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RADIATION DOSE–VOLUME EFFECTS IN THE LARYNX AND PHARYNX

Tiziana Rancati, Ph.D.,* Marco Schwarz, Ph.D.,† Aaron M. Allen, M.D.,‡ Felix Feng, M.D.,§ Aron Popovtzer, M.D.,‡ Bharat Mittal, M.D.,¶ and Avraham Eisbruch, M.D.§

*Fondazione IRCCS-Istituto Nazionale dei Tumori, Milan, Italy; †Agenzia Provinciale per la Protonterapia, Trento, Italy; ‡Rabin Medical Center, Petah Tikvah, Israel; §University of Michigan, Ann Arbor, MI; ¶Northwestern University, Chicago, IL

The dose–volume outcome data for RT-associated laryngeal edema, laryngeal dysfunction, and dysphagia, have only recently been addressed, and are summarized. For late dysphagia, a major issue is accurate definition and uncertainty of the relevant anatomical structures. These and other issues are discussed. © **2010 Elsevier Inc.**

Larynx, pharynx, dysphagia, radiotherapy, dose effect.

1. CLINICAL SIGNIFICANCE

Radiotherapy (RT) is the primary modality allowing larynx preservation in patients with tumors in the upper aerodigestive tract. RT-induced laryngeal edema (due to inflammation and lymphatic disruption) is a common and expected side effect. Progressive edema and associated fibrosis can lead to long-term problems with phonation and swallowing (1). Since the primary goal of larynx preservation is speech and swallowing retention, RT-induced laryngeal dysfunction could undermine this therapeutic approach. In many instances, the larynx and pharynx are target structures and purposefully receive high radiation doses.

Dysphagia is common after chemoradiotherapy of head-and-neck (HN) cancer. For example, patients included in the Radiation Therapy Oncology Group (RTOG) 91-11 trial were randomized to receive RT with or without concurrent cisplatin. The combined modality arm demonstrated improved tumor control rates (2). However, 1 year after therapy, 23% of the patients in the chemo-RT arm were unable to eat solid food compared with 9% who had undergone RT alone. Aspiration pneumonia associated with dysphagia after intensive chemo-RT has recently been reported (3). The topics reviewed in the present report are the subjects of current intensive research. This review examined key studies published through June 2008.

A. LARYNX

A2. Endpoints

Larynx edema. Edema can be assessed using flexible fiberoptic examination. The grade of larynx edema can be scored according to the RTOG scale as follows: 0, no edema; 1, slight edema; 2, moderate edema; 3, severe edema; and 4, necrosis. Some degree of uncertainty is intrinsic to the subjectivity in the interpretation of ''slight'' and ''moderate'' in the RTOG scale. Grade 1 edema would correspond to ''minimal'' thickening of the epiglottis, aryepiglottic folds, arytenoids, and false cords. Grade 2 is a more diffuse and evident edema, although still without significant or symptomatic airway obstruction.

Vocal function. Vocal function can be assessed objectively using instruments (*e.g.,* videostroboscopy for direct visualization to assess supraglottic activity, vocal fold edge, amplitude, mucosal wave, phase symmetry, and glottic closure [4]; aerodynamic measurements of phonation time [5], or human observation [6]). Subjective assessments can be made with validated patient-focused questionnaires to assess various combinations of voice, eating, speech, and social function.

A3. Challenges defining volumes

The identification of the most important anatomic sites whose dose–volume parameters would primarily affect vocal function remains controversial. Dornfeld *et al.* (7) considered the dose points in various structures (*e.g.,* base of tongue, epiglottis, lateral pharyngeal walls, pre-epiglottic space, aryepiglottic folds, false vocal cords, and upper esophageal sphincter) to be related to vocal injury. Sanguineti *et al.* (8) considered the larynx from the tip of the epiglottis superiorly to the bottom of the cricoid inferiorly; the external cartilage framework was excluded from the laryngeal volume. Because of the small size and close proximity of these structures, high-resolution, contrast-enhanced computed

Reprint requests to: Avraham Eisbruch, M.D., Department of Radiation Oncology, University of Michigan Hospital, Ann Arbor MI 48109. Tel: (734) 936-9337; Fax: (734) 936-7370; E-mail: eisbruch@umich.edu

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tomography has been suggested to facilitate accurate substructure definition.

