J Bras Patol Med Lab. 2020; 56: 1-11.

10.5935/1676-2444.20200046

Deglutition manifestations in patients with oropharyngeal cancer subjected to conservative therapy: systematic review

Manifestações da deglutição em pacientes com câncer de orofaringe submetidos à terapia conservadora: revisão sistemática

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ABSTRACT

Objectives: To characterize scientific production and identify deglutition changes in individuals with oropharyngeal cancer subjected to conservative therapy. **Methods:** The search was applied to five electronic database [Scientific Electronic Library Online (Scielo), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), US National Library of Medicine National Institutes of Health (PubMed), Web of Science, and Scopus], besides the search of grey literature in the databases (OpenThesis e OpenGrey), avoiding selection and publication bias. Prospective longitudinal studies concerning the theme: deglutition disorders in individuals with oropharyngeal cancer subjected to conservative therapy were considered eligible. The risk of bias and the evaluation of individual methodological quality of the selected studies were measured by "The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews" for prospective and longitudinal studies. **Results:** The search resulted in 899 records and after analysis four of them fulfilled the eligibility criteria. Among the studies included, all individuals presented some type of deglutition changes, the most common were: reduced of strength and retraction of the base of the tongue, delayed deglutition trigger, reduced laryngeal elevation, presence of residues on tongue and palate, in the pharyngeal area, valleculae, and posterior pharyngeal wall, as well as in the vestibules and in pyriform sinuses. **Conclusion:** The evidence from this systematic review suggests that conservative therapies cause deglutition changes or amplify the pre-existing ones, regardless of the type and magnitude of radiation, as well as tumor staging. However, there is little standardization in the research methodologies, making a meta-analysis study difficult to conduct.

Key words: cancer; oropharynx; radiotherapy; chemoradiotherapy; deglutition disorder.

RESUMO

Objetivos: *Caracterizar a produção científica e identificar as alterações da deglutição em indivíduos com câncer de orofaringe submetidos à terapia conservadora.* ***Métodos:*** *Realizou-se uma busca em cinco base de dados eletrônicas [Scientific Electronic Library Online (Scielo), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), US National Library of Medicine National Institutes of Health (PubMed), Web of Science e Scopus], além da busca da literatura cinzenta nas bases de dados (OpenThesis e OpenGrey), evitando viés de seleção e publicação. Foram considerados elegíveis estudos longitudinais prospectivos sobre o tema: alterações de deglutição em indivíduos com câncer de orofaringe submetidos à terapia conservadora. O risco de viés e a qualidade metodológica individual dos estudos selecionados foram avaliados pela ferramenta de avaliação crítica do Joanna Briggs Institute (JBI) para uso de suas revisões sistemáticas, estudos prospectivos e longitudinais.* ***Resultados:*** *A busca resultou em 899 registros e, após análise, quatro deles atenderam aos critérios de elegibilidade. Entre os estudos incluídos, todos os indivíduos apresentaram algum tipo de alteração de deglutição; os mais frequentes foram: força e retração da base da língua reduzidas, atraso no disparo da deglutição, elevação laríngea reduzida, presença de resíduo em língua e palato, em região faríngea, valéculas e*

First submission on 07/01/19; last submission on 08/20/19; accepted for publication on 08/20/19; published on 06/01/20

parede posterior da faringe, bem como no interior dos vestíbulos e em seios piriformes. ***Conclusão:*** *Esta revisão sistemática sugere que as terapias conservadoras produzem distúrbios de deglutição ou intensificam os já existentes, independentemente do tipo e da intensidade de radiação, bem como do estadiamento do tumor. Há, no entanto, pouca padronização nas metodologias das pesquisas, dificultando um estudo de metanálise.*

Unitermos: *câncer; orofaringe; radioterapia; quimiorradioterapia; transtorno de deglutição.*

RESUMEN

Objetivos: *Caracterizar la producción científica e identificar las alteraciones de deglución en personas con cáncer de orofaringe sometidas a tratamiento conservador.* ***Métodos:*** *Se realizó una búsqueda en cinco bases de datos electrónicas [Scientific Electronic Library Online (Scielo), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), US National Library of Medicine National Institutes of Health (PubMed), Web of Science y Scopus], además de la literatura gris en las bases de datos OpenThesis y OpenGrey, evitando sesgo de selección y publicación. Se consideraron elegibles los estudios longitudinales prospectivos sobre el tema: trastornos de deglución en pacientes con cáncer de orofaringe sometidos a tratamiento conservador. El riesgo de sesgo y la calidad metodológica individual de los estudios seleccionados se evaluaron mediante la herramienta de evaluación crítica del Instituto Joanna Briggs (JBI) para uso de sus revisiones sistemáticas, estudios prospectivos y longitudinales.* ***Resultados:*** *La búsqueda encontró 899 registros y, tras análisis, cuatro de ellos cumplieron los criterios de elegibilidad. Entre los estudios incluidos, todos los pacientes presentaron algún tipo de trastorno de la deglución. Los más frecuentes fueron: fuerza y retracción reducidas de la base de la lengua, retraso en el disparo de la deglución, elevación laríngea reducida, presencia de residuo en lengua y paladar, en región faríngea, valléculas y pared posterior de la faringe, así como en el interior de los vestíbulos y en los senos piriformes.* ***Conclusión:*** *Esta revisión sistemática sugiere que los tratamientos conservadores producen alteraciones de deglución o intensifican aquellas que ya existen, independientemente del tipo y de la intensidad de radiación, así como de la estadificación del tumor. Hay, sin embargo, poca estandarización en las metodologías de investigación, lo que hace difícil un estudio de metanálisis.*

