates that a modest "correction", to consider anatomic factors, may improve dose/volume/outcome correlations (Fig. 9 and Table 5).

The QUANTEC review summarized the findings from several studies that identified dosimetric and/or clinical factors as being associated with esophagitis (Table 5) (Werner-Wasik et al. 2010). The review by the QUANTEC group suggested that there is a dose response for acute esophagitis, with V70 > 20, V50 > 40, and V35 > 50 % associated with a >30 % rate of acute Grade ≥2 esophagitis. Metrics that consider the circumferential/longitudinal character of the dose (e.g., esophageal length receiving full circumference dose >40–66 Gy or 50–65 Gy) have also been reported to be associated with the risk of acute esophagitis. Other parameters including maximal esophagus dose, absolute area receiving 55 Gy (aA55) 80 Gy (aA80),

absolute volume (aV60 and aV80) have also been suggested to be predictive (Werner-Wasik et al. 2010).

Several general conclusions may be reached regarding analyses of the associations among dosimetric parameters and late esophagitis. There appears to be a dose-volume effect for the esophagus at approximately 50 Gy, as suggested by Maguire et al. and confirmed by Ahn and coworkers, who reported a predictive association between the length of 100 % circumference receiving ≥50 and ≥55 Gy the occurrence of grade 1 or greater late toxicity (Ahn et al. 2005; Maguire et al. 1999). In addition, the delivery of higher RT doses (more than 70 or 80 Gy) to an increasing portion of the organ circumference may predict for higher risk of grade 1 or higher late esophageal toxicity (Ahn et al. 2005; Maguire et al. 1999). The QUANTEC review analyzed the associations among dose-volume and clinical parameters for both acute and late toxicity (Table 5), and provided some dose-response data for acute toxicity (Fig. 9). Some of the dosimetric parameters that are associated specifically with increased risk of late esophagitis are summarized in Table 4.

5.2.1 Recommended Dose/Volume Constraints

In 1991, Emami, Lymen and others published consensus dose/volume recommendations for the tolerance of the esophagus to irradiation, using stricture and perforation as the endpoint (Table 3) (Emami et al. 1991). Although there has been a proliferation of published dose/volume guidelines for esophageal irradiation, the wide range of reported parameters and variety of clinical protocols (e.g., fractionation and chemotherapy) precludes the identification of an optimal dose/volume threshold. As a general rule of thumb during RT planning, it is essential that the maximum dose to the esophagus does not exceed the prescription dose. This consideration may be particularly relevant for radiation oncologists who plan to utilize IMRT or hypofractionated RT to treat thoracic malignancies. In designing the protocol for the current study of CRT with dose-escalated, conventionally fractionated RT in Stage III NSCLC (RTOG 06-17), the RTOG investigators elected to recommend, but not mandate, that the mean dose to the esophagus be kept below 34 Gy and that the V60 Gy be calculated and recorded. The parameters are computed with the esophagus contoured from the bottom of the cricoid to the gastroesophageal junction (Radiation Therapy Oncology Group. RTOG 0617 Protocol). Based on the authors' interpretation of the literature regarding late esophagitis (Ahn et al. 2005; Qiao et al. 2005; Kahn et al. 2005; Maguire et al. 1999), the most relevant dosimetric parameters to consider include the amount of esophagus, by volume or by full-circumference length, exposed to 50–60 Gy, as well as the maximum amount of esophagus treated to very high doses (around 70–80 Gy). Threshold values or cut-points for these dosimetric parameters cannot be recommended based on the available literature. However, it seems prudent to consider these factors during radiation planning and to make efforts to limit them in order to minimize risk of late esophagitis. Perhaps future research on the association between dosimetric factors with late esophagitis will provide specific dose-volume threshold recommendations that can be applied to clinical practice. The QUANTEC group review did not identify a single dose-volume threshold for irradiation of the esophagus, but concluded that volumes receiving >40 Gy are associated with acute esophagitis, and that RT doses above the prescription dose should be avoided to even small volumes of the esophagus (Werner-Wasik et al. 2010).