A4. Review of dose–volume data

Laryngeal edema. Sanguineti *et al.* (8) found that neck stage, nodal diameter, mean laryngeal dose, and percentage of laryngeal volume receiving ≥30–70 Gy were all significantly associated with edema Grade 2 or greater on univariate analysis. On multivariate analysis, the mean laryngeal dose or percentage of volume receiving ≥50 Gy and neck stage were the only independent predictors. The investigators suggested that the percentage of volume receiving ≥50 Gy and the mean laryngeal dose should be kept as low as possible, ideally <27% and <43.5 Gy, respectively, to minimize the edema (*i.e.,* <20% actuarial incidence at 1 year compared with 45% of patients receiving 44–57 Gy and >80% in patients receiving >57 Gy). Only a few of their patients received concurrent chemotherapy, which might have affected the dose–response relationships.

A5. Vocal dysfunction

Many studies have shown a good voice outcome after RT for Stage T1 laryngeal cancer (typically 60–66 Gy without chemotherapy). In the locally advanced setting, less information is available regarding voice quality after treatment. Dornfeld *et al.* (7) found a strong correlation between speech and doses delivered to the aryepiglottic folds, pre-epiglottic space, false vocal cords, and lateral pharyngeal walls at the level of the false vocal cords. In particular, they noted a steep decrease in function after 66 Gy to these structures. Their study was limited by not having full three-dimensional dose metrics. Fung *et al.* (5) evaluated the subjective and objective parameters of vocal function. Changes in voice were related to doses to the larynx and pharynx and oral cavity. This suggests that saliva, pharyngeal lubrication, and soft tissue/structural changes within the surrounding musculature play an important role in voice function.

A6. Factors affecting risk

Locally advanced laryngeal cancer frequently causes voice dysfunction that might not improve, even if the cancer has been eradicated. This is one of the reasons patients presenting with marked laryngeal dysfunction might be advised to undergo laryngectomy, rather than a trial of chemo-RT. The addition of concurrent chemotherapy to high-dose RT at least doubles the risk of laryngeal edema and dysfunction. In contrast, RT without chemotherapy, delivered to small fields for Stage T1 glottic larynx cancer, usually results in excellent voice quality (9).

A7. Mathematical/biologic models

Rancati *et al.* (10) studied the same study population analyzed by Sanguineti *et al.* (8). Using Grade 2-3 edema within 15 months after RT as an endpoint, 38 of 66 patients were available for analysis, and 21 of 38 experienced Grade 2-3 edema. Two normal tissue complication probability models were fitted using a maximum likelihood analysis: the Lyman-Kutcher-Burman model and the logit model with the dose–volume histogram reduced to the equivalent uniform dose (EUD). A significant volume effect was found for edema, consistent with a prevalent parallel architecture of the larynx for this endpoint. Both normal tissue complication probability models fit the clinical data well. The relationship between the EUD and normal tissue complication probability can be described with n = 0.47 ± 0.3, D50 (the dose causing 50% risk of complications). replace subsequent ''TD50'' mentions with ''D50'' in all instances of 46.0 ± 1.85 Gy, and a steepness parameter of k = 9.95 ± 3.46 Gy. The best fit parameters for the Lyman-Kutcher-Burman were n = 0.45 ± 0.28, m = 0.16 ± 0.05, and TD50 of 46.3 ± 1.8 Gy (Table 1). According to these findings, the investigators suggested an EUD of <30–35 Gy to reduce the risk of Grade 2-3 edema.

