Chapter

Radiation-Related Dysphagia: From Pathophysiology to Clinical Aspects

Stefano Ursino, Paola Cocuzza, Stefania Santopadre, Fabiola Paiar and Bruno Fattori

Abstract

In Western countries, head and neck cancers (HNCs) account for about 5% of all tumors. Due to tumor locations at the aero-digestive crossroad, patients frequently suffer from swallowing dysfunction caused both by primary cancer (baseline dysphagia) and cancer therapies (treatment-related dysphagia). In this regard, radiation-induced dysphagia represents a real "Achille's heel" which historically occurs in more than 50% of patients and can lead to a malnutritional status and an increased risk of aspiration pneumonia. In fact radiotherapy, by restricting the driving pressure of the bolus through the pharynx and/or limiting the opening of the cricopharyngeal muscle, leads to a post-swallowing pharyngeal residue that may spill into the airway causing ab ingestis pneumonia. On the contrary, an organ preservation strategy should provide both the highest tumor control probability (TCP) and the minimum function impairment with the subsequent maximum therapeutic index gain. In this regard, intensity-modulated RT (IMRT) might reduce the probability of postradiation dysphagia by producing concave dose distributions with better avoidance of several critical structures, such as swallowing organs at risk (SWOARs), which might result in better functional outcomes. Similarly, a prompt swallowing rehabilitation provided before, during, and soon after radiotherapy plays an important role in improving oncologic swallowing outcomes.

Keywords: swallowing, dysphagia, intensity and modulated radiotherapy, chemotherapy, aspiration, videofluoroscopy

1. Introduction

Nowadays, radiotherapy (RT) alone or most frequently combined with chemotherapy (RCT) is considered a valid alternative treatment to surgery for patients affected by head and neck cancers (HNCs) in order to preserve the deglutition organ [1, 2]. Historically, conventional RT has been burdened by severe and potentially "life threatening" toxicity that limited the delivery of high tumor radiation dose and in most cases affected the final treatment result [3–6]. In this regard, radiation-induced dysphagia, as a final multifactorial side effect often requiring enteral nutrition, has always represented a real "Achille's heel" occurring in more than 50% of patients and leading to a malnutritional status, increased risk of aspiration pneumonia, and long-term percutaneous endoscopic gastrostomy (PE) tube placement positioning [7–10].

Moreover, eating together is a defining social activity among family, friends, and colleagues. For most people, the ability to enjoy eating helps to define quality of life (QoL), whereas labored swallowing, prolonged eating times, and the limited range of foods that can be swallowed can lead to disruption of relationships and social isolation [11].

Indeed, in the last decades, an improvement of oncologic outcomes such as local control and overall survival has come from an increasing use of the more aggressive altered fractionation RT schedules and the frequent use of RCT sometimes preceded by induction chemotherapy [1, 12]. Therefore, the common use of high intensified organ preservation strategies has resulted in "potentially" high rates of swallowing dysfunction prompting to consider postradiation dysphagia as the real "barrier to winning the battle of HNC" [13].

2. Basic concepts of oropharyngeal swallowing physiology

Swallowing is a functional complex process, requiring the involvement and perfect sequential coordination of more than 30 pairs of muscles and 6 cranial nerves (V, VII, IX, X,XII) [14–16].

In this regard, pharynx plays a crucial role as an aero-digestive crossroad region both at its upper (naso and oropharynx) and lower part (hypopharynx and larynx) to ensure the constant and effective protection of the airways from the entrance of the bolus together with the safe passage of the bolus into the upper esophagus. This process implies a very complex anatomical change of the pharyngeal tract from a respiratory to a deglutitory configuration to fastly return to the respiratory one in less than a second [17–19].

This process starts with the passage of the bolus through the palatoglossus sphincter (the beginning of the involuntary deglutition) and ends with the relaxing of the cricopharyngeal muscle and the passive opening of the upper esophageal sphincter that moves the bolus into the lower digestive tract (pharyngeal phase). This phase can be further divided into three different subphases: oropharyngeal, pharyngeal, and pharyngo-esophageal phase.

The oropharyngeal subphase corresponds to the activation of "trigger area" located between the anterior palatine pillars, palatine veil and the base of tongue which is innervated by the IX and X cranial nerves. This subphase is mostly characterized by the uplift of the palatine veil which contacts with the posterior pharyngeal wall to close the nasopharynx avoiding the nasal reflux of the bolus (or regurgitation) and by the contraction of the hyoglossus muscle which causes the tilt of the base of tongue favoring the slip of the bolus into the pharynx [20].

The Pharyngeal phase is characterized by the reinforcement of the nasopharynx sealing for the anterior movement of the posterior pharyngeal wall due to the contraction of superior pharyngeal muscle, by the closure of glottic larynx to protect the lower respiratory tract through the activation of superior laryngeal nerve and by the progression of the bolus to the superior esophageal sphincter.

This is the most crucial phase of deglutition as it corresponds to the crossing and overcoming of the bolus of the aero-digestive crossroad.

The closure of the glottic larynx represents the principle mechanism of inferior airways protection which sequentially starts with the true vocal cords adduction (contraction of inferior and medium tyroarytenoid muscles, lateral cricoarytenoid muscles, and interarytenoid muscles), continues with the false vocal cords adduction (tyroarytenoid muscles contraction), and ends with the epiglottis retroflexion [21]. In this regard, the glottic closure is recognized as the main mechanism to protect inferior airways, the retroflexion of epiglottis being the less important.

Specifically, the protection of inferior airways is mostly guaranteed by the early closure of the glottic larynx (due to the true and false vocal cords adduction) together with the combination of the anterior and upper movement of hyolaryngeal complex (due to the contraction of the suprahyoid musculature and inhibition of subhyoid musculature) and the back-forward movement of the base of tongue (due to the contraction of stylo and hyoglossus muscles) that contributes to protect the laryngeal aditus from the spilling of the bolus [17, 22–26].

Indeed, the progression of the bolus through the pharynx is sequentially related to the tongue base retraction and the pharyngeal peristalsis combined with the force of gravity and the downward aspiration of the bolus. Specifically, the tongue base retraction just precedes the pharyngeal peristalsis that is characterized by a craniocaudal stripping wave that propagates toward the hypopharynx and is performed by the sequential contraction of superior, medium, and inferior constrictor muscles. The force of gravity also plays an important role as well as the downward aspiration that is produced in the hypopharynx by the hyolaryngeal complex elevation [19, 27, 28].