6 Chemotherapy Tolerance

It is generally accepted that concurrent chemotherapy results in higher incidence of acute esophagitis (Byhardt et al. 1998), but its relationship to late esophagitis is not as well-described in the literature. Chemotherapy, when delivered concomitant with RT, may contribute to slight increases in rate of late esophagitis (Lepke and Libshitz 1983; Greco et al. 1976). The University of North Carolina (UNC) reports do not demonstrate a correlation between late esophagitis and concurrent chemotherapy (Ahn et al. 2005; Maguire et al. 1999). However, other authors have described increased rate of esophagitis with concurrent chemotherapy. For example, the long-term results of the RTOG 92-04 trial revealed an increase in grade 3–4 late esophageal toxicity from 4 % with *sequential* chemotherapy and RT, to 17 % with *concurrent* chemotherapy and hyperfractionated RT (Komaki et al. 2002). Werner-Wasik et al. showed that concurrent chemotherapy and twice-daily RT are associated with higher Esophagitis Index in patients with NSCLC (Fig. 10a) (Werner-Wasik et al. 2000), compared to RT alone or to once-daily RT with concurrent chemotherapy. Rate of ≥grade 1 acute esophagitis as a function of the volume esophagus receiving ≥60 Gy (V60) is shown in Fig. 10b (Bradley et al. 2004). In a review of 207 NSCLC patients who received RT at Washington University, concurrent chemotherapy was a significant predictor of grade 3 or greater acute or chronic esophagitis (Singh et al. 2003). In short, the intensification of chemoradiotherapy by utilizing concurrent chemotherapy and twice-daily RT is associated with an increased incidence of late esophageal toxicity.

Maguire et al. reported an 18 % incidence of grade 1–3 late esophagitis after RT for NSCLC. Among the clinical variables analyzed, only the presence of dysphagia prior to RT showed a trend toward a significant association with the development of esophagitis on univariate analysis ($p = 0.06$). Other clinical variables evaluated include

gender, age, twice-daily RT fractionation, and concurrent chemotherapy (Maguire et al. 1999). In a subsequent publication by Duke investigators, Ahn et al. showed that, among all clinical variable studies, only severity of acute esophagitis was associated with increased risk for late esophageal toxicity (Ahn et al. 2005) (Fig. 5c). In a recent analysis of RTOG trials of patients with locally advanced NSCLC, the majority of patients developed acute esophagitis from concurrent CRT, and hyperfractionated RT was associated with more severe esophagitis (Werner-Wasik et al. 2011).

6.1 Clinical Parameters Including Chemotherapy Tolerance

A variety of clinical factors have been associated with increased risk of late esophageal toxicity after RT, (some information regarding clinical factors is also included in Table 5 summarizing the dosimetric predictors). Patient age has been reported to be a predictor for development of late esophagitis, with esophageal strictures reported after modest RT doses (<40 Gy) in pediatric patients exposed to RT (Mahboubi and Silber 1997). However, the administration of radiosensitizing chemotherapy confounds interpretation of the few, small reports pertaining to pediatric patients (Kaplinsky et al. 1991; Ellenhorn et al. 1993; Mahboubi and Silber 1997) (Table 5).