A8. Special situations and recommended dose–volume limits

The exact correlation between voice abnormalities and the degree of laryngeal edema has not been assessed. Also, most studies have not considered pre-RT voice abnormalities (common with advanced lesions) and thus might have overestimated the degree of RT-related damage. Nevertheless, to minimize the risks of laryngeal edema, it is recommended that the percentage of larynx volume receiving ≥50 Gy be ≤27% and the mean laryngeal dose ≤44 Gy. For model-based predictions, we recommend that the EUD be <30–35 Gy, with a volume parameter (n) of ≈0.45 (Table 2).

A9. Recommendations

Radiotherapy affects voice quality in locally advanced HN cancer but less so in early-stage larynx cancer. An interesting conclusion follows this observation: clinically significant vocal dysfunction requires both the larynx and surrounding supralaryngeal structures to be affected. The surrounding tissues might be indirectly affected by a reduction in salivary function or directly by effects on the intrinsic musculature and soft tissue. From the published data, it seems reasonable to suggest limiting the mean noninvolved larynx dose to 40–45 Gy and limiting the maximal dose to <63–66 Gy, if possible, according to the tumor extent.

Table 1. Larynx edema: estimated parameter values for various NTCP models with their 1D-68% confidence intervals

Model			*n*
LKB	D50	m	
Rancati *et al.* (10)	46.3 Gy	0.16	0.45
SD	1.8 Gy	0.05	0.28
LOGEUD	D50	k	
Rancati *et al.* (10)	46.0 Gy	9.95	0.47
SD	1.85 Gy	3.46	0.3

Abbreviations: NTCP = normal tissue complication probability; LKB = Lyman-Kurcher-Burman; D50 = dose causing 50% risk of complications; LOGEUD = log equivalent uniform dose.

Table 2. Larynx toxicity: summary of dose–volume relationship and constraints above which toxicity is significantly increased

Investigator/patients (*n*)	Critical organs	Predictive dose–volume parameter	Endpoint
Dornfeld *et al.* (7)/27 patients*	Aryepiglottic folds, pre-epiglottic space, false vocal cords, lateral pharyngeal walls	Point dose <68 Gy	Vocal function
Sanguineti *et al.* (8)/66 patients†	Larynx	V_{50} <27%; mean dose <43.5 Gy	Laryngeal edema (fiberoptic examination)
Rancati *et al.* (10)/38 patients‡	Larynx	EUD <30–35 Gy (n = 0.45)	Laryngeal edema (fiberoptic examination)

Abbreviation: EUD = equivalent uniform dose.
* Twenty-two of 27 patients who received chemotherapy plus radiotherapy.
† Twelve of 66 patients received chemotherapy plus radiotherapy.
‡ Seven of 38 patients received chemotherapy plus radiotherapy.

A10. Future toxicity studies and toxicity scoring

Longitudinal studies consisting of objective scoring of laryngeal edema, voice quality, and patient-reported measures are necessary to assess the intercorrelations among these measures. Such studies should include pretherapy assessments to account for tumor-related voice abnormalities and should concentrate on patients receiving concurrent chemo-RT who are at the greatest risk of laryngeal toxicity.

B. DYSPHAGIA

B2. Endpoints

Objective evaluation: instrumental assessment. Videofluorography includes modified barium swallow and esophagography to visualize the oral, pharyngeal, and esophageal phases of swallowing (11). Additional instrumental assessors include manometry and functional endoscopic evaluation of swallowing.

Subjective evaluation: observer-assessed. Common Terminology Criteria for Adverse Events (CTCAE) are frequently used to assess acute toxicity, as is the RTOG/European Organization for Research and Treatment of Cancer criteria and the Subjective Objective Management Analytic (SOMA) scale. None of these tools has been tested for its validity in measuring dysphagia.

Patient-reported quality of life. Various instruments have been developed to assess the quality of life (QOL) of patients with HN cancer, all of which include questions about swallowing dysfunction. Although these instruments all measure some aspects of HN cancer-related QOL, it is not clear which best applies to the assessment of swallowing dysfunctions. All the HN-specific QOL instruments include domains or few questions related to dysphagia. Although each instrument as a whole has been tested for validity, similar tests of the specific dysphagia-related questions have not been performed.

