ISABELA PORTO DE TOLEDO

Sequelas Fonoaudiológicas após tratamento para câncer de cabeça e pescoço

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UNIVERSIDADE DE BRASÍLIA
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Dissertação apresentada como requisito parcial para a obtenção do título de Mestre em Ciências da Saúde pelo programa de Pós-Graduação em Ciências da Saúde da Universidade de Brasília.

Orientadora: Profª. Drª. Eliete Neves da Silva Guerra
Coorientadora: Profª. Drª. Graziela De Luca Canto

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BANCA EXAMINADORA

Profª. Eliete Neves da Silva Guerra – presidente
Universidade de Brasília

Profª. Paula Elaine Diniz dos Reis
Universidade de Brasília

Prof. Paulo Tadeu de Souza Figueiredo
Universidade de Brasília

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RESUMO

As desordens de deglutição são sequelas comumente associadas ao tratamento oncológico. Contudo, ainda não existe um consenso quanto a frequência de alterações do processo de deglutição nessa população. O estudo tem por objetivo estimar a frequência de desordens da deglutição no pré e pós-tratamento de pacientes com câncer de cabeça e pescoço. Uma revisão sistemática foi desenvolvida seguindo o guia para relato de itens de revisão sistemática e meta-análises (PRISMA). Estratégias de busca foram desenvolvidas para as seguintes bases de dados: PubMed, LILACS, Scopus, Web of Science, LIVIVO e SpeechBITE. Adicionalmente, uma busca da literatura cinzenta foi realizada através do Google Scholar, Open Grey e ProQuest. Somente estudos que realizaram avalição diagnóstica da deglutição utilizando exames objetivos como videofluroscopia da deglutição ou videoendoscopia da deglutição foram incluídos na análise. O risco de viés dos estudos incluídos foi analisado com a ferramenta “The Critical Appraisal Checklist for Studies Reporting Prevalence Data from the Joanna Briggs Institute”. A meta-análise de proporção, com efeito fixo ou randômico, foi realizada através do Software estatístico MedCalc versão 14.8.1 (MedCalc Software, Ostend, Belgium). A seleção dos estudos foi realizada em duas fases, por dois revisores, independentemente. Dezesseis estudos passaram pelos critérios de elegibilidade e foram incluídos para análise. Em todos os estudos a deglutição foi avaliada antes e até 12 meses após o tratamento oncológico. Aspiração prévia a tratamento de câncer teve frequência de 11,3% (desvio padrão (SD), 8,7 a 14,3%; amostra total=517), entre 1 a 6 meses após tratamento ocorreu um aumento para 27,1% (SD, 1,0 a 36,0%; amostra total=478) e até 12 meses pós-tratamento teve uma queda para 17,9% (SD, 12,3 a 2,8%; amostra total=153). Penetração de volume acima das pregas vocais e redução de elevação laríngea também foram mais frequentes no período de 1 a 6 meses após tratamento oncológico. Os resultados encontrados nesse estudo indicam que a frequência de desordens de deglutição e suas complicações como a aspiração, em pacientes com câncer de cabeça e pescoço aparenta ser maior no período de até 6 meses após tratamento para o câncer.

ABSTRACT

The deglutition disorders are common sequelae of the oncologic treatment. However, there is no consensus over the frequency of the alteration in the swallowing mechanisms in this population. The study aims to estimate the frequency of deglutition disorders in patients pre and post-treatment for head and neck cancer. A systematic review was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Search strategies were developed for the following databases: PubMed, LILACS, Scopus, Web of Science, LIVIVO, and SpeechBITE. Additionally, a search of the grey literature was performed through Google Scholar, Open Grey, and ProQuest. Only studies that performed evaluation of deglutition before and after cancer treatment were included in this systematic review. The studies had to use diagnostic exams for deglutition disorders as Videofluoroscopy swallowing exam, Fiber-optic endoscopic evaluation of swallowing, modified barium swallow or Videofluorographic swallow study. The Critical Appraisal Checklist for Studies Reporting Prevalence Data from the Joanna Briggs Institute was used to assess the risk of bias of the included studies. A proportion of fixed or random effects meta-analysis using the MedCalc Statistical Software version 14.8.1 (MedCalc Software, Ostend, Belgium) were conducted. The selection of the studies was divided in two phases where two reviewers worked independently. Sixteen studies met the eligibility criteria and were included. In all of the studies an assessment of the deglutition was performed previous and up to 12 months after receiving treatment for the cancer. Aspiration previous to the cancer treatment had a frequency of 11.3% (Standard deviation (SD), 8.7 to 14.3%; total sample=517), between 1 to 6 months after treatment, this increased to 27.1% (SD, 19.0 to 36.0%; total sample=478), and up to 12 months after there was a decrease to 17.9% (SD, 12.3 to 24.8%; total sample=153). Penetration above the vocal cords and reduced larynx elevation were also more frequent in the 1 to 6 months' period after the treatment for the head and neck cancer. The results found in this study indicates that the frequency of deglutition disorders and its complications as aspiration, in patients with head and neck cancer, appears to be higher in the immediate to 6 months' post-treatment period.