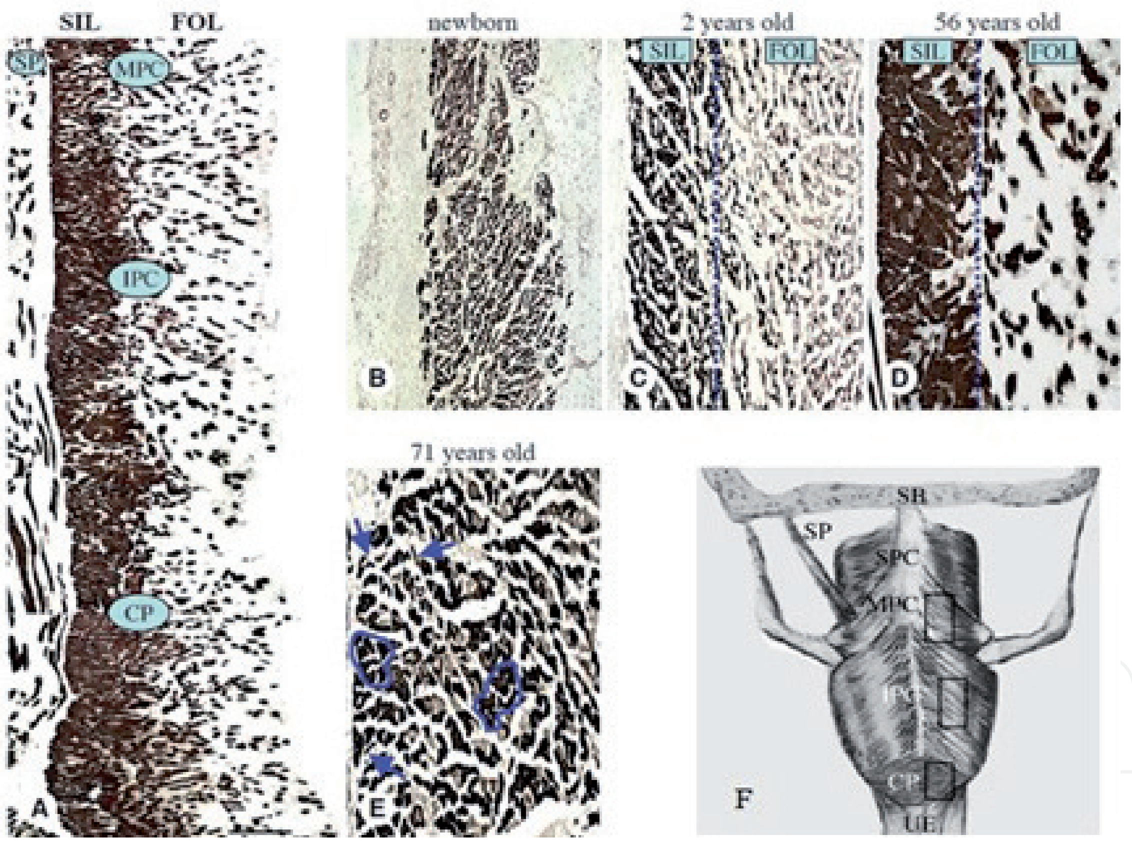

Figure 1.
Developmental (humans at different ages) changes in PC fiber layers. (A) Low-power photomicrographs of immunocytochemically stained cross sections from adult human MPC, IPC, and CP muscles. Scale bar—1 mm. (B)–(G) High-power photomicrographs of IPC muscles of (B) human newborn, (C) 2-year-old human, (D) adult human, and (E) elderly human, (Scale bar—100 μm). All sections were incubated with monoclonal antibody NOQ7-5-4D specific to slow type I myosin heavy chain (MHC) isoform by avidin-biotin complex method. In all sections, slow type I fibers were stained dark, whereas fast type II fibers were stained light. Slow inner layer (SIL), which contained predominantly slow type I fibers, stained dark, whereas fast outer layer (FOL), which contained primarily fast type II fibers, stained light. Note that layered structure of PCs was identified in 2-year-old human (C) and normal adult humans (A, D), but not in human newborn (B) Also note that PC fiber layers in elderly human (E) were obscured because of fast-to-slow MHC transformation that occurred mainly in FOL of PCs. In addition, fiber type grouping (circled fibers) and fiber atrophy (arrows) were apparent in aged (E) muscle (F). Schematic of human pharynx (posterior view) illustrates arrangement of pharyngeal constrictor (PC), cricopharyngeus (CP), and stylopharyngeus (SP) muscles and tissue sampling sites (enclosed regions) for immunocytochemistry. IPC, inferior PC; MPC, middle PC; SB, skull base; SPC, superior PC; and UE, upper esophagus.

Lastly, the pharyngo-esophageal phase is characterized by the opening of the superior esophageal sphincter due to both the hyolaryngeal complex elevation and the cricopharyngeal muscle relaxation, the latter produced by the reduction of basal tonic activity of the vagus nerve [29].

Finally, after the passsage of the bolus into the upper esophagus, the superior esophageal sphincter closes, the hyolaryngeal complex lowers down to the baseline position and the glottic larynx opens leading the pharynx to the baseline respiratory conformation.

The neuronal pathways also play a central role in the swallowing process.

Sensory inputs from physicochemical properties of the bolus (taste, pressure, temperature, and nociceptive somatic stimuli) from oropharynx and larynx are transported through cranial nerves V, VII, IX, and X to the central pattern generator within the nucleus tractus solitarius, where they are integrated and organized with information from the cortex. The somatic sensorial input required for proper swallowing is perceived by the lingual branches of the trigeminal and glossopharyngeal nerves, the pharyngeal branches of the glossopharyngeal and vagus nerves, and the laryngeal branch of the vagus nerve. The swallow response is elicited in the brain stem swallowing center, which receives strong modulating inputs from both the oropharynx and the cortex [30].