Palabras clave: *cáncer; orofaringe; radioterapia; quimioradioterapia; trastornos de deglución.*

INTRODUCTION

Cancer is the abnormal growth of cells. These cells tend to be very aggressive and uncontrollable, causing the formation of tumors that can spread to other regions of the body, known as metastasis. Cancer arises from a genetic mutation, that is, from a change in the cell's deoxyribonucleic acid (DNA), which starts to receive the wrong instructions for its activities. The changes can occur in special genes, called proto-oncogenes, which are inactive in normal cells. When activated, proto-oncogenes become oncogenes, responsible for transforming normal cells into cancer cells[1].

If the cancer origin in epithelial tissues, such as the skin or mucous membranes, it is known as carcinoma, which is present in the head and neck cancers. According to Ordinance no. 516, of June 17, 2015, from the Brazilian Ministry of Health[2], information from population-based cancer registries and hospital-based cancer registries report that the head and neck cancer in Brazil is more common among men, aged between 40 and 69 years, smokers or alcoholics. In the period from 2000 to 2008, the most common disease sites were the oral cavity (46.9%), the larynx (23.3%), and the oropharynx (18.5%), with a disease diagnosed predominantly in advanced stages.

The Brazilian National Cancer Institute [Instituto Nacional de Câncer (Inca)] estimated 14,700 new cases of oral and oropharyngeal cancer in Brazil, in 2019 (11,200 in men and 3,500 in women). These values corresponded to an estimated risk of 10.86 new cases per 100 thousand men, occupying the fifth position among the types of cancer, and 3.28 per 100 thousand women, and it is the 12th most frequent among all types of cancers. According to the Mortality Information System [Sistema de Informações sobre Mortalidade (SIM), 2011], squamous cell carcinoma is the most prevalent type among the various types that affect the oropharynx in more than 90% of patients. The most common sites of oral and oropharyngeal cancers are the tongue, palatine tonsils, gums and floor of the mouth; and are diagnosed less frequently on the lips and minor salivary glands[3].

The estimated annual incidence of oropharyngeal cancer is approximately 130,300 cases per year worldwide, with an estimated 15,000 new cases diagnosed annually in the United States. In the last decades, the incidence of oropharyngeal cancer has increased dramatically in developed countries, such as the United States, Canada, Australia, the United Kingdom, Denmark, the Netherlands, Norway and Sweden[4]. This increase in the incidence of oropharyngeal cancer is also attributed to the human papillomavirus (HPV). HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) have better response to treatment and lower overall recurrence rates when compared to HPV-negative OPSCC[5].

The type of treatment is defined based on the stage at which the disease is presented, whether they are conservative or radical[6]. Most treatments for oropharyngeal cancers are conservative, and it is possible to perform surgeries that involve the removal of the tumor, with no need to remove the entire organ in which the tumor is installed, radiotherapy, chemotherapy or a combination of these modalities. In more advanced cases at the time of diagnosis, treatment with isolated radiation or chemoradiotherapy is usually chosen[2]. Currently, in order to preserve the organ, radiotherapy, alone or associated with chemotherapy, is considered a good treatment alternative for patients with head and neck cancer. Historically, conventional radiotherapy has been burdened by severe and potentially fatal toxicity, which, in most cases, affects the final result of treatment[7].

Depending on the affected areas, individuals may present organic and functional changes, such as difficulties in mobility and performing functions of orofacial structures (speech articulation, voice and deglutition – dysphagia)[8]. In this perspective, radiation-induced dysphagia, as a final multifactorial side effect, which often requires enteral nutrition, occurs in more than 50% of patients, which can lead to a state of malnutrition and an increased risk of aspiration pneumonia. Rates of one and two years of dependence on percutaneous endoscopic gastrostomy are reported in 24% and 14% of cases, respectively, while clinical aspiration pneumonia is reported in 3% of those affected by the disease[7].

It is known that depending on the clinical procedures, the location and size of the resection, mobility of the orofacial structures, type of reconstruction and speech-language sequelae vary in severity, complexity, and frequency of occurrence. Thus, the importance of speech therapy monitoring is obvious from the lightest to the most advanced stages, in which speech disorders are more evident and worrying, especially when related to deglutition disorders[8].