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LISTA DE ABREVIATURAS E SIGLAS

AJCC = American Joint Committee on Cancer
CCP = Câncer de Cabeça e Pescoço
DARS = Dysphagia/aspiration-related structures
EUA = Estados Unidos da América
IMRT = Radioterapia de intensidade modulada
MA = Meta-análise
RAD = Late radiation-associated dysphagia
RS = Revisão Sistemática
SWAL-QOL= Swallowing quality of life questionnaire
WHO = Oral Mucositis Grading Scale

SUMÁRIO

1. INTRODUÇÃO

A conduta terapêutica nos quadros oncológicos de cabeça e pescoço requer ação multiprofissional, incluindo profissionais como: cirurgião de cabeça e pescoço, oncologista, radiologista, fonoaudiólogo, cirurgião-dentista, nutricionista, assistente social, psicólogo, fisioterapeuta, enfermeiro, entre outros. A atuação do fonoaudiólogo é voltada, principalmente, para as funções relacionadas à alimentação e à comunicação. Essa atuação, quando possível, deve ocorrer desde o período de diagnóstico do câncer[1].

As desordens de deglutição são exemplos de alterações comumente associadas às neoplasias em cabeça e pescoço. A avaliação da deglutição e demais funções do sistema estomatognático é realizada pelo fonoaudiólogo em ambiente clínico. Se necessário, a avaliação complementar pode ser realizada com exames objetivos, como a videofluoroscopia[2].

Na reabilitação da função de deglutição, o fonoaudiólogo pode empregar diferentes estratégias, como modificação de consistência alimentar, estratégias posturais, manobras de proteção das vias aéreas e ainda, exercícios terapêuticos para os grupos musculares envolvidos no processo de deglutição[3]. Contudo, não há na literatura um consenso quanto à utilização dessas estratégias para terapia profilática nos pacientes oncológicos.

Essa lacuna no meio científico pode levar à falta de consenso sobre dados de frequência das desordens de deglutição antes e após o tratamento oncológico. Um maior conhecimento sobre essa frequência previamente à terapia oncológica e após a sua conclusão são fundamentais para o entendimento dessas alterações e para as possibilidades de intervenção.

2. REVISÃO DE LITERATURA

2.1 Câncer de cabeça de Pescoço

O Carcinoma de Cabeça e Pescoço (CCP) pode surgir na região de lábios, cavidade oral, orofaringe, hipofaringe, nasofaringe, laringe, glândulas salivares, cavidade nasal e seios paranasais, meato acústico externo e ouvido médio[4]. O CCP tem como característica uma incidência maior em homens do que em mulheres, comumente encontrados na população de baixo nível socioeconômico, com diagnostico após a meia-idade. Fatores de risco relacionados com o surgimento desses tipos de carcinomas incluem o tabaco, álcool e infecções de papilomavírus humano (HPV), especialmente do subtipo 16[5].

A prevalência dos casos de tumores em cavidade oral e lábios no mundo é de 2,2%, seguida de 1,4% em laringe, 1,0% em faringe e 0,7% em nasofaringe[6]. Nos EUA estima-se que mais de 50 mil novos casos de câncer de cavidade oral e faringe irão ocorrer em 2018, sendo 37.160 desses casos em homens[7]. No Brasil, estima-se que para o biênio de 2018-2019, mais de 11.200 mil casos de câncer de cavidade oral acometerão a população masculina, mais do que o dobro do valor comparado a população feminina (3.500)[8].