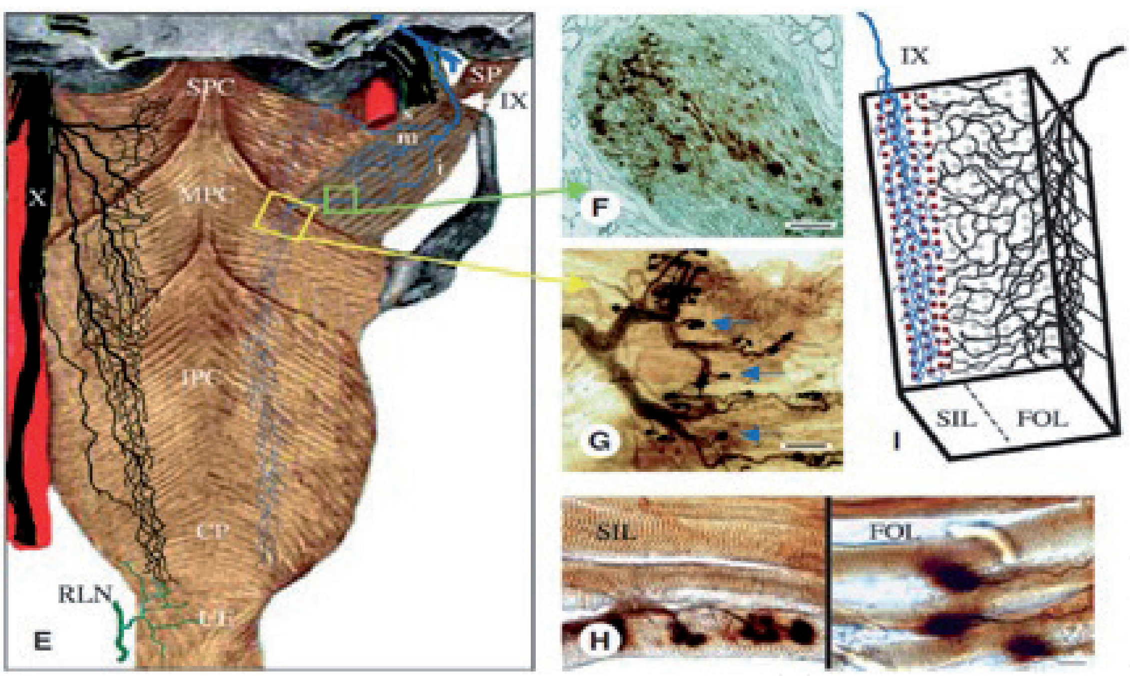

Figure 2.
(A) Schematic of adult human pharynx (posterior view) shows motor innervation of FOL and SIL in PCs. Note that FOL is supplied by Ph-X (left side), whereas SIL is innervated by Ph-IX (right side). After leaving skull through jugular foramen, nerve IX (right side) is subdivided into sensory (cut end) and motor (arrow) divisions. Motor division of Ph-IX gives off three branches—superior (s), middle (m), and inferior (i)—which supply SIL of SPC (dotted lines), stylopharyngeus (SP) muscle, and SIL in MPC, IPC, and CP muscles (dotted lines), respectively. Boxes indicate sampling sites for nerve segment from inferior branch of motor division of Ph-IX (small box) and its innervating muscle tissue (large box). (B, C) Histochemical evidence for motor contribution of IX to SIL in PCs. (B) Karnovsky-Roots AChE-stained cross section of nerve segment sampled from inferior branch of Ph-IX (small box in (E)). Note that this nerve branch contained motor axons (brown staining). Scale bar—100 μm. (C) Whole mount acetylcholinesterase and silver (AChE-Ag)-stained SIL in MPC muscle innervated by nerve terminals (large box in (A)) distal to sampled nerve segment. Note that terminals of this nerve branch innervated motor end plates (MEPs; arrows) on SIL muscle fibers. Scale bar—100 μm. (D) High-power view of AChE-Ag-stained MEPs shows types of MEPs (en plaque or en grappe) and preterminal branching patterns (single or multiple) of axons innervating MEPs. Note that single SIL fiber had multiple en grappe MEPs (left), whereas most FOL fibers (right) had en plaque MEPs with single preterminal axon. Scale bar—20 μm. (E) Schematic illustration of cross section from PC muscle in (A) shows intramuscular distribution patterns of nerve IX innervating SIL and nerve X innervating FOL in muscle.

Besides, the histological and biochemical structure of the pharynx is considered of prior importance for the understanding of radiation-related swallowing damage as well as baseline deglutition impairment in elderly patients. Adult human pharynx is divided in two distinct and separate layers, an inner one (slow inner layer or SIL) that is innervated by the IX cranial nerve and an outer one (fast outer layer or FOL) that is innervated by the X cranial nerve. The first one is composed by a high prevalence of myofibers containing slow-twitch myosin (Type I) characterized by a slow time contraction, high mitochondrial density, and high oxidative capacity, and is mostly responsible for the tone, stiffness of the pharynx, and fine adjustments; whereas the second one is composed by a high prevalence myofibers containing fast-twitch myosin (Type IIb) characterized by a fast contraction, low mitochondrial density, and low oxidative capacity and is mostly responsible for the contraction of the pharynx. Based on the fiber type and response to radical oxygen species, muscles with the highest glycolytic capacity (Type IIB) are most at risk for radiation damage. The immunohystochemical analysis of the pharynx has shown that the ratio between the width of the two layers (SIL/FOL) changes in a craniocaudal direction approximately from 2:1 in the cranial portion to 1:2 in the caudal portion of the pharynx. A physiological transformation process of the fast fibers into slow ones in the outer layer (also known as "fast to slow transformation") has been shown with the aging process reporting an overall 32% and 73% representation of type I fibers in the outer layer of the adult and elderly, respectively [31–33] (**Figures 1** and **2**).

3. Pathophysiology of postradiation swallowing impairment

Generally, based on the above reported mechanisms, anything that restricts the craniocaudal driving pressure, including the back-forward movement of the base of tongue, or impairs the hyolaryngeal complex elevation, or limits the cricopharyngeal muscle and/or superior esophageal sphincter opening, leads to post-swallowing pharyngeal residue that may spill into the airways. Thus, the post-swallowing aspiration is the risky consequence of a severe radiation-related dysphagia with the subsequent life-threatening risk of aspiration pneumonia (**Figure 3**). In this regard, the maintenance of cough reflexes is considered essential to avoid the spillage of the bolus below the vocal cords and prevent silent aspiration [11].

Moreover, a pathophysiological neuromuscular vicious circle can be described regarding postradiation dysphagia mechanism mainly consisting in a selective loss of the more radiosensitive type IIb myofibers together with a damage of peripheral nerves that innervate the swallowing musculature [29, 34, 35]. In the early phase

Figure 3.
Example of post-swallowing aspiration in an oropharyngeal cancer patient after RT. (A) Severe pharyngeal residue on Videofluoroscopy, (B) severe pharyngeal residue both on glossoepiglottic folds and pyriform sinuses on fiberoptic endoscopic evaluation of swallowing and (C) aspiration on videofluoroscopy (black arrow).

(during and immediately after radiotherapy), the neuropathic radiation damage usually arises from the breakdown of epithelium lining of pharyngolaryngeal mucosa, triggering a cascade of inflammatory mediators (i.e., cytokines, neuropeptides, and glutamate signals) that cause significant pain and discomfort and result in persistent sensory deficit [36, 37]. In the late phase (after months from radiotherapy), the replacement of muscular fibers with fibrotic tissue, characterized by loss of vascularity and matrix disorganization that disrupts well-defined compartmentalized structures as well as excessive collagen deposit that entraps nerve trunks or alters the vascular network between or within the nerve tracts, leads to muscular and neurological deficits [38, 39]. Then, the degeneration of muscular fibers probably related to the disuse of swallowing muscles (oral intake strongly declines during and immediately after radiotherapy) contributes to the transformation of fibrosis to atrophy leading to the final fibroatrophic damage [40].