7 Special Topics

7.1 Hypofractionated Radiation Therapy

The incidence of late esophageal toxicity with hypofractionation has not been well studied/reported. Nevertheless, it is expected that large fractions sizes utilized in stereotactic body RT (SBRT) for lung cancer may result in higher risk of late effects, if indeed meaningful portions of the esophagus are irradiated at high fraction sizes. In a series of 70 NSCLC patients who received hypofractionated SBRT to 60–66 Gy in 3 fractions, published by Timmerman et al., no cases of acute or late esophagitis were observed at a median follow-up time of 17.5 months (Timmerman et al. 2006). Similarly, Nagata et al. reported no acute or late esophagitis in their experience of 45 patients receiving SBRT to 48 Gy in 4 fractions, with a median follow-up time of 30 months. The maximum point dose to the esophagus in this study was low, 1.9 Gy (Nagata et al. 2005). Thus, a lack of toxicity may be an expected observation. Onimaru et al. administered SBRT to 45 patients with NSCLC, prescribing 60 Gy for peripheral tumors and 48 Gy for central tumors in a total of 8 fractions. The dosimetric dose constraint used for esophageal dose in RT planning was 40 Gy in 8 fractions. One case of grade 5 esophagitis occurred in a patient with metastatic NSCLC who received 48 Gy for a 3.5 cm tumor in central location adjacent to the right main bronchus. Following the resolution of grade 1 esophagitis shortly after RT, the patient developed odynophagia 3 months after RT. Death occurred 5 months after RT due to a bleeding esophageal ulcer. When the esophageal segmentation was reviewed retrospectively, a region of the esophagus near the ulcer was found to have received a maximum dose of 50.5 Gy (in 8 fractions). The highest dose administered to 1 cubic centimeter of esophagus in this region was 42.5 Gy. In their analysis of the toxicity for this patient, the authors suggested that special attention be paid to esophageal segmentation during planning and to setup uncertainty during delivery for hypofractionated RT of central lung lesions. More stringent dose constraints for the esophagus were also recommended, and the investigators planned to revise their guidelines before initiating additional trials (Onimaru et al. 2003). Although dosimetric parameters for hypofractionated RT may not be extrapolated from the above studies, it seems prudent to limit maximum esophageal dose and to exercise caution during RT planning and delivery. In the protocol for the ongoing RTOG trial of SBRT for patients with operable Stage I/II NSCLC (RTOG 0618), in which 60 Gy is delivered in 3 fractions, the maximum permitted dose to any point within the esophagus is 27 Gy (9 Gy per fraction). Exceeding this maximum dose constitutes a major protocol violation (Radiation Therapy Oncology Group. RTOG 0618 Protocol). The RTOG has developed a Phase I/II trial to evaluate SBRT for early-stage NSCLC in medically inoperable patients with centrally located tumors (RTOG 0813) (Radiation Therapy Oncology Group. RTOG 0813 Protocol). In this protocol, it is anticipated that target volumes will be adjacent to the esophagus and other midline critical structures at risk for radiation injury. For RTOG 0813, the dose constraints chosen for the esophagus, with endpoints for avoidance of stricture and fistula, are: less than 5 cc receiving a dose of 27.5 Gy (5.5 Gy per fraction), and maximum point dose of 105 % the prescription dose. Exceeding the maximum dose point limits by 2.5 % constitutes a minor, and by 5 % a major, protocol violation (Radiation Therapy Oncology Group. RTOG 0813 Protocol). Data are still emerging regarding the risk of late esophagitis after hypofractionated RT for lung cancer. Presently, the careful evaluation of doses delivered to the esophagus, and adherence to constraints employed by the RTOG, seem to be prudent to reduce the risk of late toxicity.

Table 6 Dietary rules recommended in the prospective clinical trial by Sasso et al. *Adapted by permission* (Sasso et al. 2001)

Dietary rules	
Avoid	Smoking, alcohol, citrus fruit juices, coffee, acidic foods and drinks, spicy foods, chips, crackers and other similar hard breads, chocolate, mint, fatty foods or indigestible foods
Suggested	Drink between meals. Have six light meals a day (especially liquids). Consume semisolid foods like semolina, pastina (small pasta), soup, finely diced or ground food, puree of legumes and vegetables and fresh food with high liquid content such as puddings, melon, grapes, butter, cream milk, custard, milk, and biscuits. Add to any solid food sauces, gravies, clear soups, melted butter, mayonnaise, yogurt. Take a teaspoon of olive oil before every meal