In view of the above, the need for care to patients undergoing radiotherapy or chemoradiotherapy due to oropharyngeal carcinoma is clear. The attention to this population needs to be modified, aiming at the integrity of the local functional system. Risk reduction can be achieved by decreasing the intensity of treatment in cancers with favorable survival rates and early speech therapy. Therefore, the analysis of deglutition changes in individuals with oropharyngeal cancer undergoing conservative therapy, as well as their functional conditions, is justified, since these aspects are extremely important for establishing the type of treatment chosen and the stability of their vital functions. Thus, this study aimed to characterize the scientific production and to identify the swallowing changes present in individuals with oropharyngeal cancer submitted to conservative therapy.

METHODS

Protocol

This study is a systematic review regarding the manifestations of deglutiton in individuals with oropharyngeal cancer undergoing conservative therapy. We follow the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P)[9], as well as the Cochrane guidelines[10]. The systematic review protocol was submitted to the PROSPERO database.

Study design and eligibility criteria

The systematic review was developed to answer the question: what are the deglutition changes in individuals with oropharyngeal cancer undergoing conservative therapies?

Eligible (inclusion criteria) were adults with a confirmed diagnosis of oropharyngeal cancer that detailed the swallowing assessment, the treatment adopted for cancer (radiotherapy or chemoradiotherapy) and prospective longitudinal studies.

Exclusion criteria were: 1. studies outside the objective; 2. insufficient presentation of results; 3. studies that did not present a form of evaluation; 4. studies that did not characterize deglutition changes; 5. studies with medium and high risk of bias, and low methodological quality; 6. review studies, brief communications, editorials/letter to the editor, case reports, monographs, conference abstracts, books/book chapters, teaching material and reports; and 7. patients in the studies could not be on speech therapy.

It should be noted that the studies were unrestricted for year, language and publication status.

Sources of information and research

The key words were selected from the Health Sciences Descriptors [Descritores em Ciências da Saúde (DeCS)] and the

Medical Subject Headings (MeSH). The databases used were the Latin American and the Caribbean Literature on Health Sciences [Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS)], US National Library of Medicine National Institutes of Health [(PubMed) – including MedLine], Scientific Electronic Library Online (Scielo), Scopus, and Web of Science. Grey literature was used for searching OpenThesis and OpenGrey.

The Boolean operators *and* and *or* were used to enhance the search strategy through various combinations (**Table 1**). The bibliographic search was carried out in January 2019. The records obtained were exported to the Mendeley Web™ software, in which the duplicates were removed electronically. The remaining records were exported to the Microsoft Word™ 2010 (Microsoft™ Ltd, Washington, USA); the remaining duplicate studies, removed manually.

Selection of studies

The selection of articles was carried out in three phases. In the first, as a calibration exercise, the reviewers discussed the eligibility criteria and analyzed, separately, 20% of the total sample (the titles and abstracts), individually separating those that presented the previously established criteria. In a meeting to verify the agreement between the examiners, the included and excluded references were analyzed, with the reasons for exclusion, applying the Kappa statistical test, an adequate agreement value considered for the continuation of the next phase (Kappa ≥ 0.81). Soon after, the study titles were methodically analyzed by two eligibility reviewers, independently, who were not blinded to the names of the authors and journals.

The second phase included reading the abstracts of the remaining studies by the reviewers independently. The records whose titles corresponded to the objectives of the study, but did not have available abstracts, were kept for the third phase. Finally, in the third phase, the previously eligible studies were read in full, obtained and evaluated in order to verify whether they met the eligibility criteria. When these two reviewers did not reach an agreement, a third reviewer was consulted to make a final decision. The rejected studies were registered separately, making the reasons for exclusion clear.

Data collection and extraction process

The studies were synthesized and distributed in a table prepared for this purpose, containing the following information: author, place and year of publication, type of study, sample, age group, form of swallowing assessment, staging, type of treatment/volume of doses, follow-up period, description of deglutition changes, and main results. The synthesis of the data was carried out through a qualitative, descriptive analysis of the eligible studies and the final result was presented in a narrative form and through tables.

Risk of individual bias in the included studies

The risk of study bias and assessment of the individual methodological quality of the included studies was assessed by The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews, following criteria for prospective longitudinal studies[11]. Two authors evaluated independently, according to the PRISMA-P recommendations[9]. Any disagreements between the reviewers were resolved through discussion of the items assessed and when these two reviewers did not reach an agreement, a third reviewer was consulted to make a final decision.

Each study was categorized according to the percentage of positive responses in the questions corresponding to the assessment tool. The risk of bias was considered high when the study obtained up to 49% of the answers classified as "yes"; moderate when the study obtained 50% to 69%; and low when the study reached more than 70% "yes"[12].

