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Review

Dysphagia after radiotherapy: State of the art and prevention

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ABSTRACT

Adjuvant radiotherapy after surgery or exclusive radiotherapy, with or without concurrent chemotherapy is a valuable treatment option in the great majority of patients with head and neck cancer. Recent technical progress in radiotherapy has resulted in a decreased incidence of xerostomia. Another common toxicity of radiotherapy is dysphagia, which alters the nutritional status and quality of life of patients in remission. The objective of this review is to describe the physiology of swallowing function, the pathophysiology of radiation-induced dysphagia and the various strategies currently available to prevent this complication.

1. Introduction

New radiotherapy techniques for head and neck cancer allow delivery of a curative dose to the tumour volume while sparing healthy tissues, thereby decreasing radiation-induced sequelae and consequently improving the quality of life of patients in remission. Healthy tissues included in or adjacent to the irradiated tumour volume, including the skin, mucous membranes, cartilage and bone, teeth and salivary glands, constitute the main limitation to radiotherapy. However, in order to prevent radiation damage of these anatomical structures, all structures involved in the function studied must be clearly identified. For example, the incidence of xerostomia has been decreased by mainly sparing the parotid glands or the parotid gland contralateral to the tumour. As swallowing function is much more complex (involving 30 pairs of muscles and 6 cranial nerves), the incidence of dysphagia can only be decreased after clearly identifying all structures involved in order to exclude them from radiation fields. In this review, after recalling the physiology of swallowing, we will analyse the pathophysiology of swallowing dysfunction observed after radiotherapy and the various options available to prevent these disorders.

2. Physiology of swallowing

The process of swallowing is generally defined as all of the mechanisms allowing progression of food from the oral cavity to the upper oesophageal sphincter. It is associated with protection of the airways and involves both voluntary and reflex mechanisms.

2.1. Preparatory oral phase

The preparatory oral phase consists of preparing food by chewing and impregnating the food with saliva to transform it into a homogeneous bolus. This phase is both voluntary and involuntary and involves masticatory muscles, teeth, tongue, salivary glands, sensory receptors of the oral mucosa and reflex arcs, which allow the tongue to correctly dispose food in the oral cavity so that it can be ground by the teeth, while at the same time excluding the tongue from the chewing process. This phase is innervated by cranial nerves V, VII and XII.

2.2. Oral phase

The bolus is then formed on the dorsal surface of the tongue, in the midline and compressed against the palate by the tongue, then propelled posteriorly by the base of the tongue, pressing against the posterior pharyngeal wall while the soft palate is elevated flush against the posterior pharyngeal wall to prevent the passage of the bolus into the nasopharynx.

2.3. Pharyngeal and oesophageal phases

The bolus then advances in the pharynx in the valleculae between the base of the tongue, the epiglottis and the posterior pharyngeal wall. The valleculae play a temporary storage role of the bolus during this phase. The epiglottis then tilts posteriorly to

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protect the laryngeal orifice. The aryepiglottic folds, arytenoid and true and false vocal cords form the laryngeal sphincter, which closes to prevent aspiration. At the same time, the larynx and pharynx rise and extend anteriorly by the action of the longitudinal pharyngeal muscles, while successive contraction of circular constrictor muscles allows downward progression of the bolus followed by opening of the lower oesophageal sphincter, allowing access to the stomach by peristaltic movements of the oesophageal wall [1].

The first two phases are essentially voluntary. Pharyngeal and oesophageal phases are controlled by a reflex arc in which the sensory afferents are carried in cranial nerves V, VII, IX and X (especially the superior laryngeal nerve and recurrent laryngeal nerve) and XII. All these sensory stimuli are integrated in the brainstem in a centre called the swallowing centre, the main two nuclei of which are situated in the nucleus of the solitary tract and in the nucleus ambiguous of the medulla oblongata. This swallowing centre also receives cortical and subcortical afferents. Efferents from these centres travel in cranial nerves V, VII, X and XII to the pharynx [2,3].

When one of these mechanisms is defective, resulting in the passage of part of the bolus into or below the vestibule (aspiration), sensory receptors of the pharyngeal mucosa are stimulated, triggering cough via a reflex arc involving cranial nerves X, IX, V and the brainstem designed to expel the bolus from the larynx [4]. In the absence or in the case of failure of this "rescue mechanism", part of the bolus descends below the glottis (inhalation).

3. Pathophysiology of radiation-induced dysphagia

Not all of the radiation-induced changes of the structures involved in swallowing have been fully elucidated. Dysphagia can also be exacerbated by xerostomia.