7.2 Brachytherapy

The use of endoluminal brachytherapy in the treatment of esophageal cancer has been associated with increased incidence of esophageal stricture and ulceration. When a single fraction of 20 Gy was administered via high-dose rate (HDR) brachytherapy after external beam RT, a 90 % rate of esophageal ulceration was reported (Hishikawa et al. 1985, 1987, 1991). In order to reduce incidence of late esophageal toxicity after intraluminal brachytherapy for esophageal cancer, fractionated regimens, which deliver 2–3 fractions of 5–6 Gy, have been investigated. RTOG 9207, a phase I/II trial of 49 patients with esophageal carcinoma, delivered concurrent 5-fluorouracil and cisplatin with external beam RT to 50 Gy, and a brachytherapy boost. Patients received HDR brachytherapy, consisting of three 5 Gy fractions, or low-dose rate brachytherapy to 20 Gy. Significant, life-threatening toxicities were observed, including esophageal strictures (3 patients) and fistulas (6 patients). Three patients with fistulas died due to esophageal toxicity. The cumulative yearly incidence of esophageal strictures was 17.5 % per year. Due to the significant treatment-related toxicity for patients enrolled on RTOG 9207, brachytherapy was not recommended in combination with external beam RT and concurrent chemotherapy (Gaspar et al. 1997, 2000).

8 Prevention and Management

8.1 Prevention

Dietary rules are the simplest and effective elements in avoiding the enhancement of esophagitis. The most important factors: no smoking or imbibing alcohol. These are usually the inciting elements that have initiated the carcinogenesis process (Table 6).

8.1.1 Physical Efforts to Prevent Esophagitis

During the planning of RT, several considerations may help prevent late esophageal toxicity, in addition to the dose-volume recommendations above. One obvious tactic is to limit the volume of the esophagus contained within the irradiated volume. This approach is limited directly by the anatomic location and size of the clinical target volume to be treated. Sparing of part of the esophageal circumference should be attempted if the entire esophagus cannot be avoided, which would presumably limit the risk of stricture by maintaining a portion of pliable, non-fibrotic tissue. IMRT is a potentially useful technique and has been used to avoid a portion of the esophageal circumference by creating a concave dose distribution for treatment of lung cancer (Xiao et al. 2004). It has been shown that beam weight optimization and intensity-modulation in RT planning can produce improved dose to central normal tissue structures, including the esophagus (Derycke et al. 1998; De Gersem et al. 2000). Improved understanding of esophageal motion during treatment may enhance the ability to reduce esophageal dose when using highly conformal RT. Using data obtained from four-dimensional CT scans in 29 patients, Dieleman et al. described a differential margin of 5–9 mm to account for esophageal mobility during thoracic RT Dieleman et al. 2007. Careful RT planning using contemporary techniques may improve dosimetric concerns regarding the esophagus, with reasonable, but unproven, potential for clinical enhancement. It is important that one should be careful not to compromise target coverage with modern "esophagus sparing" approaches, as the target is often exceedingly close to the esophagus. Thus, in many patients with unresectable lung cancer, incidental irradiation of the esophagus is necessary to achieve the desired target coverage.

8.1.2 Radioprotective Agents to Reduce the Risk of Esophagitis

The radioprotecting agent, amifostine, has been studied extensively for the prevention of acute esophagitis. This approach is based upon reducing oxidative stress, which is considered an initiating factor for RT injury. Given the shared pathophysiology and the clinical correlation between acute and late esophagitis, it is logical that amelioration of acute esophageal injury may reduce delayed effects after RT (Ahn et al. 2005). Amifostine (Ethyol; WR-2721) possesses a thiol group that allows it to scavenge free radicals generated by RT in an aerobic environment. The clinical trials of amifostine have produced mixed results. Institutional trials by Antonadou and coworkers, and by Komaki et al., suggested that amifostine

Table 7 Randomized trials assessing the efficacy of amifostine on RT-induced injury in patients with lung cancer (Mao et al. 2008)

