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Evaluation and Management of Dysphagia in Patients Receiving Chemoradiation for Head and Neck Cancer

1. Introduction:

Head and neck squamous cell carcinomas occur frequently with over 500,000 new cases diagnosed worldwide each year [1]. Chemoradiation therapy (CRT) has become an increasingly used treatment modality for head and neck cancer. Studies have shown CRT to be successful in improving locoregional control, disease free survival and overall survival [2, 3]. The significant aim of organ preservation therapy is cancer treatment with retention of healthy tissue, allowing for the maintenance of normal mechanisms for breathing, deglutition, and communication. As the number of patients receiving CRT continues to increase it is important to pay careful attention to the long-term quality of life (QOL) issues affecting this population. Dysphagia is the most common QOL issue in CRT patients and has been observed to affect up to 50% to 64% of patients after CRT [4, 5]. For this reason, it is important for the clinical team to be well versed on the methods available to prevent and treat dysphagia that may develop after CRT.

2. Definition:

Dysphagia is the inability to swallow safely or efficiently. It can lead to weight loss, malnutrition, and aspiration and its related complications.

3. Etiology:

Acute toxicities related to CRT such as mucositis, pain, nausea, and loss of appetite can decrease the ability of the patient to take nutrition by mouth. Furthermore, CRT can cause severe dysfunction of the base of tongue, larynx, and pharyngeal muscles, which may lead to stasis of the bolus, vallecular residue, epiglottic dysmotility, and aspiration [6, 7].

The formation of fibrosis has also been considered a primary source of late CRT-induced dysphagia. This fibrosis is thought to start with the dysregulation of normal wound healing mechanisms and the addition of regional oxidative stress secondary to the effects of CRT to surrounding tissue may lead to overproduction of transforming growth factor β 1 (TFG- β 1), a commonly studied regulator of the fibrotic process [8]. The fibrosis process may occur independently, extending to adjacent regions. This progression may account for the chronic clinical presentation of fibrosis in radiotherapy patients [9].

Although neuropathy is clinically considered to be a less common cause of CRT induced dysphagia, it can occur as the result of neural tumor infiltration, chemotoxicity, or as a late effect of radiotherapy [9]. The NIH Laryngeal Study Section presented preliminary data that has allowed for an improved understanding of the neuromuscular etiology of chronic dysphagia after CRT [10]. In this study, Martin et al. found electromyographic evidence of at least partial denervation of the geniohyoid, mylohyoid and thyrohyoid muscles, required to achieve supraglottic closure and upper esophageal opening, in 90% of patients that had undergone RT or CRT for head and neck cancer. Of note, in the study, intramuscular stimulation at rest induced hyolaryngeal movement similar to that of healthy controls, which implies that the muscles in these patients were not entirely fibrotic. Although the etiology of neuropathy after chemoradiotherapy has not been completely described, there is possibility that brainstem neurotoxicity, peripheral devascularization, and compressive injury from surrounding fibrosis may be play a role [9,10].

The formation of strictures after CRT has also been linked to the development of dysphagia (Figure 1). Approximately 21% of patients develop symptomatic strictures after undergoing concurrent CRT [11]. CRT results in an increased severity of side effects, as compared with RT alone [11]. Furthermore, patients who undergo altered fractionation RT have an increased risk of developing a stricture [11]. Another significant risk factor for stricture formation is the hypopharyngeal location of the tumor. This site appears susceptible to stricture formation as it is in close proximity to mucosal membrane, such as the post-cricoid area and the posterior pharyngeal wall [11]. The mucosal apposition predisposes to fibrosis and stricture formation after acute mucositis resolves. Female gender has also been implicated as a risk factor for stricture formation [11]. This association may be linked to the fact that females have a decreased pharyngeal circumferential area as compared with males, which makes the strictures more symptomatic. It has also been noted that patients who receive a gastrostomy tube during the course of therapy may be at an increased risk of stricture formation secondary to the relative inactivity of the upper esophageal and hypopharyngeal musculature. For instance patients who had been without oral intake for more than 2 weeks during CRT have been found to have worse swallowing scores [12]. Lastly, the duration of treatment-induced mucositis

during CRT has been linked to the development of strictures [13]. Specifically, duration of 15 weeks of treatment-induced mucositis was found to be highly predictive of stricture formation [13].

