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Review

Late radiation-associated dysphagia in head and neck cancer patients: evidence, research and management

F. De Felice[a,*], M. de Vincentiis[b], V. Luzzi[b], G. Magliulo[c], M. Tombolini[c], G. Ruoppolo[c], A. Polimeni[b]

[a] Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome, Rome, Italy
[b] Department of Oral and Maxillo Facial Sciences, Policlinico Umberto I "Sapienza" University of Rome, Italy
[c] Department of Sense Organs, Policlinico Umberto I "Sapienza" University of Rome, Italy

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ABSTRACT

In head and neck cancer (HNC) scenario, newer radiotherapy (RT) techniques, such as intensity modulated RT (IMRT), aim to reduce acute and late toxicity without impair tumor response and loco-regional control rates. However, late radiation-associated dysphagia (RAD) remains a major clinical problem and has gained a growing importance in the last few years, especially due to human papilloma virus (HPV)-related HNC favorable prognosis.

The aim of this review was to provide clinical information about late RAD. The main anatomical structures involved in swallowing were described, in order to define potential organ at risk and available radiation-dose constraints in IMRT plan. Finally, possible rehabilitation strategies were proposed. This is expected to represent an opportunity for improved multidisciplinary management in HNC patients.

Introduction

In the last decades there has been a significant progress in treatment modalities of head and neck cancer (HNC) patients, especially in radiation therapy (RT) field. Globally, RT improved from three-dimensional to intensity modulated RT (IMRT) technique, which showed to be more effective in terms of target volume coverage and organs at risk (OAR) sparing [1]. Since IMRT plus concomitant chemotherapy – the standard treatment in locally advanced disease – improves survival outcomes achieved after RT alone, as well as increases side effects, great interest has been shown in the clinical evaluation of late RT-related toxicity [2]. Over the years, a growing number of studies have been published on this issue. This may be explained by the fact that such improvements in terms both of RT technique and survival outcomes have resulted in an increased prevalence of long term toxicities in survivors.

Late radiation-associated dysphagia (RAD) is recognized as a frequent complication in HNC patients. It refers to difficulty in swallowing and represents a long-term or even permanent sequel that negatively impacts on patients' quality of life (QoL) and ability to function in society.

The aim of the present manuscript is to review the available evidence-based data on late RAD and to ascertain how it has severe adverse effects on QoL. We focused on IMRT era, showed the increased attention for RT morbidity in HNC patients, and the value of RAD in the future data context. The major characteristics of swallowing complex were described. We propose the delineation of dysphagia/aspiration-related structures (DARS) to facilitate routine radiation oncology practice. The recent advances in RAD management are also discussed.

Search strategy

PubMed and Clinicaltrials.gov databases were searched for electronic publications, written in English. The following combination of research terms were used: "dysphagia", "swallowing", "late radiation-associated dysphagia", "RAD", "dysphagia/aspiration-related structures", "DARS", "toxicity", "side effects", "radiation therapy", "radiation", "chemoradiotherapy", "head and neck cancer", "organ at risk", "delineation", "contouring". We have selected the studies that have reported on swallowing assessments after a follow-up of at least one year. In addition, clinical studies of contouring and consensus guidelines of OAR in HNC were analyzed. Reference lists of selected studies and review papers were manually searched for additional relevant publications. Search strategy was performed up to October 2017.

* Corresponding author at: Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome, Viale Regina Elena 326, Rome, Italy.
E-mail address: francesca.defelice@uniroma1.it (F. De Felice).

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Swallowing anatomy

Swallowing anatomy is complex and comprises the oral cavity, the pharynx and the larynx. The main role of these swallowing structures is to transport food/bolus from the mouth to the esophagus (which is then part of the gastrointestinal tract). This process involves approximately 50 pairs of muscles and five cranial nerves – trigeminal (V), facial (VII), glossopharyngeal (IX), vagus (X) and hypoglossal (XII). Swallowing is divided into three phases, including the voluntary oral phase and the involuntary pharyngeal and esophageal phases [3]. Bolus formation occurs in the oral cavity and requires coordination of lip, buccal, mandibular and tongue movements. During normal swallowing, once the tongue propels the bolus into the pharynx, the epiglottis closure over the laryngeal vestibule, the laryngeal elevation and the closure of the glottis prevent aspiration into the airway. The pharyngeal wall consists of an inner longitudinal layer (palatopharyngeus muscle, stylopharyngeus muscle and salpingopharyngeus muscle) and an external circular layer, including superior constrictor muscle, middle constrictor muscle and inferior constrictor muscle (that consists of thyropharyngeus muscle and the cricopharyngeus muscle). Contraction of the pharyngeal constrictor muscles, as well as negative hypopharyngeal pressure and gravity accomplishes bolus propagation [3].