RESULTS

Research strategy and methodological assessment

During the first phase of study selection, 899 records were found, distributed in seven electronic databases, including grey literature. After removing the duplicate records, 664 proceeded to the titles and abstracts analyze, which resulted in twenty-one records eligible for the full text analysis. After reading the full text, 16 studies[8, 13-27] were eliminated, as they presented insufficient

TABLE 1 – Analysis of the risk of bias and individual methodological quality of articles evaluated by The Joanna Briggs Institute Critical Appraisal tool

Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Q.10	Q.11	Total	% yes/risk of bias
Graner *et al*. (2003)	√	√	√	--	--	√	√	--	√	√	√	8	73%/low
Pauloski *et al*. (2006)	√	√	√	--	--	√	√	--	√	√	√	8	73%/low
Feng *et al*. (2007)	√	√	√	--	--	√	√	--	√	√	√	8	73%/low
Logemann *et al*. (2008)	√	√	√	--	--	√	√	√	√	√	√	9	82%/low

Q.1: Were the two groups similar and recruited from the same population? Q.2: Were exposures measured in the same way to assign people to exposed and unexposed groups? Q.3: Was the exposure measured validity and reliability? Q.4: Have confounding factors been identified? Q.5: Have strategies for dealing with confounding factors been stated? Q.6: Were the groups/participants free of the result at the start of the study (or at the time of exposure)? Q.7: Were the results measured validity and reliability? Q.8: Was the follow-up time reported and sufficiently long for the results to occur? Q.9: Was the follow-up complete and, if not, were the reasons for the loss to follow-up described and explored? Q.10: Were strategies used to deal with incomplete follow-up? Q.11: Was an appropriate statistical analysis used? √: yes; -: no.

results for study. Thus, four studies were selected for analysis. The **Figure** demonstrates the process of searching, identifying, including and excluding articles.

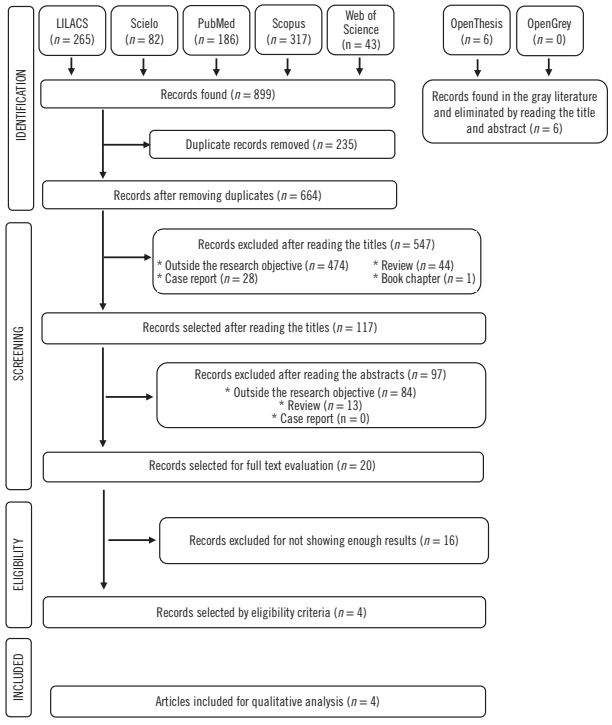

FIGURE – *Flowchart with the process of searching and selecting articles*

Characteristics of eligible studies

The studies were published between 2003 and 2008. All selected articles are American and published in the following locations: Minnesota[28], Washington[29], Michigan[29], and New York[30]. The age of the population ranged between 34 and 80 years, with an average of 58 years. Regarding gender, the majority were male (78.11%), concluding that there was a significant difference in this variable. As for the type of study, all were longitudinal prospective studies.

From the selected articles, all dealt with cancer in the oropharynx and other anatomical locations, including the nasopharynx, oral cavity, hypopharynx and larynx. Only Feng *et al.* (2007)[31] exclusively included cancer of the oropharynx and nasopharynx. Cancers of the base of the tongue and palatine tonsils have been related, these were the most common locations of oropharyngeal cancers.

All patients in the studies were examined with the same swallowing assessment instrument, namely, by videofluoroscopy of oropharyngeal swallowing, at different points in time: before the start of treatment and after treatment. Regarding the type of diet offered for such a test, the studies used similar consistencies, but distributed in different ways. Graner *et al.* (2003)[28] used two swallows of 3 ml and 10 ml of barium (in liquid and thickened form), two and a half teaspoons of applesauce with equal amounts of barium paste and two swallows of a small portion of *Lorna Doone* shortbread cookie coated with barium paste. Pauloski *et al.* (2006)[29] followed a protocol that included two swallows of 1 ml, 3 ml, 5 ml, and 10 ml of liquid with barium and three spoons of barium paste mixed with chocolate pudding. In the study by Feng *et al.* (2007)[31], reported the use of modified barium swallowing, however, they did not report types of consistencies and volumes offered. Logemann *et al.* (2008)[30] ordered fourteen swallows, including two swallows of 1 ml, 3 ml, 5 ml, and 10 ml of thin liquids (thin EZ-EM liquid barium), two swallows while drinking tea (thin EZ-EM liquid barium), 3 ml of barium paste (EZ-EM of barium paste), and chewable material (1/4 small portion of *Lorna Doone* shortbread cookie coated with 1 ml of barium paste – EZ-EM barium paste, EZ-EM Company, NY).

In general, all eligible studies showed patients with changes in swallowing before and after treatment. Graner *et al*. (2003)[28] evaluated patients before treatment and observed that nine (81.8%) from the eleven patients evaluated showed changes. After five months, with the reassessment, they identified a significant difference in changes after treatment in all aspects evaluated; most swallowing impairment parameters occurred more frequently and all patients (100%) reported some type of change.