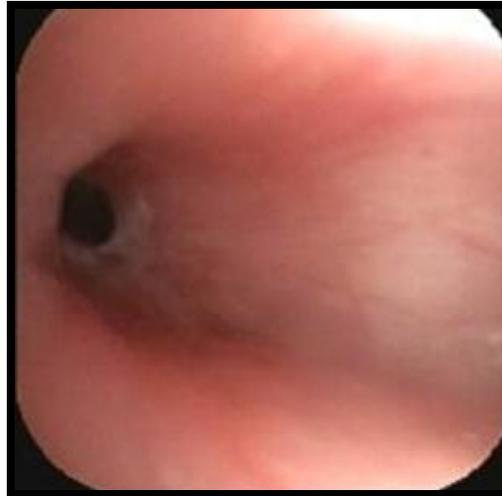


Figure 1: Esophageal Stenosis after CRT for base of tongue cancer evaluated with office based trans-nasal esophagoscopy (TNE). The formation of stenosis leads to dysphagia that is highly amenable to surgical dilation with improvement in swallowing QOL outcomes.

4. Epidemiology:

Based on published population-based estimate of swallowing outcomes from the Surveillance Epidemiology and End Results (SEER) registry and Medicare databases in 8,002 patients with oral, pharyngeal, and laryngeal squamous cell carcinoma, dysphagia was found to occur in approximately 64% of patients who had received CRT [4]. Of these, approximately 12% were found to have been diagnosed with strictures. In addition, there was more than 2.5-times-greater odds of dysphagia in CRT patients compared to surgery alone [4].

One of the most commonly reported swallowing outcome in the clinical literature is the rate of feeding tube dependence. However, it should be mentioned that feeding tube dependence may underestimate the burden of dysphagia, since patients often eat despite clinical evidence of dysphagia or aspiration [9]. The rates of feeding tube dependence have been reported in most clinical trials as <10% at 1 year and <5% at 2 years [9]. An exception was noticed in the RTOG 99-14 study, which found tube dependence in 41% of patients at 1 year and 22% at 2 years [14].

It is generally agreed that aspiration rates are likely underreported in studies that only evaluated symptomatic patients with instrumental

assessment as silent aspiration has been observed in at least a third of aspirators after treatment with CRT. For instance, in studies that only evaluated symptomatic patients, the aspiration rates are between 24% and 31% [15,16]. On the other hand, studies that examine both symptomatic and asymptomatic patients with the use of instrumental swallowing evaluations have reported higher aspiration rates of 30% to 62% [17, 18].

5. Quality of Life:

Patients suffering from dysphagia have the risk of becoming isolated and depressed, since they find it difficult to engage in social activities. [19] For instance, having dinner in a social setting can cause fear of embarrassment secondary to the inability to have normal swallowing function. Nguyen et al. showed that the degree of anxiety, depression, and compromised quality of life that head and neck cancer patients can experience after treatment can be correlated with the severity of their dysphagia. [20] In the same study, it was shown that patients with aspiration, who required prolonged tube feedings had the worst quality of life [20]. In a different study Nguyen et al. showed that dysphagia after CRT rarely returned to normal after swallow therapy alone, as assessed by sequential Modified Barium Swallow Studies to monitor long-term dysphagia [21]. Dysphagia specific quality of life assessment tools are available [22, 23].

6. Diagnosis:

The evaluation of dysphagia and aspiration risk after CRT can be complex. Most patients after CRT suffer from sensory loss of the laryngeal and pharyngeal structures. Therefore the cough reflex is often absent or reduced, thus placing the patient at a high risk for silent aspiration. Therefore, instrumental assessments such as videofluoroscopic and endoscopic evaluation of swallowing are important components of swallowing evaluation.

A complete history and physical examination of the swallowing mechanism from the lips to the esophagus is essential. Patients will complain of a sensation of food being stuck, reduced ability to swallow, or inability to swallow. Coughing upon swallowing attempts may be present. In severe cases of dysphagia patients may be unable to manage their secretions or there may be a history of aspiration pneumonia. Patients with structural lesions such as pharyngoesophageal stenosis will more likely complain of solid food dysphagia unless there is complete stenosis, in which case they will not pass food of any consistency.