Hyposensitivity and pharyngeal hypo/dysmotility are the clinical consequences of the neuromuscular radiation damage. Therefore, patients usually suffer from reduced sensory inputs (i.e., bolus size and consistencies) that may lead to "intradeglutitory" silent aspiration or impaired bolus movement through the pharynx tube with a consequent "post-swallowing" pharyngeal residue [38].

On the other hand, preclinical data clearly show that with aging, the number of satellite cells for myofiber decreases and those cells that remain exhibit a limited potential of regeneration. Also chronic inflammation and reactive oxygen species, such as those produced after irradiation, have been implicated in this aged effect.

However, endurance exercise has been reported to restore regenerative potential through changes in satellite cell number and function. As a matter of fact, in the study by Schadrach and Wagers [41, 42], the potential benefit of endurance exercise on satellite cells has been proven.

Myofibers of the inferior limb muscles were then isolated from exercised and sedentary mice, both young and old, and used for monitoring satellite cell numbers, and an expansion of the satellite cell pool in the exercised groups was compared with the sedentary one, regardless of the age (young and old).

4. Clinical aspects

4.1 The role of preventive swallowing exercises

Preradiation prophylactic swallowing therapy may be beneficial due to the upregulation of antioxidant enzymes and the enhancement of mitochondrial activity to increase the muscle fatigue resistance, as emerged from preclinical experiments [43–47]. In fact, it is crucial for myofibers of swallowing muscles to have efficient antioxidant capabilities to fight radiation-induced ROS that would, otherwise, cause irreversible damages.

Besides, atrophy is a consequence of both alterations of muscle proteins synthesis resulting in loss of muscle mass and the reduction of renewal of stem cells after radiotherapy [48–51].

Again, this knowledge might suggest that the initiation of the prescribed prophylactic swallowing exercises (i.e., before, concomitantly, or immediately following treatment) might improve functional swallowing outcomes [51–54].

Therefore, despite a strong preclinical rationale for the use of prophylactic strength-based exercises as well as to maintain oral intake throughout the entire radiation treatment to prevent or reduce the occurrence of radiation-induced dysphagia, data from the literature have some methodological concerns such as heterogeneity in the prescribed exercise regimen, in the tumor site/stage and the onset of intervention.

However, a recent study by Hutcheson et al. [55] analyzed the independent effect of maintaining oral intake and proactive swallowing therapy in patients who underwent radiotherapy or chemoradiation for pharyngeal cancers. More specifically, the primary independent variables were:

1. Per oral nutrition status at the end of treatment (defined as NPO (nothing by mouth) and fully PEG tube dependent; partially PO, PEG tube supplemented by consistent daily oral intake; fully PO, 100% oral intake regardless of dietary level) and

2. Self-reported swallowing exercises adherence (adherent versus nonadherent). The results reported a greater proportion of patients who returned to a regular diet at 2 years for those who performed exercises and maintained full PO intake compared to those partial PO and adherent to exercises ($p = 0.02$) and those full PO and nonadherent to exercises ($p = 0.02$). Likewise, a significantly higher persistence of PEG-tube dependence was reported in those NPO and nonadherent to exercises compared to those part PO and adherent to exercises (39% versus 6%; $p = 0.03$). Besides, a previous work by Carnaby-Mann et al. [54] proved a superior maintenance of swallowing musculature structure (determined by T2-weighted magnetic resonance imaging) and a

Maneuver	Indications	Rationale
Supraglottic swallow	Reduced airways closure Aspiration during swallow	The patient is instructed to swallow and push hard with the tongue against the hard palate
Supra-s upraglottic swallow	Reduced airways closure Aspiration before and during swallow	The patient is instructed to hold his or her breath just before swallowing to close the vocal folds. The swallow is followed immediately by a volitional cough.
Mendelsohn maneuver	decreased range / duration of hyolaryngeal elevation, crycopharyngeal opening, pharyngeal swallow coordination	The patient holds the larynx in an elevated position at the peak of hyolaryngeal elevation
Effortful swallow	Vallecular residue Reduced base of tongue retraction	The patient is instructed to swallow and push hard with the tongue against the hard palate
Masako	Reduced base of tongue strenght Reduced pharyngeal contriction	Protrude tongue between teeth and swallow; strenghtens pharyngeal constrictors toimprove contraction
Shaker	Upper esophageal sphincter dysfunction Reduced anterior and superior movement of the hyolaryngeal complex	Lie supine, raise chin to chest and mantain for 60 s; improves opening of upper esophageal sphincter, reduces pyriform sinus residue, strengthens the suprahyoid muscles

Table 1.
Characteristics of swallowing exercises.

better swallowing functional ability in patients who completed the program of swallowing exercises compared with those who did not.

Rehabilitation swallowing exercises in irradiated patients mainly consist of interventions aimed to reinforce supra-hyoid musculature (Mendelsohn maneuver), airway closure capability (supraglottic and super-supraglottic maneuver), base of tongue retraction (effortful swallow and Masako maneuver), and crico-pharyngeus muscle opening (Shaker maneuver). A summary of the swallowing exercises advised in patients undergone to RT is reported in **Table 1**.

4.2 Intensity and modulated radiotherapy (IMRT) as a strategy to reduce swallowing dysfunction

An organ preservation strategy such as a radiation-based treatment should provide both the highest tumor control probability (TCP) and the minimum function impairment with the subsequent maximum therapeutic index gain [56].

In this regard, in the last few decades, the advancement of new treatment technologies, such as intensity and modulated radiotherapy (IMRT), has shown