The following parameters were noted as being compromised in nine of the 11 patients (82%): reduction in the retraction of the tongue base and laryngeal elevation, penetration of the laryngeal vestibule with thin barium, and penetration of the laryngeal vestibule with thick barium. Aspiration, defined as material that reaches the lower surface of the vocal folds, was seen in seven patients (64%) after treatment. Significant differences were also found in relation to the environment and type of diet. From the 11 patients evaluated after treatment, only one did not describe restrictions on location, nutrition or company; from this total, eight patients (73%) placed a percutaneous endoscopic gastrostomy (PEG) tube due to an increase in dysphagia[28].

The study conducted by Palouski *et al.* (2006)[29] showed deglutition disorders related to reduced oral intake and dietary restrictions in 170 patients treated with radiotherapy with or without chemotherapy, followed for up to one year after treatment. It was possible to identify that before cancer treatment, 5.1% of all patients presented oral intake reduced by 50% of their nutrition, with an increase in this number one month after treatment, with a decrease during the first year.

In the pre-treatment swallowing study, motility disorders that were significantly related to 50% oral intake were reduced anteroposterior movement of the tongue, reduced tongue strength and laryngeal elevation, and classification of non-functional swallowing. In post-treatment assessments, disorders related to reduced oral intake

varied depending on the assessment point. In one month, there was reduced retraction of the tongue base and elevation of the larynx, and the disorders most related to oral intake were reduced by 50%. At three months after treatment, the delay in pharyngeal swallowing, the closure of the incomplete laryngeal vestibule, the elevation of the reduced laryngeal, and the classification of non-functional swallowing were more often related to a reduced oral intake. Finally, at six and twelve months after treatment, the elevation of the reduced larynx and classification of non-functional swallowing continued to be significantly related, and the reduced cricopharyngeal opening appeared as a new manifestation[29].

Logemann *et al.* (2008)[30] examined the function of oropharyngeal swallowing with videofluoroscopic studies in patients treated only with radiation or chemoradiation at three specific moments: initial assessment, at three and twelve months after completion of treatment. It was possible to observe that all 48 patients presented deglutition disorders in the pre-treatment, probably due to the tumor. Its frequency ranged from 6% to 67%; the most frequent disorders were reduced retraction of the base of the tongue (67%), reduced tongue strength (51%), and delay in the triggering of pharyngeal swallowing (40%). For all patients in the study, the rates of reduced retraction of the base of the tongue, delay in closing the vestibule, reduced movement of the anteroposterior tongue and laryngeal elevation increased significantly in the three moments (except reduction of the larynx) between zero points and three months. The late closing of the vestibule and the reduced movement of the tongue maintained this significant increase in twelve months. At three months post-treatment, the frequency in the other nine disorders worsened, but not significantly. In general, the frequency of occurrence of the disorders changed significantly between three and twelve months.

The frequency of functional swallowing decreased significantly from 98% at baseline to 79% at three months. At the same time, the percentage of patients who ate less than 50% orally increased significantly at three months and decreased significantly at twelve months. At twelve months post-treatment, five patients had a gastrostomy tube placed and two patients were on a tracheostomy[30].

Feng *et al.* (2007)[31] measured swallowing dysfunction and aspiration before and three months after therapy in 36 subjects with oropharyngeal and nasopharyngeal cancer. According to the videofluoroscopy pretreatment, three patients (8%) aspirated, and 16 (44%) aspirated three months after treatment ($p = 0.002$). Other changes found to be statistically significant after treatment compared to before therapy were decreased epiglottic function, laryngeal elevation, function of the base of the tongue, increased pharyngeal transit time (for liquids) and residues after deglution. No patient had stenosis before therapy, while three (8%) developed stenosis after three months ($p = 0.25$).

Other data characterizing the studies can be seen in **Table 2** and the main changes in swallowing at different times can be seen in **Table 3**.

Risk of individual study bias

All studies[28-31] had a low risk of bias or low methodological quality. Detailed information on the risk of bias in the included studies can be found in **Table 4**.