First author year	Institution	Number of patients	RT dose (Gy)	Chemotherapy	Amifostine usage		Acute grade >2 pneumonitis rate (%)			Lung fibrosis rate (%)			Severe esophagus toxicity rate (%)		
					Dose (mg)	Timing (min)	Amif	Contr	ρ	Amif	Contr	*P*	Amif	Contr	*P*
Movsas et al. 2005	RTOG	242	69.6 (1.2 bid")	ind + conc	500 IV Mon.-Thu.	Pre-afternoon RT	27	28	NS	–	–	–	30[a]	34[a]	NS
(Komaki 2004)	MD Anderson cancer center	62	69.6	conc	500 *IV* 500 *IV*	20–30 pre-ChT 20–60 pre-ChT	0[a]	16[a]	0.02	–	–	–	16[a]	35[a]	0.02
Antonadou et al. 2003	Metaxa cancer, greece	73	60−67 (2 qd)	conc	300/ m^2IV	15 pre-ChT/RT	30	67	0.009	29	50	0.16	39[a]	84[a]	<0.001
Leong 2003	Singapore	60	60−66 (2 qd)	ind + conc	740/ m^2 IV	pre-ChT	–	–	–	–	–	–	43[b]	70[b]	<0.08
Senzer	Sammons	100	64.8	conc +	500 IV	15–30	–	–	–	–	–	–	11′	12·	NS
Antonadou	Metaxa Cancer	146	55–60	none	340/ m^2IV	15 pre-RT	12	52	<0.001	28	53	<0.05	$_4$t	42[b]	<0.0001
Koukourakis	University	60	50–64 (2 qd)	not specified	500 SC	20 pre-RT	–	–	–	–	–	–	20[t]	54[b]	0.05[b]

RTOG Radiation Therapy Oncology Group; *ind* induction, *conc* concurrent; *ChT*chemotherapy; *Amif* amifostine group; *Contr* control group; *NS* nonsignificant

[a] Grade 3 or greater

[b] Grade 2 or greater

[c] Three patients with thymoma and one with neuroendocrine tumör included

Table 8 Medical management guidelines for the treatment of acute esophagitis, as recommended for use in patients treated on an RTOG trial of chemoradiotherapy for non-small-cell lung cancer (0617) (Mao et al. 2008)

Suggested management of acute esophagitis (RTOG 0617)
Ketoconazole 200 mg *po* daily OR
Fluconazole 100 mg *po* daily until the completion of RT
Mixture of
2 % viscous lidocaine: 60 cc
Mylanta®: 30 cc
Sucralfate (1 g/cc): 10 cc
*Take 15–30 cc *po* q3–4 h PRN
(Contraindications: Patients on dilantin, ciprofloxacin, or digoxin)
Ranitidine 150 mg *po* BID (or other H2 blocker or proton-pump inhibitor) until the completion of RT
Grade 4 esophagitis: Hold RT and chemotherapy until grade 2 or less

may reduce acute esophagitis (Antonadou 2002; Antonadou et al. 2003; Komaki et al. 2002). In the largest published study, amifostine was evaluated in a Phase III, randomized, cooperative group trial (RTOG 98-01) of 243 patients undergoing RT, with induction and concurrent carboplatin/paclitaxel chemotherapy, for locally advanced NSCLC. The rate of grade ≥3 esophagitis in the experimental arm (intravenous amifostine), 30 %, was not significantly lower than in the control arm (no amifostine), 34 % (Movsas et al. 2005). Although amifostine did not influence the rates of esophagitis, analyses of secondary endpoints demonstrated improvements in patient-rated dysphagia and pain, as well as weight loss (Movsas et al. 2005; Sarna et al. 2008). Further, in this study, the amifostine was given only once daily, while the RT was given twice daily. Thus, "optimal potential protection" was likely not achieved. Nevertheless, taken as a whole, the prospective data do not clearly support the routine use of amifostine to prevent esophagitis in patients receiving RT for thoracic malignancies. The patient-reported outcomes, as well as potential advantages to subcutaneous administration (Koukourakis et al. 2000), may encourage further trials of amifostine, but it is not clear whether a clinically meaningful benefit will be attained. The published results of randomized trials of amifostine for the prevention of RT-induced injury in the treatment of lung cancer are summarized in Tables 6 and 7).