The videofluoroscopic swallow study, also known as a modified barium swallow study (MBSS), allows assessment of the physiology of the patient's

swallowing mechanism from the lips to the upper esophagus while feeding the patient with food of different consistencies from liquids to solids [19] (Figure 2). Furthermore, if abnormalities in swallowing function are found, various compensatory maneuvers to improve swallowing and decrease the risk of aspiration can be implemented. The clinician should recognize that aspiration has been documented in 68-81% of patients prior of following chemoradiation of the head and neck, as detected with MBSS [19].



Figure 2. Modified Barium Swallow Study (MBSS) – Lateral View. Note barium solution is unable to pass beyond the level of the upper esophagus, signifying presence of an esophageal stricture.

Another objective tool to evaluate swallowing dysfunction is functional endoscopic evaluation of swallowing (FEES). During this procedure, the pharyngeal swallowing phase is visualized from above with a trans-nasal flexible laryngoscope. The advantage of FEES over MBSS is that direct observation of the swallowing anatomy is possible. By using this technique, the anatomy and function of the soft palate, tongue base, pharynx, and larynx can be assessed during speech and swallowing. Similar to MBSS, food of various consistencies is given to the patient and the swallowing efficiency and abnormalities are directly observed. In addition, the sensitivity of the pharynx can be evaluated by lightly touching the pharyngeal structures with the tip of the endoscope. Furthermore, premature leakage of food or fluid from the mouth into the pharynx before a voluntary swallow can be directly visualized, as well as residue in the vallecula, aryepiglottic region, and piriform sinuses [24] (Figure 3). Laryngeal penetration and aspiration, as well as the patients' reaction to residues or aspiration can be noted [24]. It should be mentioned that FEES can be combined with sensory testing (FEESST), with the use of air pulse stimuli delivered through a port in the flexible endoscope to the mucosa innervated by the superior laryngeal nerve [24]. However, addition of

sensory testing has played very limited roles in the clinical decision making process to recommend a safe diet.



Figure 3: Functional Endoscopic Evaluation of Swallowing (FEES). FEES of a post-CRT patient who developed dysphagia. Notice the significant food residue within the vallecula and the bilateral pyriform sinuses. Also, note the edematous and thickened epiglottis, which contributes to the dysphagia symptoms.

FEES and MBSS are complementary tools for evaluation of dysphagia. FEES main advantage is in the direct evaluation of pharyngeal swallow anatomy, whereas MBSS is superior in the dynamic evaluation of the oral and upper esophageal phases of swallowing [24]. Of importance, FEES is a practical and cost-effective test that can be easily performed at bedside without radiation exposure and is a critical assessment tool for the otolaryngologist to evaluate dysphagia [24]. However, FEES only provides indirect information about oral cavity function, and only very limited impression of the upper esophageal sphincter function can be made. [25].

Another important modality of swallow assessment is esophagoscopy, which can now be performed transnasally in the clinic. This has revolutionized the assessment and management of modern swallow assessment and therapy. In order to directly evaluate the aerodigestive mucosa and detect structural abnormalities, office esophageal endoscopy can be used. In order to perform an in office trans-nasal esophagoscopy (TNE), the nasal cavity needs to be well anesthetized, since the diameter of the scope ranges from 4.3 mm to approximately 6.0 mm [26]. After the TNE scope is advanced trans-nasally into the hypopharynx, the patient is asked to swallow, which allows the hyolaryngeal complex to elevate and open the upper esophageal sphincter. This provides an appropriate entrance for the TNE scope past the cricopharyngeus muscle into the esophagus. One of the major advantages of this procedure is fact that it can be done without general anesthesia or

sedation. Modern endoscope use distal video chip technology that allows the clinician to capture and transmit the image from the distal end of the endoscope. The diagnostic capability of TNE is similar to conventional esophagoscopy under sedation or general anesthesia. The endoscope has internal channels that allow for suction, air and irrigation to be used (Figure 4). This is important as air insufflation allows for visualization of the esophagus and stomach, which are normally decompressed [26]. The channel also allows procedures such as instillation of medications, biopsy, injection, and other procedures to be performed at the same time.