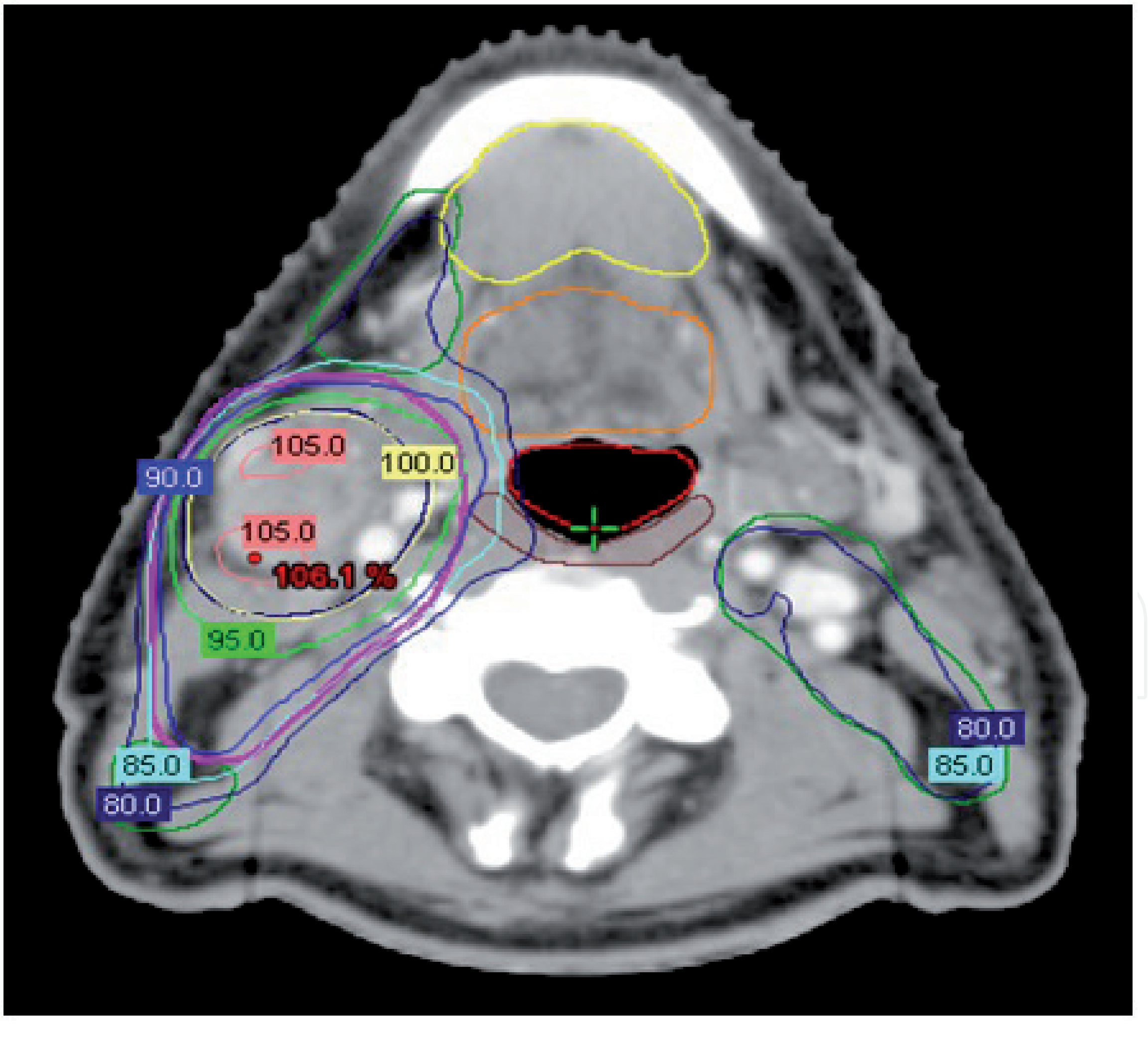

Figure 4.
Example of SWOARs-sparing IMRT plan for a patient affected by a right tonsillar cancer with omolateral adenopathies (Stage cT3N2b). Dose distributions (Gy) are labeled as percentage isodose line (coral line: 105% isodose; yellow line: 100% isodose; green line: 95% isodose; celestial line: 90% isodose line; cyan line: 85% isodose line; blue line: 80% isodose line). Dark green contour: low-risk target volume (54 Gy); purple contour: intermediate risk target volume (60Gy); dark blue: high risk target volume (66 Gy); brown contour: medium pharyngeal constrictor muscle; red contour: pharyngeal mucosa; orange contour: base of tongue; and yellow contour: oral cavity.

promising results in terms of better oncologic and functional outcomes reducing the dose to the surrounding normal tissues.

Briefly, IMRT is an advanced treatment delivery technique that, exploiting the concomitant movement of multilamellar collimator during X-ray delivery through a computer-guided optimization system, produces concave isodose distributions. As a consequence, a better conformation of high treatment doses to the tumor target volume while significantly reducing the high doses to the nearest healthy tissues through a steep gradient dose is performed.

Studies on swallowing dysfunction using videofluoroscopy after radiation-based treatment revealed abnormalities in most of the previous described pharyngeal swallowing mechanisms. Hutcheson et al. [57], in those patients who referred clinical dysphagia, reported a high rate of minimal or absence of hyolaryngeal elevation and laryngeal vestibule closure, incomplete or absence of pharyngeal contraction, and minimal or no base of tongue retraction. These structures were therefore called "swallowing organs at risk (SWOARs)," and it was recommended that doses to these structures be minimized and studied to gain the potential clinical benefits and to find out the relationship between the absorbed doses to these structures and the risk of aspiration. To this aim, Christianen et al. [58] accurately defined an anatomically CT-image-based guideline for the proper delineation of these structures supposing that a RT-plan optimization to reduce doses to these structures (SWOARs-sparing IMRT) will result in better swallowing functional outcomes. An example of SWOARs-sparing IMRT plan is reported in **Figure 4**.

To date, despite the rationale to use IMRT to reduce posttreatment dysphagia has been well acknowledged, this assumption is still to be confirmed due to the heterogeneity of the current clinical data. Nevertheless, a positive trend seems to emerge by the literature data reporting an overall lower pattern of aspiration after IMRT compared with 3DCRT (2.6–7% versus 7–78%, respectively) and is likely to increase as the radiation oncologist will be more and more encouraged to optimize plans to SWOARs in their clinical practice [59].

To date, the greatest experience on the role of SWOARs-sparing IMRT is from the University of Michigan on 73 patients affected by locally advanced oropharyngeal cancer without the infiltration of posterior pharyngeal wall and without lateral retropharyngeal nodes [60]. In this study, authors reported the safety of dose reduction to these structures in terms of locoregional recurrence rate together with worsening of Patient-Reported Swallowing Scores (HNQOL and UWQOL questionnaires) soon after treatment (at 1 months) followed by a slow and progressive amelioration (between 6 and 12 months) and a subsequent stabilization (after 12 months).

Also, the authors reported worse swallowing scores mostly for solid rather than liquid consistencies, the lack of recovery over time with a mean VF-based SPSS score 4 (meaning necessity of modified diet requiring therapeutic intervention to minimize the risk of aspiration) as well as a pattern of aspiration between 16 and 26% (at 6 and 24 months after therapy).

The dosimetric analysis on the same patient population was subsequently performed by Eisbruch et al. [61] reporting a 50 and 25% risk of VF-based aspiration for doses of 63 and 56 Gy to the pharyngeal constrictor muscles and for doses of 56 and 39 Gy to the supraglottic and glottic larynx.

These findings, despite on a smaller sample size, were confirmed by the University of Pisa mono-institutional prospective experience [62], in which 38 patients affected by naso and oropharynx cancers submitted to SWOARs-IMRT+CT were studied by combining FEES and VFS both at baseline and at 6 and 12 months. An overall moderate/severe dysphagia, based on the amount of pharyngeal residue (P-score) at FEES, accounted for 47 and 37% at 6 and 12 months for solid consistencies. Indeed, a low pattern of post-swallowing aspiration (14 and 10% at 6 and

12 months, respectively) was reported. Differently, videofluoroscopy (VF) findings in this studied population revealed a low pattern of post-swallowing aspiration (14 and 10% at 6 and 12 months after treatment) mostly for solid consistencies.