B3. Challenges defining volumes

Swallowing is complex and involves voluntary and involuntary stages coordinated through several cranial nerves and muscles (12). Because of this complexity, defining the most important anatomic structures whose dose–volume parameters would have a major effect on dysphagia has been difficult and only recently studied. Eisbruch *et al.* (13) noted anatomic/functional changes in pharyngeal constrictors and glottic/supraglottic larynx after intensive chemo-RT and explained the post-RT abnormalities in objective swallowing assessments (13, 14). The definition of the pharyngeal constrictors in their study was somewhat different from the definition of the constrictors by Levandag *et al.* (15). Nevertheless, both groups found significant correlations between the constrictor doses and dysphagia endpoints. Other studies have demonstrated the importance of specific anatomic points in the glottic (7) and supraglottic larynx (16) or pharynx (7). Fua *et al.* (17) noted that the glottic larynx doses were associated with dysphagia in patients who had received high doses to the larynx. Thus, most studies demonstrated relevance to various dysphagia endpoints of the doses to the glottic and supraglottic larynx and to specific points in the pharynx, notably the pharyngeal constrictors.

B4. Review of dose–volume data

Laryngopharyngeal disorders resulting in late dysphagia and aspiration are not specific and can result from edema and/or fibrosis of various structures (Table 3). In a prospective study using intensity-modulated RT to reduce dysphagia, Feng *et al.* (14) demonstrated the dose–volume relationship for swallowing structures in 36 patients treated with chemoradiotherapy. A strong correlation was observed between the mean doses and the dysphagia endpoints (Fig. 1). Aspiration was observed when the mean dose to the pharyngeal constrictors was >60 Gy and the dose–volume threshold for the percentage of volume receiving ≥40, ≥50, ≥60, and ≥65 Gy was 90%, 80%, 70%, and >50%, respectively. For aspiration to occur, the glottic/supraglottic larynx dose–volume threshold was a percentage of volume receiving ≥50 Gy of >50%. In a retrospective study, Jensen *et al.* (16) found that doses <60 Gy to the supraglottic area, larynx, and upper esophageal sphincter resulted in a low risk of aspiration. Because their study used conventional radiation fields, it is likely that the lack of correlation between the pharyngeal doses and dysphagia was related to the relative uniformity among the patients in the doses delivered to these structures.

Table 3. Organs at risk and dose–volume relationship above which swallowing dysfunction increases significantly

Investigator/patients (*n*)	Critical organs	Dose–volume data					Endpoint	Evaluation method
		Mean dose (Gy)	Median dose (Gy)	V_{50}	V_{60}	V_{65}		
Eisbruch *et al*. (13),	Larynx	60		50%	—	—	Aspiration	VF
Feng *et al*. (14)/36 patients	PC	66		80%	70%	50%	Aspiration	
IMRT + chemotherapy	PC			85%	70%	60%	Stricture	
Caglar (19)/96 patients	Larynx	48*		21%			Aspiration and stricture	VF
IMRT + chemotherapy	IC	54		51%				
Doornaert *et al*. (18)/81 patients	Pharyngeal mucosa and	45					QOL	RTOG/EORTC
RT + chemotherapy	constrictors							C30 and H/N 35
O'Meara *et al*. (20)/148 patients	Pharyngoesophageal inlet		50				Grade 3 plus pharyngoesophageal	RTOG late
2D-RT plus chemotherapy							dysfunction	Toxicity
Levandag *et al*. (15)/81 patients	Superior and middle	55					Grade >3 EORTC	RTOG
3D-CRT/IMRT plus	constrictors						PSS–HN MDADI	QOL
brachytherapy + chemotherapy								QOL
Dornfeld *et al*. (7)/27 patients	Aryepiglottic fold	50					Diet score	QOL
IMRT + chemotherapy	False cord						HN QOL	Clinical assessment
	Lateral pharyngeal						Weight loss	
	Wall near false cord						PEG tube	
Jensen *et al*. (16)/25 patients	Larynx/upper esophageal	60					Aspiration	EORTC QOL
3D-CRT	sphincter						QOL	FEES
RT alone								