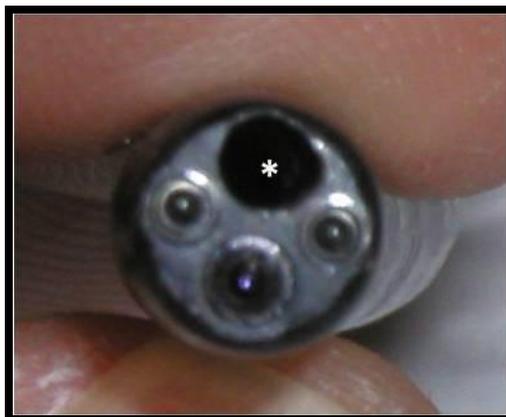


Figure 4: Trans-nasal Esophagoscope (TNE). The distal end of the scope has light, camera, and a working channel. The working channel port (*asterisk*) allows instrumentation to be passed to perform procedures.

7. Treatment:

A. Prevention of Dysphagia

The prevention of dysphagia in chemoradiation patients is extremely important. In order to accomplish this, three approaches can be utilized: Radioprotectors, Radiation Modifications, and Swallow Exercises.

Radioprotectors:

The radioprotector amifostine (WR2721) is a thiol compound that protects normal tissue from the effects of radiation by binding of the sulfhydryl group with hydroxyl radicals [24]. Although there haven't been good level I studies to suggest that radioprotectors can alleviate dysphagia, there has been evidence that when head and neck cancer patients are treated with concomitant CRT with or without amifostine, given before each chemotherapy cycle and less than 45 minutes before RT, the side effect profile of treatment is improved. For instance, patients

who received the amifostine regimen experienced less acute levels of mucositis, xerostomia, loss of taste, and dysphagia [27-29]

Radiation Modifications

As there is a relationship between xerostomia and dysphagia [30], there is a possibility to decrease dysphagia by improving salivary gland function. One approach to accomplish this is to use parotid gland-sparing conformal RT or Intensity-Modulated Radiation Therapy (IMRT) [31, 32] In IMRT, the intensity of the radiation beam can be modulated in order to decrease the doses normal tissue is exposed to without compromising the doses to the tumor. In order to reduce xerostomia and dysphagia, a mean radiation dose to the parotid gland of approximately 26 Gy or less should be the goal [33]

In the same way, there have been studies to explain dysphagia-aspiration-related structures (DARS), which when damaged can cause dysphagia and aspiration. These structures include: the superior, middle and inferior pharyngeal constrictor muscles, the cricopharyngeal muscle, the esophagus, the glottis and the supraglottis [34, 35, 36]. IMRT can allow for reduced doses to DARS which could potentially lead to improved swallowing [32, 37, 38]. There have been a number of retrospective studies that have shown a correlation between either subjective or objective assessment of dysphagia and dose volume parameter of swallowing structures. The data shows that in order to reduce swallowing dysfunction, there needs to be a reduction in the mean doses and volumes of the DARS that receive 50 Gy or more [39, 35-38].

Swallowing Exercises

Swallowing exercise programs are designed to improve swallow physiology, with the hope of potentially decreasing the severity of dysphagia before it develops. These exercises can be easily learned by the patient with the help of the speech language pathologist [40]. There are a number of procedures designed to improve the function of particular muscles or muscle groups. One these exercises are the range of motion (ROM) exercises, which are designed to improve the movement of the target swallowing structures. ROM exercises are available for the oral tongue, tongue base, lips, larynx, and hyoid-related musculature [40].

Another type of exercises are the resistance exercises, which are designed to strengthen the target structure by stretching it as far as possible and holding it in extension for several seconds [40]. With this type of exercise, one can target the tongue, jaw, larynx, and lips. In addition to these exercises, other frequently performed pre-treatment swallowing exercises include Mendelsohn maneuver, tongue hold, tongue resistance, effortful swallow, and Shaker exercise. It is recommended that these exercises are performed five times a day and are started 2 weeks before RT [40]. The literature has few studies that show an improvement in post-treatment swallowing function and QOL from performing pretreatment swallowing exercises [41].