3.1. Functional changes after radiotherapy

Videoendoscopic analysis of the swallowing process after radiotherapy reveals [5–7]:

- decreased pharyngeal peristalsis and poor synchronization between pharyngeal contractions, opening of the upper oesophageal sphincter and closure of the larynx;
- decreased or defective posterior inversion of the base of the tongue towards the posterior pharyngeal wall;
- incomplete and/or delayed closure of the larynx with decreased laryngeal abduction during swallowing;
- decreased elevation of the hyoid bone and larynx and decreased inversion of the epiglottis;
- delayed opening of the upper oesophageal sphincter.

All of these abnormalities are responsible for dysphagia, a risk of aspiration and/or persistence of residues of the bolus in the oropharynx, valleculae and hypopharynx at the end of the swallowing phase, which may then be subsequently inhaled. The cough reflex is also often deficient or even absent after radiotherapy [8].

3.2. Histological changes after radiotherapy

Radiation-induced lesions can be schematically classified into two main pathophysiological processes affecting all tissues: inflammation (and the resulting oedema) and fibrosis [9,10]. Microvascular changes, atrophy of muscle fibres and vessels, and collagen deposits are also observed.

3.2.1. Mucous membranes

Late radiation-induced mucositis comprises loss of colour, thinning, rigidity of the mucosa and induration of the subcutaneous tissues and can be complicated by ulceration and necrosis. These disorders are due to ischaemia secondary to fibrosis and occlusion of small vessels. These effects are progressive and irreversible and may be observed between 6 months and 5 years after radiotherapy.

3.2.2. Muscles

In a prospective study on 26 patients, CT scans were acquired before and after radiotherapy to identify the structures damaged by radiotherapy. Pharyngeal constrictor muscles, with a mean thickness of 2 mm before radiotherapy, were thicker after radiotherapy, reaching a mean thickness of 7 mm [6]. In another study on 12 patients, Popovtzer et al. [11] studied MRI signal changes on T1- and T2-weighted sequences as well as variations of the thickness of pharyngeal constrictor muscles 3 months after radiotherapy. The mean thickness of pharyngeal constrictor muscles increased from 2.9 mm before radiotherapy to 5.4 mm after radiotherapy. These authors also compared the thickness of the pharyngeal constrictor muscles with that measured on sternocleidomastoid muscles (SCM). They observed a reduction of the T1 signal after radiotherapy in both the pharyngeal constrictor muscles and the SCM, while the T2 signal was markedly increased after radiotherapy in the pharyngeal constrictor muscles, but only very moderately increased in the SCM. This signal increase was dose-dependent for pharyngeal constrictor muscles, but not for the SCM. On average, the thickness of the pharyngeal constrictor muscles was doubled after radiotherapy, while the thickness of SCM tended to decrease. These findings suggest that pharyngeal constrictor muscles are more susceptible to radiation-induced inflammation than the SCM, as the high-intensity T2 signal reflects the presence of oedema and inflammation. This inflammation of pharyngeal constrictors appears to be secondary to acute inflammation of the pharyngeal mucosa covering these muscles, suggesting that inflammation is propagated contiguously to the underlying constrictor muscles.

Other muscles may also be involved, such as the pterygoid and masseter muscles, associated with temporo-mandibular joint lesions due to thinning of cartilage and rarefaction of synovial fluid, responsible for radiation-induced trismus [12]. Cricopharyngeus muscle dysfunction has also been reported [13].

3.2.3. Nerves

It is difficult to determine whether pharyngeal constrictor muscle dysfunction is exclusively due to muscle lesions, or whether nerve lesions may also be involved. Fajardo et al. [14] did not demonstrate any morphological lesions of the ganglia innervating the oesophagus and pharynx after radiotherapy. However, possible nerve dysfunction with no morphological changes cannot be excluded. The terminal innervation of the pharynx is essentially ensured by the pharyngeal plexus, innervated by cranial nerves V, VII, IX and X situated in the connective tissue sheath surrounding the pharyngeal muscles, which terminal fibres pierce the muscle layer to terminate in the mucosa and submucosa [15]. Mucosal changes can damage the terminal afferent and efferent nerve fibres present in the mucosa, responsible for sensory and motor disorders, for example denervation of one half of the tongue by late fibrotic stenosis [stenosis or damage?] of the hypoglossal nerve [16].

4. Consequences of radiation-induced dysphagia

Depending on the site and initial stage of the tumour, swallowing disorders may already be present prior to any treatment, making it difficult to assess dysphagia due exclusively to radiotherapy. In the meta-analysis by Machtay et al., 43% of patients in remission presented grade 3–4 late dysphagia [17].