TABLE 2 – Databases search strategies

Database	Search strategy (January, 2019)	Results
LILACS (http://lilacs.bvsalud.org/)	• tw:((Dysphagia and Radiotherapy)) AND (instance:"regional") AND (db:("LILACS"))	49
	• tw:((Disfagia and Radioterapia)) AND (instance:"regional") AND (db:("LILACS"))	79
	• tw:((Dysphagia and Chemoradiotherapy)) AND (instance:"regional") AND (db:("LILACS"))	4
	• tw:((Disfagia and Quimiorradioterapia)) AND (instance: "regional") AND (db:("LILACS"))	0
	• tw:((Deglutition Disorders and Radiotherapy)) AND (instance:"regional") AND (db:("LILACS"))	18
	• tw:((Deglutition Disorders and Chemoradiotherapy)) AND (instance:"regional") AND (db:("LILACS"))	1
	• tw:((Swallowing Disorders AND Radiotherapy)) AND (instance:"regional") AND (db:("LILACS"))	17
	• tw:((Swallowing Disorders AND Chemoradiotherapy)) AND (instance:"regional") AND (db:("LILACS"))	0
	• tw:((Dysphagia and Oropharyngeal Neoplasms)) AND (instance:"regional") AND (db:("LILACS"))	97
Scielo (http://www.scielo.org/)	Dysphagia and radiotherapy	32
	Disfagia and radioterapia	29
	Dysphagia and chemioradiotherapy	0
	Disfagia and quimioradiotherapy	1
	Deglutition disorders and radiotherapy	5
	Swallowing disorders and radiotherapy	9
	Dysphagia and oropharyngeal neoplasms	3
	Disfagia and cancer orofaringe	3
PubMed (http://www.ncbi.nlm.nih.gov/pubmed)	"Deglutition Disorders" [All Fields] OR "Swallowing Disorders" [All Fields] OR "Dysphagia" [All Fields] OR "Oropharyngeal Dysphagia" [All Fields] AND ("Oropharyngeal Neoplasms" [All Fields] OR "Oropharyngeal Cancers" [All Fields] OR "Oropharynx Cancer" [All Fields] OR "Oropharyngeal Neoplasm" [All Fields] OR "Pharyngeal cancer" [All Fields] AND "Radiotherapy" [All Fields] OR "Radiation Therapy" [All Fields] OR "Chemoradiotherapy"[All Fields]	186
Scopus (http://www.scopus.com/)	(("Deglutition Disorders" OR "Swallowing Disorders" OR "Dysphagia") AND ("Oropharyngeal Neoplasms" OR "Oropharyngeal Cancers" OR "Pharyngeal cancer") AND ("Radiotherapy" OR "Radiation Therapy" OR "Chemoradiotherapy"))	317
Web of Science (http://apps.webofknowledge.com/)	(("Deglutition Disorders" OR "Swallowing Disorders" OR "Dysphagia" OR "Oropharyngeal Dysphagia") AND ("Oropharyngeal Neoplasms" OR "Oropharyngeal Cancers" OR "Oropharynx Cancer" OR "Oropharyngeal Neoplasm" OR "Pharyngeal cancer") AND ("Radiotherapy" OR "Radiation Therapy" OR "Chemoradiotherapy"))	43
OpenThesis (http://www.openthesis.org/)	("Deglutition Disorders" OR "Swallowing Disorders" OR "Dysphagia") AND ("Oropharyngeal Neoplasms" OR "Oropharyngeal Cancers" OR "Pharyngeal cancer") AND ("Radiotherapy" OR "Radiation Therapy")	6
OpenGrey (http://www.opengrey.eu/)	"Deglutition Disorders" AND "Chemorradiotherapy"	0
Total		899

TABLE 3 – Main characteristics of eligible studies for qualitative analysis

Author and year	Study location	Sample	Age range	Type of study	Evaluation	Cancer site	Staging	Type of treatment/ volume of dosage	Follow-up period
Graner *et al*. (2003)	Minnesota	- 11 individuals - 7 men - 4 women	37 to 78 years	Longitudinal and prospective	Videofluoroscopy	Oropharynx, hypopharynx and larynx	Stages III and IV	Dose fracionada 72 Gy and 150 mg/m^2	Before treatment and five months after
Pauloski *et al*. (2006)	Washington	- 170 individuals - 132 men - 38 women	34 to 80 years	Longitudinal and prospective	Videofluoroscopy	Nasopharynx, oral cavity, oropharynx, hypopharynx and larynx	Stage IV	22 – Radiotherapy 147 – Chemoradiotherapy (total dose 6947 to 6919 cGy)	Before treatment, one, three, six and 12 months after
Feng *et al*. (2007)	Michigan	- 36 individuals - 30 men - 6 women	Average 56 years	Longitudinal and prospective	Videofluoroscopy	Nasopharynx and oropharynx	Stages III and IV	-	Before treatment and three months after
Logemann *et al*. (2008)	New York	- 48 individuals - 38 men - 10 women	38 to 76 years	Longitudinal and prospective	Videofluoroscopy	Nasopharynx, oropharynx, hypopharynx and larynx	Stages I, II, III, and IV	36 – Chemoradiotherapy 12 – Radiotherapy (total dose 6500 to 7920 cGy)	Before treatment, three, and 12 months after

TABLE 4 – Main results of eligible studies for qualitative analysis

Authors	Reduced tongue-base retraction		Reduced laryngeal elevation		Delayed pharyngeal swallowing		Presence of pyriform sinuses residue		Vallecule residue		Incomplete cricopharyngeal closure		Aspiration	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Graner *et al*. (2003)	45%	82%*	45%	82%*	27%	36%	21%	60%	36%	72%	18%	36%	15%	45%
Pauloski *et al*. (2006)	-	-	14.6%	26.9%*	-	-	-	-	-	-	10.3%	37.5%	-	-
Feng *et al*. (2007)	61%	92%*	22%	67%*	-	-	14%	19%	28%	48%	58%	61%	8%	47%*
Logemann *et al*. (2008)	68%	84%*	5%	26%	37%	53%	0%	16%	-	-	-	-	-	-

*$p < 0.05$.