Interestingly, despite the lack of dosimetric correlation due to the low sample size, higher doses (median doses > 50 Gy) were delivered to the upper SWOARs (such as superior and medium constrictor muscle and base of tongue) and lower doses (median doses < 40 Gy) to the inferior SWOARs.

In this regard, a different radiation-related impairment of upper and lower SWOARs, depending on the primary tumor location (i.e., naso/oropharynx versus larynx/hypopharynx), might justify a variation in the swallowing dysfunction for different consistencies of the bolus suggesting a different involvement of the single SWOARs in the deglutition act.

5. Future directions

Postradiation swallowing disorders is an ongoing issue that is likely to be further developed in a near future both due to its clinical relevance (mostly in the HPV era with many long-term survivor patients) and to the potential clinical benefit of modern advanced radiotherapy techniques.

At first, based on the previous findings by Pearson et al. [63], other structures to function involved in the hyolaryngeal complex elevation (the supra-hyoid musculature) are likely to be considered in the RT plan optimization process as critical organs.

In this regard, Gawryszuk et al. [64] recently integrated the SWOARs-CT image atlas with the so-called "functional swallowing units (FSUs)" involved in the hyolaryngeal elevation (floor of mouth, posterior digastric/stylohyoid complex and longitudinal pharyngeal muscles), tongue base retraction (hyoglossus and styloglossus muscle complex), and tongue motion (genioglossus and intrinsic tongue muscles) for a RT planning use.

Last but not least, despite being a discussed issue due to the current lack of evidence, the next step is likely to come out from the increasing use of proton therapy. As favorable beam properties of protons allow a higher dose conformity and thus better sparing of normal tissues without jeopardizing target dose coverage, its clinical use is likely to be translated into clinical benefits. Therefore, the SWOARs-sparing Intensity and Modulated Proton Therapy (SWOARs-IMPT) is likely to provide further advantages in terms of swallowing impairment reduction, compared with the standard SWOARs-IMRT (at least in patients with more complex clinical situations) [65].

In the meantime, we are waiting for the results from the British and Italian ongoing prospective clinical trial addressing the role of standard SWOARs-sparing IMRT (ISRCTN25458988 and NCT03448341) [66, 67].

6. Conclusions

Oropharyngeal dysphagia is the most frequent sequela occurring early and late after a nonsurgical RT-based treatment for HNC often leading to life threatening consequences of a "nonsafe" and/or "inefficacious swallowing act."

As such, an inefficient deglutition can cause malnutrition and dehydration with a consequent immunosuppression, immunodepression, sarcopenia, and hypovolemia-induced state. Concomitantly, an altered oropharyngeal swallowing induces a bacterial colonization in the pharyngeal tract that, in case of nonsafe deglutition causing aspiration, increases the risk to develop clinical aspiration pneumonia.

Therefore, a proper management of radiation-related oropharyngeal dysphagia is a key issue to prevent patients from infectious-related morbidity and mortality that are reported to occur in 7–9% of patients [68].

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Conflict of interest

Authors declare no conflict of interest.

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References

[1] Pignon JB, Bouris J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: Three meta-analyses of updated individual data. Lancet. 2000;**355**:949-955. DOI: 10.1016/S0140-6736(00)90011-4

[2] Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. The New England Journal of Medicine. 2003;**349**:2091-2098. DOI: 10.1056/NEJMoa031317

[3] Delaney GP, Fisher RJ, Smee RI, et al. Split-course accelerated therapy in head and neck cancer: An analysis of toxicity. International Journal of Radiation Oncology, Biology, Physics. 1995;**32**:763-768. DOI: 10.1016/0360-3016(95)00093-E

[4] Nguyen TD, Panis X, Froissart D, et al. Analysis of late complications after rapid hyperfractionated radiotherapy in advanced head and neck cancers. International Journal of Radiation Oncology, Biology, Physics. 1988;**14**:23-25. PMID: 3335458

[5] Cooper JS, Fu K, Marks J, et al. Late effects of radiation therapy in the head and neck region. International Journal of Radiation Oncology, Biology, Physics. 1995;**31**:1141-1164. DOI: 10.1016/0360-3016(94)00421-G

[6] Nguyen NP, Sallah S, Karlsson U, et al. Combined chemotherapy and radiation therapy for head and neck malignancies: Quality of life issues. Cancer. 2002;**94**:1131-1141. DOI: 10.1002/cncr.10257

[7] Nguyen NP, Moltz CC, Frank C, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Annals of Oncology. 2004;**15**:383-388. DOI: 10.1093/annonc/mdh101

[8] Batth SS, Caudell JJ, Chen AM. Practical considerations in reducing swallowing dysfunction following concurrent chemoradiotherapy with intensity-modulated radiotherapy for head and neck cancer. Head and Neck. 2014;**36**:291-298. DOI: 10.1002/hed.23246

[9] Caudell JJ, Schaner PE, Meredith RF, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head and neck cance. International Journal of Radiation Oncology, Biology, Physics. 2009;**73**:410-415. DOI: 10.1016/j.ijrobp.2008.04.048

[10] Raber-Durlacher JA, Brennan MT, Verdonck-de Leeuw IM, et al. Swallowing dysfunction in cancer patients. Supportive Care in Cancer. 2012;**20**:433-443. DOI: 10.1007/s00520-011-1342-2

[11] Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. Journal of Clinical Oncology. 2006;**24**:2636-2643. DOI: 10.1200/JCO.2006.06.0079

[12] Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: A comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. Journal of Clinical Oncology. 2013;**31**(7):845-852. DOI: 10.1200/JCO.2012.43.6097

[13] Robbins KT. Barriers to winning the battle with head and neck cancer. International Journal of Radiation Oncology, Biology, Physics. 2002;**53**(1):4-5. PMID: 12007934

[14] Jean A. Brain stem control of swallowing: Neuronal network and cellular mechanisms. Physiological Reviews. 2001;**81**:929-969. DOI: 10.1152/physrev.2001.81.2.929

[15] Rofes L, Cola P, Clavé P. The effects of sensory stimulation on neurogenic oropharyngeal dysphagia. Journal of Gastroenterology and Hepatology Research. 2014;**3**:1066-1072. DOI: 10.1136/gutjnl-2011-300753

[16] Alvarez-Berdugo D, Rofes L, Casamitjana JF, Padrón A, Quer M, Clavé P. Oropharyngeal and laryngeal sensory innervation in the pathophysiology of swallowing disorders and sensory stimulation. Annals of the New York Academy of Sciences. 2016;**1380**(1):104-120

[17] Logemann JA. Evaluation and Treatment of Swallowing Disorders. Austin: Pro-ed, An International Publisher; 1998. p. 5-47; 281-298

[18] Palmer JB, Tanaka E, Siebens AA. Motion of the posterior pharyngeal in swallowing. Laryngoscope. 1988;**98**:414-417. DOI: 10.1288/00005537-198804000-00012