Abbreviations: V_{50}, V_{60}, V_{65} = percentage of volume receiving ≥50, ≥60, ≥65 Gy; IMRT = intensity-modulated radiotherapy; PC = pharyngeal constrictors; IC = inferior constrictor; VF = videofluoroscopy; RTOG = Radiation Therapy Oncology Group; 2D-RT = two-dimensional radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; C30 and H/N 35 = EORTC questionnaire modules; PSS–HN = performance status scale for head-and-neck cancer patients; MDADI = M. D. Anderson Dysphagia Inventory; HN = head and neck; QOL = quality of life; PEG = percutaneous endoscopic gastrostomy; FEES = functional endoscopic evaluation of swallowing.

* No correlation with stricture formation.

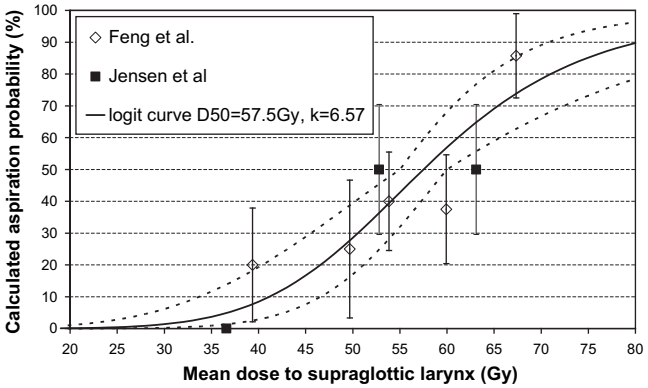

Fig. 1. Dose–effect relationship for dysphagia according to data from Feng *et al*. (14) and Jensen *et al*. (16). Solid line fit to combined data; dotted line fit to 68% confidence area for normal tissue complication probability-logit curve.

Dornfeld *et al*. (7) reported that swallowing difficulties and the type of diet tolerated worsened progressively with radiation doses >50 Gy to the aryepiglottic folds, false vocal cords, and lateral pharyngeal walls near the false cord. Levandag *et al*. (15) reported on patients with oropharyngeal carcinoma treated with three-dimensional conformal RT or intensity-modulated RT with or without brachytherapy plus chemotherapy. The use of brachytherapy, which reduces the doses to some of the pharyngeal tissues, significantly reduced patient-reported dysphagia. A significant correlation was observed between the mean dose to the superior and middle pharyngeal constrictor muscles and patient complaints of severe dysphagia. A median dose of 50 Gy predicted a 20% probability of dysphagia. This probability increased significantly beyond a mean dose of 55 Gy, with an increase of 19% associated with each additional 10 Gy to the superior and middle constrictors. Doornaert *et al*. (18) reported a steep dose–effect relationship beyond 45 Gy to the pharyngeal wall and concluded that a mean dose of 45 Gy is the optimal threshold dose for predicting swallowing difficulties. Similar findings were reported in retrospective series by Caglar *et al*. (19) and O'Meara *et al*. (20).

A paucity of dose–volume data is available on hypopharyngeal/upper esophageal stricture in HN cancer patients treated with RT plus chemotherapy. Laurell *et al*. (21) recommended a mean dose of <65 Gy to the first 2 cm of proximal esophagus and a mean dose of <60 Gy to the first 5 cm of proximal esophagus as the tolerance dose below which the incidence of esophageal stricture is low. Caglar *et al*. (19) found that the volume of the larynx or the inferior constrictor receiving >50 Gy was associated with strictures.