Swallowing Maneuvers:

Swallowing maneuvers are voluntarily controlled during swallow to change a selected aspect of neuromuscular control [40]. These maneuvers include:

1. The **supraglottic swallow**: involves holding vocal fold closure for a longer period of time to protect the airway [42].
2. The **super-supraglottic swallow**: involves closing the airway entrance before and during the swallow [43].
3. The **effortful swallow**: increases the pressure generated in the pharynx and the oral cavity during the swallow [42].
4. The **Mendelsohn maneuver**: prolongs and increases the diameter of the opening of the upper esophageal sphincter during the swallow by manually keeping the larynx elevated during swallow [44, 45].

It should be mentioned that it is crucial to obtain an excellent swallowing function evaluation, in order to identify the abnormal physiological aspect of the swallowing mechanism [40]. In the same way, one can instruct the patient to perform a trial of the appropriate maneuver during radiologic evaluation of swallowing (i.e. MBSS), to determine the effectiveness of the therapy.

B. Surgical Treatment:

The etiology of dysphagia must be identified via clinical examination and diagnostic studies to develop a surgical treatment plan. First, it is important to rule out the possibility of cancer recurrence as the cause of any progressive dysphagia. In the case of patients with pharyngeal and esophageal stenosis,

as diagnosed with MBSS and endoscopic examination, dilatation of the stenotic region should be performed to decrease obstruction [19]. Sullivan et al. reported that endoscopic dilation can be used successfully in this patient population [46]. Furthermore, our own preliminary data, assessing swallowing function after serial stenosis dilation, shows 38% of our chemoradiation patients resuming a regular diet with no residual dysfunction (Figure 5). More importantly from a QOL perspective, we have found that 89% are gastrostomy-tube (G-tube) independent after serial esophageal dilations in CRT patients who were initially G-tube dependent during or right after CRT.

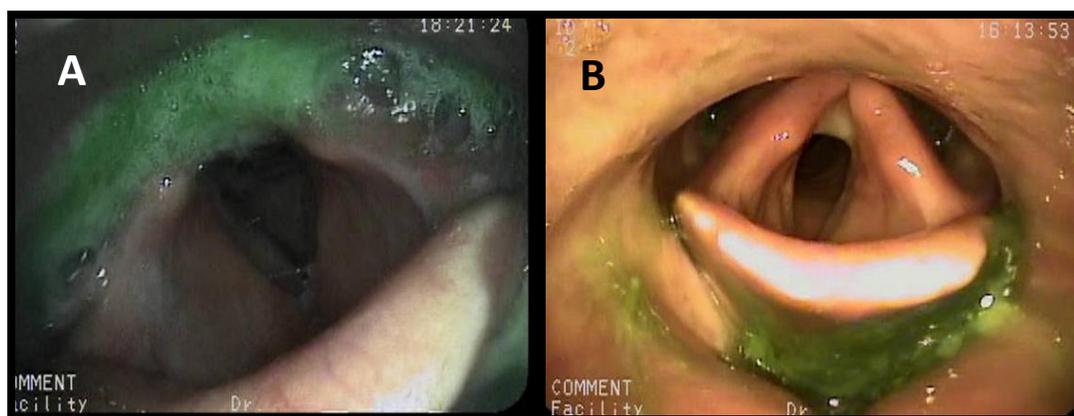


Figure 5: Typical outcome after esophageal stenosis dilation procedure. A: Pre-dilation FEES of post-CRT patient who developed esophageal stenosis. Notice pooling of food residue in post-cricoid and bilateral pyriform sinuses. Patient is completely G-tube dependent. B: Post-dilation FEES. Note the significant improvement in the clearing of food residue from the post-cricoid region and the bilateral pyriform sinuses. Patient's G-tube has been removed.

It's important to recognize that patients with dysphagia must be referred to a speech pathologist in the post-operative period for continuing aggressive rehabilitation of swallowing.