O diagnóstico de CCP possui como guia a classificação criada pelo *American Joint Committee on Cancer* (AJCC), que classifica o câncer em diferentes estágios, de inicial (estágios I e II) a avançado (estágios III e IV)[9]. Conhecer a extensão e/ou estágio de câncer quando este é diagnosticado é um fator importante para a formação de decisão quanto ao tratamento e prognóstico. A média de tempo para diagnóstico de CCP é de 17 semanas[10].

O principal objetivo quando se planeja a proposta terapêutica para tumores malignos é a cura. Contudo, objetivos secundários também são importantes para manejo das possíveis sequelas pós-tratamento. Um dos objetivos secundários do tratamento de CCP é a preservação de funções[11]. As modalidades convencionais e aplicadas na prática clínica para CCP são: cirurgia como primeira opção de tratamento curativo, radioterapia e quimioterapia quando indicado. Dependendo do estágio em que o câncer foi diagnosticado (estágios avançados), pode-se realizar uma combinação de duas ou das três modalidades[11].

Dentre as diferentes técnicas para execução de radioterapia, a de intensidade modulada (IMRT), auxilia na preservação de estruturas essenciais para realização de funções. Essa modalidade terapêutica possui tecnologia de conformação de radiação, o que auxilia na distribuição da dose de radiação, como na diminuição da exposição de estruturas e tecidos circunjacentes ao tumor, porém não afetados pela doença[12]. IMRT associada a técnica de imagem guiada, também auxilia na distribuição da dose da radiação, permitindo reprogramações em tempo real da posição, volume e da dose a ser aplicada[13].

2.2 Sequelas Bucais

Sequelas durante e pós-tratamento para CCP são esperadas e muitas vezes prejudiciais às funções do sistema estomatognático, como mastigação, deglutição e fala. Durante e/ou após a radioterapia, quimioterapia ou combinação dessas, é comum aparecerem alterações como mucosite, dor em região oral, disfagia, perda de peso, alterações no paladar, xerostomia, diminuição da abertura de boca e osteorradionecrose[14].

A mucosite oral é uma inflamação da mucosa oral e/ou orofaríngea, geralmente com surgimento durante a radioterapia e/ou quimioterapia. Essa inflamação causa dor, desconforto na região oral e interfere na ingestão de alimentos, deglutição, e higiene oral[15]. A severidade da mucosite oral pode ser classificada por meio da escala *Oral mucositis grading scale* (WHO), onde zero é o equivalente a sem alteração da mucosa e 4 é a mucosite severa com impossibilidade de alimentação por via oral. O surgimento dessa inflamação em mucosa é comum nas semanas iniciais do tratamento de radioterapia (2-3 semana)[16]. A prevalência de mucosite em pacientes com CCP, durante tratamento combinado de IMRT e cisplatina foi de 54% (n=39). Após três meses do término do tratamento, ocorreu uma queda para 23% (n=39)[17].

Outra sequela comumente presente durante e após terapêutica de CCP é a xerostomia. Esse sintoma é caracterizado pela sensação de boca seca e/ou saliva espessa[18]. A hipossalivação é uma alteração que ocorre nas glândulas salivares, podendo ser causada pela radioterapia/quimioterapia, e possui como característica a baixa produção de saliva, acarretando em sensação de boca seca[19]. A ocorrência de xerostomia em pacientes com CCP após três e seis meses do final do tratamento

foi de 43% e 36%, respectivamente[20]. Um dos fatores que podem contribuir com a diminuição dessa sequela, é o planejamento radioterapêutico. Numa amostra de pacientes com câncer em orofaringe submetida a radioterapia poupando as glândulas submandibulares contralaterais, foi observado diminuição de xerostomia quando comparado ao grupo onde as glândulas não foram poupadas[21]. Contudo, outros fatores podem estar associados com o surgimento da xerostomia, como o uso de opioides, consumo de álcool, cigarro, idade, entre outros.

O trismo consiste da redução da abertura da boca (<35 mm), geralmente associada a radiação em cabeça e pescoço, causando mudanças na contratura das estruturas da mastigação[18]. Essa alteração na abertura de boca gera consequências para as funções de mastigação e fala. Dez anos após tratamento de radioterapia, numa amostra com CCP, foi observado que 55% (n=22) dos pacientes apresentavam trismo[21]. A dose de radioterapia também foi associada a probabilidade de desenvolver trismo, onde observou-se que a cada 10 Gy adicionais no músculo pterigoideo, depois de uma dose de 40 Gy, houve aumento de 24% (n=56) na probabilidade de desenvolver trismo[22].