DISCUSSION

The eligible studies were carried out exclusively in the United States, in the last decade, showing the need for other researchers in the area to address the issue. Due to its relevance, both for further studies that may compare different variables (dosages, treatment time, and sequelae for swallowing) as well as to outline appropriate therapeutic plans and guide those involved (professional team, patients and family) concerning possible changes in swallowing and, thus, to carry out preventive, protective and therapeutic measures for this orofacial function that provides human subsistence.

Among different factors that may alter swallowing, cancer can be one of those factors. Oropharyngeal cancer was more prevalent in males (75.93%) in all studies chosen for this systematic review. The reasons cited by the Inca[32] that justify such result are: smoking, alcoholism, excess body fat, exposure to different substances (asbestos, wood, leather, cement, cereals and textiles dust, formaldehyde, silica, carbon soot, organic solvents, and pesticide), and HPV virus infection.

Clinical (subjective) and objective (by videofluoroscopy) assessment can provide the diagnosis of dysphagia. In this regard, videofluoroscopy was the test used in the studies of this systematic review. The justification for this choice is the fact that this test is considered the gold standard test to assess deglutition and its possible disorders. This examination allows the visualization of all phases of deglutition: from the mouth (chewing, organizing and ejecting the bolus), pharynx (shape, transit, palatal competence, and airway protection), and esophagus (esophageal lumen, its walls, relations, transit time, and sphincteric competence), enabling the detailed analysis of each structure, the entire process, in addition to allowing images to be reviewed whenever necessary[33].

It was evident that the disease site (in the oral cavity, nasopharynx, oropharynx, or hypopharynx) did not affect the nature of the deglutition disorders. However, in each study, patients presented cancer in different stages, although there was a predominance of stages III and IV, and treated with different radiation fields, covering several important organs for the swallowing mechanism, which did not allow a more detailed analysis in relation to staging and possible sequelae in swallowing, which is a limitation in the analysis of the results obtained.

Radiotherapy or chemoradiotherapy has been widely used to treat malignant lesions of the head and neck, with improved patient survival. However, this form of therapy is still associated with several adverse reactions, such as dysphagia, which significantly affect the quality of life of patients, and may even affect the treatment progress[34].

The presence of dysphagia related to the radiotherapy or chemoradiotherapy application in patients with oropharyngeal cancer occurred in 51.96% of the sample. It was possible to observe common results such as reduced tongue base retraction, reduced tongue strength, delay in triggering pharyngeal swallowing, and reduced laryngeal elevation during swallowing, corroborating the findings of other studies[35, 36].

It is important to highlight that these changes can be justified by the reduction in oropharyngeal sensitivity, xerostomia and/or mucositis resulting from chemoradiotherapy. According to Lazarus *et al.* (1996)[13], chemoradiotherapy in oropharynx also affects regions adjacent to the larynx and the oral cavity, thereby altering the healthy tissues. Mucositis occurs through a complex biological process, which can be divided into five sequential phases: initiation, signaling, amplification, ulceration, and healing. Initiation is the asymptomatic phase in which there is direct damage to the DNA of the basal cells of the epithelium and the appearance of oxidative radicals. In signaling, enzymes can be activated directly by radiotherapy and chemotherapy or indirectly by the oxidative radicals formed in the previous phase, inducing apoptosis. In the amplification phase, a series of feedback cycles occurs, further increasing cell damage due to the exacerbated production of inflammatory cytokines. The ulcerative phase is characterized by loss of mucosal integrity, providing a gateway for fungal, bacteria, and viruses, accompanied by painful symptoms. In the healing phase, there is proliferation, differentiation and migration of epithelial cells, and restoration of mucosal integrity[37].

Another important effect of chemoradiotherapy observed in the chronic phase that affects the deglutition function is the muscle fibrosis that leads to reduced mobility and justifies the changes mentioned by the sample of this study, and is ratified by other researchers[13, 38-40]. The development of fibrosis is a complicating and limiting factor in the use of radiotherapy. The mechanisms that lead to fibrosis are not clear yet, but the indirect effect of oxidative stress is believed to act in the lesions caused in the membrane lipids, DNA and constitutive proteins, in addition to the activation of pro-inflammatory factors and downward modulation of factors involved in regeneration[41].

The presence of food residue on the tongue, palate, pharyngeal region along the base of the tongue, valecules, posterior pharyngeal wall, as well as in the vestibules and in the piriform sinus region[42, 43] is due to the type of diet offered. Studies report that diets with a "honey" consistency are known to produce waste more often than thin or thick liquids, thus leading to the presence of residues by the oral route and pharynx.

In the study by Xinou *et al.* (2008)[36] the MBSImP standardized data collection protocol similar to that reported by Martin-Harris *et al.* (2015)[43] was used, they included large pills with a wide range of volumes and viscosities. An explanation for the high rates of oral and pharyngeal residues could be the type of barium powder used in the studies to coat the mucosa, in order to describe abnormalities present in the swallowing process. This produces more residues than barium suspensions used outside Europe, which are used in videofluoroscopy and typically include additives in order to smoothly flow through the oropharynx without leaving a coating on the mucosa[44-46].