[19] O'Connor A, McConnel FMS. Dysphagia associated with pharyngoesophageal segment dysfunction. Acta Oto-Rhino-Laryngologica Belgica. 1994;**104**: 1376-1382. PMID: 8209678

[20] BourguignatE,EvennouA,ButinAM, Bobin S. Insuffisance velopharyngéer. In: EMC Otorhinolaryngology. Paris: Elsevier; 1996. p. 20-618-A-10. DOI: 10.1016/S0246-0351(05)39253-1

[21] Ohmae Y, Logeman JA, Kaiser P. Timing of glottic closure during normal swallow. Head & Neck. 1995;**17**:394-402. PMID: 8522440

[22] Martin-Harris B, Brodsky MB, Michel Y, et al. MBS measurement tool for swallow impairment-MBSImp: Establishing a standard. Dysphagia. 2008;**23**:392-405. DOI: 10.1007/s00455-008-9185-9

[23] Murray J. Manual of Dysphagia Assessment in Adults. Dysphagia Series. New York: Delmar Cengage Learning; 1999. pp. 90-143

[24] Pearson WG Jr, Taylor BK, Blair J, Martin-Harris B. Computational analysis of swallowing mechanics underlying impaired epiglottic inversion. Laryngoscope. 2016;**126**:1854-1858. DOI: 10.1002/lary.25788

[25] Pearson WG Jr, Davidoff AA, Smith ZM, Adams DE, Langmore SE. Impaired swallowing mechanics of post radiation therapy head and neck cancer patients: A retrospective videofluoroscopic study. World Journal of Radiology. 2016;**8**:192-199. DOI: 10.4329/wjr.v8.i2.192

[26] Pearson WG Jr, Langmore SE, Zumwalt AC. Evaluating the structural properties of suprahyoid muscles and their potential for moving the hyoid. Dysphagia. 2011;**26**:345-351. DOI: 10.1007/s00455-010-9315-z

[27] Krespi YP, Blitzer A, editors. Aspiration and swallowing disorders. Otolaryngologic Clinics of North America. 1988;**4**:21

[28] Jacob P, Kahrilas PJ, Logemann JA, Shah V, Ha T. Upper esophageal sphincter opening and modulation during swallowing. Gastroenterology. 1989;**97**:1469-1478. PMID: 2583413

[29] Mu L, Sanders I. Neuromuscular compartments and fiber-type regionalization in the human inferior pharyngeal constrictor muscle. The Anatomical Record. 2001;**264**:367-377. DOI: 10.1002/ar.10020

[30] Alvarez-Berdugo D, Rofes L, Casamitjana JF, Padròn A, Quer M, Clavè P. Oropharyngeal and laryngeal sensory innervation in the pathophysiology of swallowing disorders and sensory stimulation treatments. Annals of the New York

Academy of Sciences. 2016;**1380**: 1104-1120. DOI: 10.1111/nyas.13150

[31] Mu L, Sanders I. Neuromuscolar specializations within human pharyngeal constrictor muscles. The Annals of Otology, Rhinology, and Laryngology. 2007;**116**(8):604-617. DOI: 10.1177/000348940711600809

[32] Mu L, Sanders I. Muscle fiber-type distribution pattern in the human cricopharyngeus muscle. Dysphagia. 2002;**17**:87-96. DOI: 10.1007/s00455-001-0108-2

[33] Venker-van Haagen AJ, Hartman W, Wolvekamp WTC. Contributions of the glossopharyngeal nerve and the pharyngeal branch of the vagus nerve to the swallowing process in dogs. American Journal of Veterinary Research. 1986;**47**:1300-1307. PMID: 3729131

[34] Lazarus CL, Logemann JA, Pauloski BR, Colangelo LA, Kahrilas PJ, Mittal BB, et al. Swallowing disorders in head and neck cancer patients treated with radiotherapy and adjuvant chemotherapy. Laryngoscope. 1996;**106**(9 Pt 1):1157-1166. PMID: 8822723

[35] Anderson EJ, Neufer PD. Type II skeletal myofibers possess unique properties that potentiate mitochondrial H(2)O(2) generation. American Journal of Physiology. Cell Physiology. 2006;**290**(3):C844-C851. DOI: 10.1152/ajpcell.00402.2005

[36] Viet CT, Corby PM, Akinwande A, Schmidt BL, Viet CT, Corby PM, et al. Review of preclinical studies on treatment of mucositis and associated pain. Journal of Dental Research. 2014;**93**(9):868-875. DOI: 10.1177/0022034514540174

[37] Simonyan K, Feng X, Henriquez VM, Ludlow CL. Combined laryngeal inflammation and trauma mediate long-lasting immunoreactivity response in the brainstem sensory nuclei in the rat. Frontiers in Integrative Neuroscience. 2012;**6**:97. DOI: 10.3389/fnint.2012.0

[38] Gillette EL, Mahler PA, Powers BE, Gillette SM, Vujaskovic Z. Late radiation injury to muscle and peripheral nerves. International Journal of Radiation Oncology, Biology, Physics. 1995;**31**(5):1309-1318. DOI: 10.1016/0360-3016(94)00422-h

[39] Rong X, Tang Y, Chen M, Lu K, Peng Y. Radiation-induced cranial neuropathy in patients with nasopharyngeal carcinoma. A follow-up study. Strahlentherapie und Onkologie. 2012;**188**(3):282-286. DOI: 10.1007/s00066-011-0047-2

[40] King SN, Dunlap NE, Tennant PA, Pitts T. Pathophysiology of radiation-induced dysphagia in head and neck cancer. Dysphagia. 2016;**31**(3):339-351. DOI: 10.1007/s00455-016-9710-1

[41] Schadrach JL, Wagers AJ. Stem cells for skeletal muscle repair. Philosophical Transactions of the Royal Society. 2011;**366**:2297-2306. DOI: 10.1098/rstb.2011.0027

[42] Shefer G, Rauner G, Reuveni Yablonka Z, Benayhau D. Reduced satellite cell numbers and myogenic capacity in aging can be alleviated by endurance exercise. PLoS One. 2010;**5**(10):e13307. DOI: 10.1371/journal.pone.0013307

[43] Shefer G, Carmeli E, Rauner G, Yablonka-Reuveni Z, Benayahu D. Exercise running and tetracycline as means to enhance skeletal muscle stemcell performance after external fixation. Journal of Cellular Physiology. 2008;**215**(1):265-275. DOI: 10.1002/jcp.21306

[44] De Lisio M, Kaczor JJ, Phan N, Tarnopolsky MA, Boreham DR, Parise G. Exercise training enhances the

skeletal muscle response to radiation-induced oxidative stress. Muscle & Nerve. 2011;**43**(1):58-64. DOI: 10.1002/mus.21797