2.3 Desordens de deglutição

As desordens no processo de deglutição ou disfagia, é uma das alterações que pode ser encontrada em pacientes com CCP no decorrer da doença, durante e após o tratamento. Na deglutição normal, o alimento passa da cavidade oral para a faringe e em seguida ao esôfago em questão de poucos segundos (~2 segundos) (Figura 1)[23]. Qualquer alteração nesse processo ou em suas estruturas podem levar a disfagia.

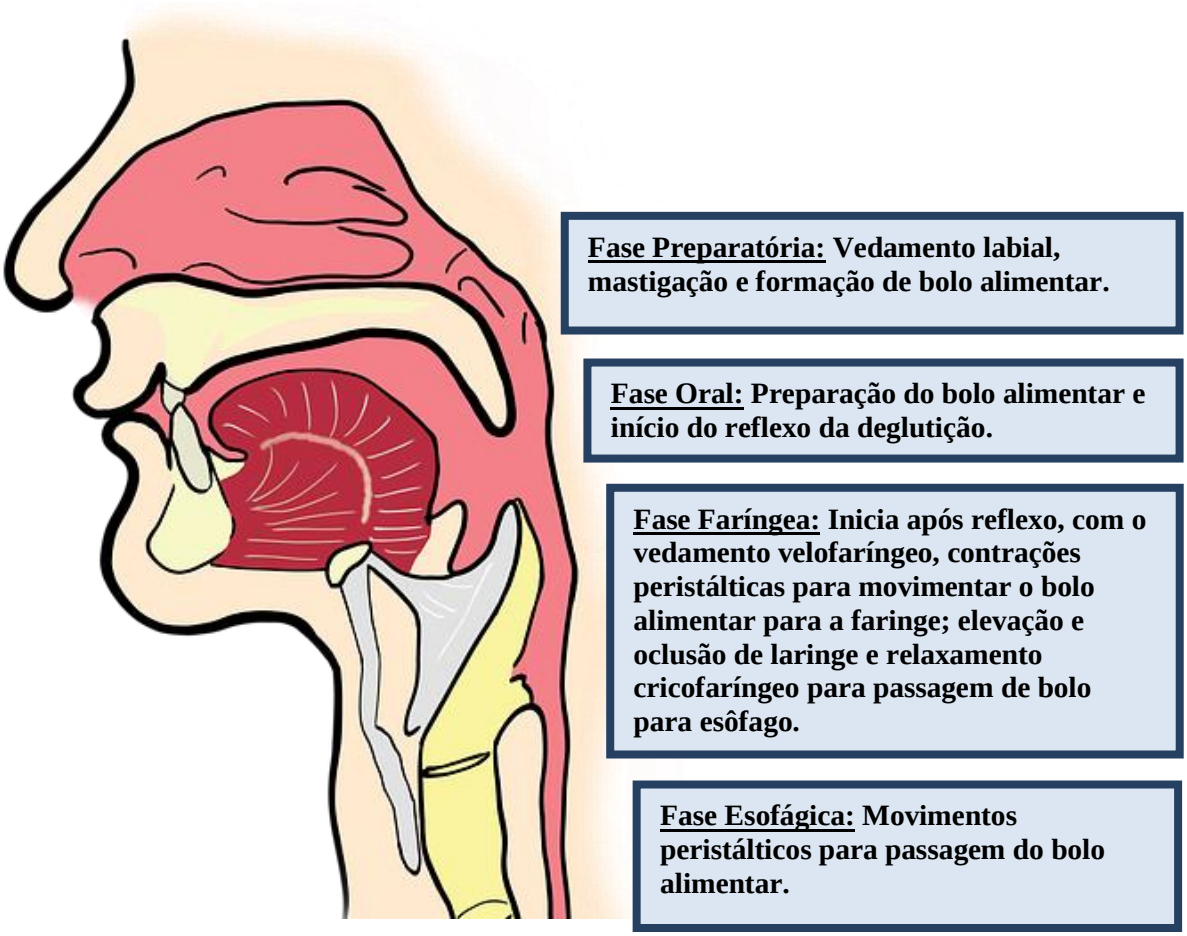

Figura 1 – Fases da deglutição normal, adaptado de Logemann e Logemann (1983)[23].