Currently, the options available for esophageal dilation include the mercury-filled rubber Maloney bougies; the wire-guided rigid Savary-Gilliard dilators, the balloon dilators, which can be used either through the endoscope or wire-guided, and serial esophagoscopes of increasing diameter used as dilators [47] (Figure 6). In general, the selection of the dilator is dependent on the characteristic of the stricture and the experience of the surgeon. For the most part, the use of the Maloney bougies can be reserved for uncomplicated and short strictures. On the other hand, the wire-guided Savary-Gilliard dilator and balloon dilators are both best used for long, tight, or tortuous strictures. The carbon dioxide laser has also been used prior to dilation to optimize results. It is very useful to have the TNE or an ultrathin esophagoscope available at the time of stricture dilation. Combined anterograde and retrograde esophagoscopy with dilation is often needed for complete strictures.

Esophageal stenosis: Dilators

	Dilator Type	Ease of Dilation	
		OR	Office
Savary-Gilliard	Mechanical Guidewire	+++	+
Balloon CRE or TTS or OTW	Balloon Guidewire and Non-guidewire	+++	++
Bougie (Maloney)	Mechanical Non-guidewire	+	-
Rigid serial esophagoscopes	Mechanical Non-guidewire	+	N/A

Figure 6: Different Types of Dilators Used for Esophageal Stenosis in CRT patients. +++ = most suitable, ++ = very suitable, + = suitable, - = not suitable, N/A = Not applicable. OR = Operating Room.

Complications related to esophageal dilation are uncommon, but not rare. For instance Sullivan et al. observed hypopharyngeal perforation (13%), abdominal wall infection (6%), stomach wall dehiscence (6%), and chondroradionecrosis of the cricoid cartilage (6%) after performing dilations in post-chemoradiation patients who presented with hypopharyngeal stenosis [46]. Therefore, the clinician should be aware of the fact that patients with radiation-induced or malignant strictures have a significantly high risk of perforation [47]. In our experience these complications have been exceedingly rare (*manuscript in preparation*).

8. Prognosis:

In general the goal for stenosis dilation should be to obtain a diameter of greater than 15 mm. Because of the risk of re-stenosis, it is recommended for the patient to undergo at least two dilations to optimize results. Also, the use of intralesional injection of steroids and Mitomycin C during the dilation procedure can decrease the probability of re-stenosis [48, 49]. Continued vigilance is needed to monitor for re-stenosis and this can be achieved with in-office FEES and TNE. Re-stenosis rate is directly related to the degree of stenosis at the initial dilation. In-office maintenance esophageal dilations can also be performed safely using balloon dilators and the trans-nasal esophagoscope.

As mentioned earlier, we have found that approximately 38% of our chemoradiation patients have been able to resume a regular diet with no limitations after serial dilation of esophageal stenosis and 89% had their gastrostomy tube removed after treatment and could maintain an oral diet.

9. Conclusions:

Chemoradiation therapy (CRT) has become an increasingly used mode of treatment of head and neck cancer. An increasing number of patients receiving CRT are surviving; therefore, it is important to pay careful attention to the long-term side effects affecting this population. Dysphagia has been observed to affect up to 50% to 64% of patients after CRT [4, 5]. Dysphagia after chemoradiation may be related to a number of issues including mucositis, severe dysfunction of the base of tongue, larynx, and pharyngeal muscles [6, 7]. The formation of fibrosis has also been considered a primary source of late chemoradiotherapy-induced dysphagia. Approximately 21% of patients develop symptomatic strictures after undergoing concurrent chemoradiation therapy [11]. Patients suffering from dysphagia have the risk of becoming isolated and depressed, since they find it difficult to engage in social activities [19]. The complete evaluation of patients with dysphagia should include a thorough history and objective measures such as modified barium swallow study (MBSS), flexible endoscopic evaluation of swallowing FEES, and esophageal endoscopy. It is important to consider preventive measures for the development of dysphagia in patients undergoing chemoradiation. The etiology of dysphagia must be identified via clinical examination and diagnostic studies to develop an adequate treatment plan. After the possibility of cancer recurrence has been ruled out, treatment strategies should include operative interventions of anatomic stenosis as well as continued aggressive swallow therapy and monitoring of swallowing with involvement of a dedicated multidisciplinary team.

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