[45] Hood DA. Invited review: Contractile activity-induced mitochondrial biogenesis in skeletal muscle. Journal of Applied Physiology (Bethesda, MD: 1985). 2001;**90**(3):1137-1157. DOI: 10.1152/jappl.2001.90.3.1137

[46] Adhihetty PJ, Irrcher I, Joseph AM, Ljubicic V, Hood DA. Plasticity of skeletal muscle mitochondria in response to contractile activity. Experimental Physiology. 2003;**88**(1):99-107. PMID: 12525859

[47] Scheele C, Nielsen S, Pedersen BK. ROS and myokines promote muscle adaptation to exercise. Trends in Endocrinology and Metabolism: TEM. 2009;**20**(3):95-99. DOI: 10.1016/j.tem.2008.12.002

[48] Venditti P, Masullo P, Di Meo S. Effect of training on H(2)O(2) release by mitochondria from rat skeletal muscle. Archives of Biochemistry and Biophysics. 1999;**372**(2):315-320. DOI: 10.1006/abbi.1999.1494

[49] Phillips SM, Glover EI, Rennie MJ. Alterations of protein turnover underlying disuse atrophy in human skeletal muscle. Journal of Applied Physiology (Bethesda, MD: 1985). 2009;**107**(3):645-654. DOI: 10.1152/japplphysiol.00452.2009

[50] Glover EI, Phillips SM, Oates BR, Tang JE, Tarnopolsky MA, Selby A, et al. Immobilization induces anabolic resistance in human myofibrillar protein synthesis with low and high dose amino acid infusion. The Journal of Physiology. 2008;**586**(Pt 24):6049-6061. DOI: 10.1113/jphysiol.2008.160333

[51] Paddon-Jones D, Sheffield-Moore M, Cree MG, Hewlings SJ, Aarsland A, Wolfe RR, et al. Atrophy and impaired muscle protein synthesis during prolonged inactivity and stress. The Journal of Clinical Endocrinology & Metabolism. 2006;**91**(12):4836-4841. DOI: 10.1210/jc.2006-0651

[52] Krisciunas GP, Sokoloff W, Stepas K, Langmore SE. Survey of usual practice: Dysphagia therapy in head and neck cancer patients. Dysphagia. 2012;**27**(4):538-549. DOI: 10.1007/s00455-012-9404-2

[53] Kraaijenga SA, van der Molen L, Jacobi I, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. European Archives of Oto-Rhino-Laryngology. 2015;**272**(11):3521-3531. DOI: 10.1007/s00405-014-3379-6

[54] Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": Randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. International Journal of Radiation Oncology, Biology, Physics. 2012;**83**(1):210-219. DOI: 10.1016/j.ijrobp.2011.06.1954

[55] Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: Use it or lose it. JAMA Otolaryngology. Head & Neck Surgery. 2013;**139**(11):1127-1134. DOI: 10.1001/jamaoto.2013.4715

[56] Ursino S, Seccia V, Cocuzza P, et al. How does radiotherapy impact swallowing function in nasopharynx and oropharynx cancer? Short-term results of a prospective study. Acta Otorhinolaryngologica Italica. 2016;**36**:174-184. DOI: 10.14639/0392-100X-640

[57] Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore M, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;**118**(23):5793-5799. DOI: 10.1002/cncr.27631

[58] Christianen M, Langendijk JA, Westerlaan HE, van de Water TA, Bijl HP. Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. Radiotherapy and Oncology. 2011;**101**:394-402

[59] Ursino S, D'Angelo E, Mazzola R, Merlotti A, Morganti R, Cristaudo A, et al. A comparison of swallowing dysfunction after three-dimensional conformal and intensity-modulated radiotherapy: A systematic review by the Italian Head and Neck Radiotherapy Study Group. Strahlentherapie und Onkologie. 2017;**193**(11):877-889. DOI: 10.1007/s00066-017-1160-7

[60] Feng FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, Feng M, et al. Intensity-modulated chemoradiotherapy aiming to reducedysphagia in patients with oropharyngeal cancer: Clinical and functional results. Journal of Clinical Oncology. 2010;**28**:2732-2738. DOI: 10.1200/JCO.2009.24.6199

[61] Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: Swallowing organs late complication probabilities and dosimetric correlates. International Journal of Radiation Oncology, Biology, Physics. 2011;**81**:e93-e99. DOI: 10.1016/j.ijrobp.2010.12.067

[62] Ursino S, Cocuzza P, Seccia V, Delishaj D, Cristaudo A, Pasqualetti F, et al. Pattern of dysphagia after swallowing-sparing intensity-modulated radiotherapy (IMRT) of head and neck cancers: Results of a mono-institutional prospective study. Strahlentherapie und Onkologie. 2018;**194**(12):1114-1123. DOI: 10.1007/s00066-018-1328-9

[63] Pearson W, Hindson DF, Langmore SE, Zumwalt AC. Evaluating swallowing muscles essential for hyolaryngeal elevation by using muscle functional magnetic resonance imaging. International Journal of Radiation Oncology, Biology, Physics. 2013;**85**(3):735-740. DOI: 10.1016/j.ijrobp.2012.07

[64] Gawryszuk A, Bijl HP, Holwerda M, Halmos GB, Wedman J, Witjes MJH, et al. Functional swallowing units (FSUs) as organs-at-risk for radiotherapy. Part 2: Advanced delineation guidelines for FSUs. Radiotherapy and Oncology. 2019;**130**:68-74. DOI: 10.1016/j.radonc.2018.09.022

[65] Langendijk JA, Boersma LJ, Rasch CRN, van Vulpen M, Reitsma JB, van der Schaaf A, et al. Clinical trial strategies to compare protons with photons. Seminars in Radiation Oncology. 2018;**28**(2):79-87. DOI: 10.1016/j.semradonc.2017.11.008

[66] Petkar I, Rooney K, Roe JW, Patterson JM, Bernstein D, Tyler JM, et al. DARS: A phase III randomised multicentre study of dysphagia-optimised intensity-modulated radiotherapy (Do-IMRT) versus standard intensity-modulated radiotherapy (S-IMRT) in head and neck cancer. BMC Cancer. 2016;**16**(1):770. DOI: 10.1186/s12885-016-2813-0

[67] Clinical and instrumental evaluation of late dysphagia in patients with oropharynx and nasopharynx cancer, candidates to combined radiochemotherapy with intensity modulated radiotherapy (IMRT). Available from: https://clinicaltrials.gov/ct2/show/NCT03448341

[68] Mirabile A, Numico G, Russi EG, Bossi P, Crippa F, Bacigalupo A, et al. Sepsis in head and neck cancer patients treated with chemotherapy and radiation: Literature review and consensus. Critical Reviews in Oncology/Hematology. 2015;**95**(2):191-213. DOI: 10.1016/j.critrevonc.2015.03.003