Other agents have been evaluated as potential radioprotective agents to prevent esophagitis, without clear demonstration of efficacy. Glutamine supplementation has been investigated as a way to prevent esophagitis. The rationale is based upon the prevalence of glutamine deficiency among cancer patients and the positive effects of glutamine on the immune system with reduction of bacterial translocation in the gastrointestinal tract. Some promising results have been obtained in prospective, non-randomized studies (Algara et al. 2007). However, there is a lack of Level I evidence to support its routine use for patients receiving RT. An oral form of sucralfate was the subject of a randomized trial of 97 patients receiving thoracic RT, but no benefit was observed in the reduction of acute esophagitis (McGinnis et al. 1997). In a double-blinded study of naproxen versus placebo in patients receiving RT, prophylactic naproxen failed to reduce acute esophagitis (Soffer et al. 1994). Another strategy that is currently under preclinical investigation is gene therapy using a human manganese superoxide dismutase plasmid, which has been effective in rodents (Epperly et al. 2001, 2002). In a small, prospective clinical trial of 29 patients, Sasso et al. evaluated a cost-effective protocol of dietary and pharmacological prophylaxis, using standard medications, to prevent acute esophagitis (Sasso et al. 2001). The dietary recommendations from this study are displayed in Table 6. Pharmacological therapy consisted of nimesulide (nonsteroidal anti-inflammatory), an antacid suspension, ranitidine (H_2-receptor blocker), domperidone (eucinetic), and sodium bicarbonate solution (alkalinizing agent). All patients tolerated the prophylactic regimen, and no patients exhibited grade 2 or higher esophagitis after a moderate dose (median, 46 Gy) of mediastinal RT without chemotherapy (Sasso et al. 2001). Though small and poorly representative of NSCLC patients, this study does demonstrate the potential impact of careful preventive management, using conservative dietary and pharmacological interventions, in the reduction of acute esophagitis during RT. The influence of these measures on the incidence of late esophageal is not known. Continued efforts are needed in order to develop novel, effective strategies to minimize acute esophagitis and to decrease the late esophageal effects of thoracic RT.

8.2 Management

8.2.1 Acute Esophagitis

Medical management of acute esophagitis centers upon supportive care with pain relief and nutritional supplementation. Topical anesthetics, opiate analgesics, sucralfate, antacids, prokinetic agents, H_2-blockers, proton-pump inhibitors, and antifungal medications are commonly prescribed (Coia et al. 1995; Choy et al. 1999; Sasso et al. 2001; Bradley and Movsas 2004; Bradley et al. 2002). Dietary recommendations typically consist of a bland diet of soft foods, with avoidance of spicy, hot or cold foods, as well as tobacco and alcohol (Choy et al. 1998). A liquid mixture ("Magic Mouthwash") commonly used in the radiation oncology clinic is composed of viscous lidocaine (2 %), benadryl elixir, saline, and baking soda. This may be used liberally by patients to ease swallowing, particularly around meal time (Werner-Wasik et al. 2004). If conservative interventions fail, a gastrostomy tube may be necessary to provide adequate nutrition during RT (Bradley

Table 9 Timeline of Literature Landmarks: A chronological summary of selected, important published contributions to the development of our contemporary understanding of the late effects of radiation on the esophagus. *Adapted from Rubin and Casarett* (Rubin and Casarett 1968) *with permission*