The findings of this analysis highlight the importance of the oropharyngeal muscles action in normal swallowing, as well as the need for greater attention in chemoradiation. The normal function of these muscles ensures that the bolus passes from the oral cavity through the pharynx and esophagus, without entering the larynx and lower airway. By elevating the larynx anteriorly, displacing the hyoid bone and with an effective downward movement of the epiglottis, negative pressure is generated that allows the protection of the airways with the entry of the bolus into the esophagus. Analyzing the deglutition process from this perspective, it is speculated that higher doses of radiation may affect the muscles present in the oropharyngeal cavity[20], reducing the range of motion and slowing down the entire deglutition process.

According to the results obtained by Pauloski *et al.* (2006)[29] and Logemann *et al*. (2008)[30], who followed up their patients for a year, there is a slight improvement in the signs and symptoms of dysphagia, without, however, eliminating it, which demystifies the belief of some professionals that deglutition disorders in these patients improve over time. The study by Graner *et al*. (2003)[28] also ratifies the above. In fact, there is some preliminary evidence that the swallowing physiology in patients treated with radiotherapy may worsen in the next few years after treatment, indicating the importance and need for continued research, monitoring and swallowing muscles exercises[47-49].

Feng *et al*. (2010)[16], aiming to reduce dysphagia, they found statistically significant responses regarding the dose-effect of volume applied in radiotherapy to combat oropharyngeal cancer and dysphagia, which could be used as initial goals for radiotherapy dosimetry. These relationships suggest that reducing

doses for structures that are part of the deglutition process can minimize the prevalence and severity of dysphagia. However, this hypothesis has not been confirmed because there is no association of cause and effect. In any case, the findings motivate efforts to further reduce these doses, without compromising the target doses and the elimination of cancer.

It is important to highlight the relevant alteration in swallowing changes after treatment, considering that 100% of the sample showed considerable worsening in all analyzed aspects related to deglutition. This implies that radiotherapy with or without chemotherapy brings some type of change in the swallowing pattern, regardless of the type and dose of radiotherapy with or without chemotherapy and the type of staging, confirming what was exposed by Jham & Freire (2006)[34].

It is evident the importance of monitoring these patients by a multidisciplinary team, including the speech therapist, even before the start of treatment, regardless of their design. This is because the studies of the sample 21.4% presented dysphagia before the application of radiation. In the context of dysphagia, the speech therapist suggests head positions or changes in position for safe swallowing; when necessary, changes the consistency of food; performs passive stimulations and active exercises in order to improve deglutition aspects. Thus, when oral feeding is no longer possible, it is up to professionals to expose reasonable alternatives to nutrition, explaining the advantages and disadvantages of each method, thus trying to minimize the anguish and suffering of the patient and family[50].

Another aspect that deserves mentioning concerns the confounding factors in the swallowing research, not mentioned by the selected sample, among which can be listed: the neurogenic factors (such as previous strokes) and aging (presbyphagia). In relation to stroke, Schelp *et al.* (2004)[51] reported that this involvement is one of the main reasons for death in Brazil, with 91% of dysphagia verified by videofluoroscopy in the study sample (102 patients). Regarding aging, it is common, according to Marcolino *et al.* (2009)[52], that the elderly complain of the sensation of food stopped after swallowing; choking or coughing during feeding; difficulties in swallowing solid consistency and xerostomy. In the speech-language evaluation, they added that the orofacial muscles flaccidity; decrease in the threshold of excitability of the swallowing reflex, and compensatory use of the multiple swallowing maneuver are usual to reduce difficulties when swallowing. The extent to which the subjects selected in the studies did not have a previous history of neurogenic events or presbyphagia are aspects that deserve attention for not to generalize the results obtained, considering that there may be analysis bias in view of the above.

However, the data from the studies identified and analyzed showed that oropharyngeal cancer is an important public health problem, where changes in swallowing are prevalent, especially after chemoradiotherapy, interfering with the patient's physical, mental and social well-being. The lack of uniformity in the definition of the results brought limitations to their analysis and the small number of selected articles made it difficult to compare the studies, however this was due to the lack of homogeneity and design of the published studies.

Despite the limitations found, studies have shown a relationship between oropharyngeal cancer, chemoradiation and changes in the deglutition process, showing the continuity of research in the area.

CONCLUSION

The findings of this systematic review showed that patients undergoing conservative therapies for the treatment of oropharyngeal cancer showed deglutition disorders such as reduced laryngeal elevation, strength and retraction of the base of the tongue, delayed swallowing trigger, presence of food residues on the tongue, palate, pharyngeal region, valecules, posterior pharyngeal wall, inside the vestibules and in the piriform sinuses, regardless of the type and intensity of radiation, as well as the tumor staging.

Such changes may be present before treatment, due to the presence of the tumor, but they intensify during and after treatment, which can vary from three to twelve months after radiation or chemoradiation. However, due to the heterogeneity of the studies, it was not possible to perform a meta-analysis, due to the little standardization in the methods of the included studies, which makes it difficult to generalize the data obtained.

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