B5. Factors affecting risk

Supportive measures during RT could affect long-term dysphagia. Rosenthal *et al*. (22) and Mekhail *et al*. (23) suggested that a nasogastric feeding tube decreases the need for esophageal dilation vs. a percutaneous endoscopic gastrostomy tube. They hypothesized that the nasogastric tube serves as a stent to prevent stricture formation. Amifostine (WR 2721) is the most commonly used cytoprotector for reducing the incidence of xerostomia and mucositis (24). However, no data are available to support its role in decreasing late swallowing disorders.

B6. Mathematical/biologic models

The relative paucity of dose–volume data relates to the questions regarding the most important anatomic structures whose dysfunction after chemo-RT causes dysphagia. Data indicating that the pharyngeal constrictors and the larynx are the most likely candidates have been very recently published, and additional data are being gathered (Table 3). At present, modeling suggests that 50% normal tissue complication probability is observed at mean doses of 50–60 Gy to these structures (Fig. 1). The limitations of these models include treatment variables, the most important of which is concurrent chemotherapy, and variations in tumor locations and pretherapy dysphagia, which have been accounted for in very few studies (14). The need to consider pretherapy dysphagia is especially important in laryngeal cancer, in which the rates of pretherapy dysphagia and aspirations are high, and tumor regression after chemo-RT might actually reduce the rate of frank aspiration (25). This could confound the results of retrospective dose–effect studies that do not take into account pretherapy findings.

B7. Special situations

Much of the data considered in the present review concern patients who underwent RT with either relatively simple techniques or intensity-modulated RT approaches that did not explicitly aim at sparing dysphagia-related anatomic structures. Thus, high doses were delivered to these structures, and drawing strict dose–volume constraints or volume–effect parameters is far from trivial. In addition, high doses to the larynx, for example, are expected in cases of laryngeal or hypopharyngeal cancers, which are associated with high rates of pre-RT dysphagia and/or aspiration, confounding evaluations of post-RT dose–effect relationships.

B8. Recommended dose–volume limits

The limited available data have suggested that minimizing the volume of the pharyngeal constrictors and larynx receiving ≥60 Gy and reducing, when possible, the volume receiving ≥50 Gy is associated with reduced dysphagia/aspiration. In several cases, such sparing can be achieved without compromising target doses (13, 14). A separate question is whether such sparing is safe clinically, taking into account the uncertainties in target delineation. This issue was beyond the scope of this report.

B9. Future toxicity studies

Late dysphagia is often a consequential effect of acute mucositis. Careful assessment and reporting of the severity of acute mucositis might shed light on the likelihood of late dysphagia and its predictors and whether successful reduction in

acute dysphagia would lead to improvements in late swallowing abnormalities.

Validation of assessors of dysphagia

The most commonly used observer-rated dysphagia grading tool is the CTCAE dysphagia item, which has not been validated formally. Similarly, multiple patient-reported QOL instruments have been used, as detailed in the present report, and few have formally been validated regarding their dysphagia components.

The issue of what are the most important anatomic structures and substructures whose damage is the likely cause of dysphagia is the subject of current research by many investigators. An important aspect of this research is the effects of the tumor on pretherapy swallowing and on the functional results after therapy. To capture these effects, prospective studies that have included pretherapy evaluations are essential.

B10. Toxicity scoring

As detailed, prospective evaluation is critical because of tumor-related dysphagia and aspiration, particularly in patients with advanced cancer. Although CTCAE-based scoring is simple and commonly applied, the evidence of ''silent aspiration'' after RT (aspiration not eliciting a cough owing to a laryngeal sensory deficit) requires objective measurement using imaging and interpretation by professional speech/language pathologists. In addition, an objective swallow assessment might help quantify the swallowing assessments. Correlating observer-rated scores such as the CTCAE system, patient-reported scores, and objective swallowing dysfunction is recommended for future focused studies. Until more data regarding this issue are available, we recommend the use of the CTCAE system, as well as a patient-reported QOL instrument, for large-scale clinical studies of chemo-RT for HN cancer.

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