Years	Author	Comments
1931	Desjardins	Presented a general review of the depressive and injurious effects of irradiation reported up to that time
1934	Engelstad	Studied histologic changes in the esophagus following varying doses of irradiation
1957	Seaman and Ackerman	Presented a clinical study of radiation effects in the esophagus produced by the betatron
1960	Jennings and Arden	Conducted a serial histopathologic study of radiation changes in the esophagus of rats following single dose exposure 3000 R
1962	Skarloff and Karayannis	Found that oxethazaine in alumina gel palliated esophageal irritation due to radiation in 51 cases
1968	Rubin and Casarett	Presented a comprehensive textbook to summarize contemporary understanding of clinical radiation pathology
1979	Northway	Described radiation dose-related pathologic changes in the muscle wall of the opossum esophagus, as a model for late esophageal complications
1991	Emami	Estimated clinical stricture or perforation rate following esophageal radiation based upon dose and volume of irradiation

et al. 2002). Intravenous hydration may be necessary if oral intake of fluids is insufficient. Hospitalization is generally required if prolonged intravenous hydration and/or pain control is needed. Although acute esophagitis is usually reversible, it is a frequent cause of treatment breaks during thoracic RT. In many patients, rapid improvement occurs after a 1–3 day treatment break. In general, it is recommended that RT is interrupted after the development of grade 4 esophagitis and is not resumed until esophagitis returns to grade 2 or less. After sufficient time for healing, most cases of acute esophagitis resolve without development of chronic effects (Rubin and Casarett 1968). In the protocol for RTOG 06-17, the randomized trial of dose escalation for locally advanced NSCLC, suggestions for management of esophagitis included: an antifungal medication (ketoconazole or fluconazole); a topical anesthetic mixture consisting of lidocaine, Mylanta, and sucralfate; and a proton-pump inhibitor or an H_2-blocker such as ranitidine (Table 8) (Radiation Therapy Oncology Group. RTOG 0617 Protocol).

8.2.2 Late Esophageal Injury

The principal management approach for late esophageal stricture after RT is endoscopy with dilatation. Esophageal dilatation is generally successful at improving patients' symptoms from esophageal stricture (Zhang and Trillis 2008). When dilatations are required, the median number of dilatations performed in 2.5 per patient at a median interprocedural interval of 5 months (O'Rourke et al. 1988). For simple strictures that are focal and of sufficient diameter to allow passage of a standard endoscope, balloon dilation using normal techniques is usually possible (Lew and Kochman 2002). Dilatation may be accomplished using bougie or balloon dilatation. The primary difference between these tools is the use of longitudinal shearing force in the former, though no clear advantage has been demonstrated for balloon versus bougie dilatation (Siersema 2008). Most simple strictures resolve permanently after one to three dilatations (Siersema 2008; Raymondi et al. 2008). Dilatation is associated with a small risk of perforation or bleeding, around 0.3 %, and this rate may increase with complex strictures (Hernandez et al. 2000). In some cases of long, complex strictures or complete stricture, a "rendezvous" approach may be utilized, which involves both antegrade and retrograde endoscopic pathways to allow for dilatation (Siersema 2008; Giever et al. 2008). For patients with strictures that are refractory to multiple dilatations, endoscopic stent placement may be an appropriate step (Siersema 2008). Esophageal stents composed of silicone and polyester have been developed to prevent growth of granulation tissue and obstruction for post-RT stricture, but results have been mixed (Siersema 2008; Repici et al. 2004; Holm et al. 2008).

Esophageal dysmotility is also observed after RT (Lepke and Libshitz 1983). Currently, there are no effective methods to restore peristalsis. Metoclopramide, which increases the rate of gastric emptying, is sometimes prescribed to reduced reflux of gastric contents into the esophagus (Ramirez-Mata et al. 1977). Diffuse esophageal spasms after RT can be treated with antispasmodics such as nitrates, anticholinergics, and calcium-channel blockers (Blackwell et al. 1981; Orlando and Bozymski 1973).