Dysphagia/aspiration-related structures (DARS)

Due to swallowing apparatus complexity, defining the importance of specific anatomic structures associated with significant correlations between dose-volume parameters and dysphagia, in a IMRT treatment plan, is difficult [4]. The main dysphagia/aspiration-related structures (DARS) include: hard and soft palate, intrinsic tongue muscles, mylo/geniohyoid musculature complex, genioglossus muscle, palatoglossus muscle, buccinator muscle, anterior and posterior digastrics muscles, medial and lateral pterygoid muscles, superior constrictor, middle constrictor and inferior constrictor muscles, supraglottic and glottis larynx, cricoesophageal sphincter. Accurate DARS delineation is paramount to maximize therapeutic ratio and reduce risk of swallowing dysfunction. In order to discriminate the DARS from surrounding tissues and thus optimize contouring process, it is recommended to supplement computed tomography planning scan with fused diagnostic magnetic resonance imaging (MRI) [5]. Actually, Eisburch et al. [6] first deemed necessary to determine the most important anatomic structures whose damage was likely to cause RAD in IMRT era. The constrictor muscles and the glottic and supraglottic larynx were identified. Then, a series of guidelines have been proposed to easily outlined DARS in treatment plan. Recently, the departments of Radiation Oncology of the VU University Medical Center (VUMC) and the University Medical Center Groningen (UMCG) described institutional guidelines for the delineation of potential DARS [7]. Data indicated that pharyngeal constrictor muscles, esophagus inlet muscles, cervical esophagus, base of tongue and larynx are involved, or potentially involved, in the development of RAD. However, they did not consider relevant structures, such as hard palate, soft palate, lateral and medial pterygoid muscles, genioglossus muscle and mylo/geniohyoid complex. Similarly, international consensus guidelines for delineating OAR for HNC RT did not specifically define DARS [5]. Whereas, recently, the MD Anderson head and neck cancer symptom working group [8] found a consistent correlation between swallowing muscles dose-volume parameters and late RAD. Of 300 oropharyngeal cancer patients, 11% of cases reported late RAD following ≥12 months after IMRT treatment. Dosimetric data pointed to mylo/geniohyoid complex V69 (the volume receiving ≥69 Gy), genioglossus V35, anterior digastrics V60 as a potential constraint for clinical implementation. We believe that a detailed explanation of swallowing structures would lead to better understanding of the factors associated with late RAD. DARS contouring details are summarized in Table 1 [7–10]. This table is hypothesis-generating. It will help to reduce subjective variations among clinicians in DARS delineation and represents an attempt to reduce the risk of late RAD. Surely, further studies including dose-volume histogram analysis of all these DARS should be undertaken. Recent evidence has examined the dosimetric parameters of specific swallowing organs at risk – base of tongue, superior, middle and inferior pharyngeal constrictors, glottic/supraglottic larynx, upper esophageal sphincter and esophagus – and their impact on post-treatment RAD, indicating that further detailed and systematic studies are required [11].

Radiation dose levels to these structures may clarify their impact on late RAD incidence and severity, although it should be difficult to observe all DARS constraints due to HNC requirement for large treatment fields and high doses.

Late radiation-associated dysphagia (RAD)

Late RAD refers to difficulty in swallowing as a result of chronic RT effects, including tissue fibrosis, strictures and lower cranial neuropathy with contribution to rigidity and loss of swallowing apparatus function. It can result in malnutrition and place HNC patients at risk of aspiration, with increased negative effects on anxiety and depression. Primary tumor involvement of sites important for swallowing, as well as target vicinity to the swallowing structures, may negatively impact on late RAD [12]. For sure, target volume coverage should maintain the highest priority, keeping the radiation dose to DARS as low as possible [13]. In order to reduce late RAD, the recommended dose-volume limits suggested to minimize the volume of the pharyngeal constrictors and larynx receiving 50–60 Gy, without compromising target doses [4]. In addition, a dose-effect relationship, with an increase of the probability of RAD of 19% with every additional 10 Gy to muscular structures, has been established [14]. Late RAD remains a major detrimental effect of RT, even in those patients receiving IMRT. Although IMRT resulted in a reduction of late RAD, its prevalence is still high, up to 38% [15]. Table 2 listed the main IMRT studies assessing late RAD [9,16–25]. The vast majority of studies are retrospective in nature. All studies are quite heterogeneous in term of treatment schedules and late RAD reporting. Therefore, it is difficult to compare the results. Globally, no attempt was made to spare DARS; however a favorable swallowing profile seems to be possible if dose to certain structures is limited. Interestingly, in Peponi et al. [22] study, despite any specific constraints was introduced, a dose reduction to DARS was obtained as a consequence of a highly conformal dose to the target volume. Whereas, Bhide et al. [18] did not find a statistically significant correlation between dose to pharyngeal constrictors and late RAD. But only observer-assessed parameters, and no robust objective assessment such as videofluoroscopy, were used, thus no definitive conclusion can be drawn. At present, no randomized controlled trials are published. The sole phase III trial available in literature is the DARS trial, in which HNC patients are randomized to dysphagia-optimised IMRT versus standard IMRT [25]. Waiting for final and confirmatory data, it is expected that dose reduction to DARS can safely improve late RAD. Interestingly, to minimize confounding factors, authors exclude patients with pre-existing dysphagia and those with posterior pharyngeal wall or post-cricoid disease and/or retropharyngeal lymph node involvement. These strict criteria ensure that RAD will be secondary to treatment alone.

In the meantime, recent HNC studies have consistently demonstrated that proton therapy significantly reduced the dose to OAR, such as anterior oral cavity and swallowing structures, over IMRT [26]. The proton dosimetric advantages should translate into decreased late RAD risk, in a near future. At present, no literature is available on such functional outcome.

Late radiation-associated dysphagia (RAD) evaluation

Swallowing disorders include three specific clinical conditions: (i) residue – food remaining in the mouth or pharynx structures; (ii) penetration – food or liquid entering the airway entrance; (iii) aspiration –