9 Future Direction and Research

Significant progress has been made in our understanding of the dosimetric parameters associated with late esophagitis, and sophisticated RT techniques such as IMRT offer the

potential to avoid delivering high radiation doses to the esophagus. Future efforts to identify threshold values for the important dosimetric factors will allow the development and validation of more reliable dose/volume guidelines for prevention of late esophagitis after thoracic RT. However, it must be remembered that biological considerations are also important, and research efforts should focus on refining our understanding of the biological mechanisms of esophagitis and associated biomarkers. There is much to be gained from continued research on radioprotective agents. Future investigations will likely involve novel approaches for the biological modulation of the esophageal response to RT as a preventive measure to reduce or eliminate esophagitis. In order to better evaluate RT-induced esophagitis, and to accelerate scientific knowledge in the field, standardized approaches should be adopted broadly. There should be uniformity in how esophageal toxicity is scored. Several options for scoring have been suggested. Just as in the QUANTEC report (Werner-Wasik et al. 2010), we recommend that the latest version of the Common Terminology Criteria for Adverse Events be used to score both acute and late esophageal injury. The use of CTCAE in cooperative group trials has been required by the National Cancer Institute since 2003 (Colevas and Setser 2004). There should be pooling of RT planning, clinical, and outcomes data across institutions contained within a permanent database, as a resource for the evaluation and re-evaluation of dose-volume constraints for esophageal irradiation. Finally, images and other data collected during image-guided radiation therapy should be incorporated into future studies of RT-induced esophageal injury. Future mathematical models based upon these improved streams of dosimetric and clinical data are expected to refine and improve recommendations regarding dose-volume thresholds for esophageal irradiation.

10 History and Literature Landmarks

In a 1931 seminal report of the effects of RT on the gastrointestinal system, Desjardins wrote that the esophagus occupies a protected anatomical location and exhibits low radiosensitivity (Desjardins 1931). The apparent lack of response to RT may be reflected the lack of deep penetration of early therapy beams. The acute and late manifestations of esophageal damage from RT were subsequently characterized during the 1950 and 1960s; a historical timeline of important achievements was provided by Rubin and Casarett in their 1968 publication of *Clinical Radiation Pathology* (Rubin and Casarett 1968) (see Table 9). In 1957, Seaman and Ackerman authored a clinical and pathologic study of the effects of betatron radiation on the esophagus. Among 20 patients treated for lung carcinoma, 5 patients developed severe reactions, and radiographic findings included visualization of stenosis as a late reaction after RT. The authors provided the first clinical estimate of tolerance dose, "6,000 rads at a rate of 1,000 rads/week" (Seaman and Ackerman 1957). Later, Northway et al. used an opossum model to study the effects, both acute and late, after a single dose of esophageal irradiation, and observed focal necrosis of the muscle wall (Northway et al. 1979). In a 1983 report, Lepke and Lipshitz used esophagograms to study RT-induced esophageal injury. They noted different types of responses at different times post-RT: dysmotility within 4–12 weeks after RT, stricture 4–6 months after RT, and fistula formation without a characteristic timeframe (Lepke and Libshitz 1983). Several studies contributed information pertinent to dose-threshold estimates for RT tolerance of the esophagus (Seaman and Ackerman 1957; Dickson 1961; Morichau-Beauchant et al. 1983; Phillips and Margolis 1972; Perez et al. 1988; O'Rourke et al. 1988; Beatty et al. 1979; DeRen 1989; Kramer et al. 1987), including lessons learned from intraluminal brachytherapy for the treatment of esophageal cancer (Hishikawa et al. 1987; Hishikawa et al. 1985, 1991a, b). The first guidelines that included both dose and volume parameters were those published by Emami et al. (1991). A review of the late effects of RT on the esophagus and other gastrointestinal organs was published in 1995, based upon the Late Effects Workshop held in San Francisco in 1992, and provided a solid foundation for understanding this topic (Coia et al. 1995). A recent review of this topic was performed by the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) group (Werner-Wasik et al. 2010). The current review is offered to update, enrich, and expand the information included in the prior documents (Table 9).

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