As disfagias associadas ao CCP são geralmente alterações mecânicas na região oral e/ou faríngea. A disfagia orofaríngea é uma alteração do processo de transferência do bolo alimentar ou líquido da cavidade oral para o esôfago. Nesse processo de transferência, as complicações podem ocorrer, como penetração de volume alimentar acima das pregas vocais e até a aspiração deste em vias aéreas. Outro tipo de disfagia é a esofágica, onde há uma alteração na passagem do alimento do esôfago até o estômago[24].

Um dos tipos de disfagia decorrentes da radioterapia na região de cabeça e pescoço é a *Late radiation-associated dysphagia* (RAD), que é resultante da fibrose de tecidos, estenose, neuropatia craniana inferior e rigidez[25]. Outras alterações associadas às terapias de câncer também podem contribuir para o surgimento ou piora da disfagia como, mucosite, xerostomia, disgeusia, trismo e odinofagia.

A dificuldade em deglutir foi relatada como moderada em 16,9% (n=39) e severa em 18,5% (n=39) no pós-tratamento de seis a doze meses[17]. Num longo período de tempo, dez anos após tratamento finalizado, 54% (n=22) dos pacientes

com CCP apresentaram alguma limitação na alimentação[21]. A disfagia também pode levar ou prolongar a alimentação por vias alternativas, que servem de aporte nutricional. Em um estudo com 243 pacientes pós-tratamento combinado (quimioterapia e radioterapia) para CCP, foi observado que mais de 60% da amostra necessitou de uso de via alternativa para alimentação[26].

Uma das formas de auxiliar no planejamento da radioterapia, com o intuito de preservar as estruturas responsáveis pela deglutição é identifica-las e evita-las durante o tratamento. As estruturas relacionadas à disfagia/aspiração (DARS) são: palato mole e duro, músculos intrínsecos da língua, complexo muscular milo/geniohioideo, músculo genioglosso, músculo palatoglosso, músculo bucinador, músculo digástrico anterior e posterior, músculo pterigoideo lateral, medial, superior e constritor, músculo constritor médio e inferior, supraglote, glote e subglote e esfíncter cricofaríngeo[25].

A disfagia e outros sintomas orais são fatores que influenciam na qualidade de vida dos indivíduos com CCP. Numa população de pacientes com tumores avançados em região de cabeça e pescoço foi observado piores pontuações no questionário aplicado (SWAL-QOL), em relação aos itens alimentação e comunicação, duração da refeição, vontade de comer e medo ou restrições em comer em público. Esses são fatores que podem levar a um declínio da vida social, isolamento e depressão[27].

2.4 Revisão Sistemática

As técnicas de construção e desenvolvimento de pesquisa são diversas para análise de sequelas orais associadas ao tratamento oncológico. Uma das metodologias de pesquisa de alto nível de evidência científica são as revisões sistemáticas (RSs). As RSs são eficientes para coletar e assimilar informações disponíveis na literatura e utilizar esse conhecimento para a prática clínica[28].

Um dos primeiros passos para a execução de uma RS é a criação de um protocolo de pesquisa. O guia para relato de itens de revisão sistemática e meta-análises (PRISMAp) auxilia na construção desse protocolo e na descrição dos itens necessários de uma RS[29]. O protocolo deve conter uma pergunta de pesquisa específica que contenha população alvo, intervenção ou exposição, uma comparação (se aplicável), os resultados esperados e os tipos de estudo que

possam responder à pergunta (PICOS). É a partir dessa pergunta que se gera todos os outros componentes da RS.

Passos para a execução de uma RS (Figura 2)[30,31]:

- Desenvolvimento de pergunta de pesquisa específica (PICOS);
- Elaboração de estratégias de busca abrangentes e reproduzíveis para diversas bases de dados;
- Construção de critérios de inclusão e exclusão bem definidos e aplicados em todos os estudos pesquisados;
- Seleção dos estudos em 2 fases, realizadas por dois revisores, independentemente. Fase 1 consiste em leitura de títulos e resumo, e fase 2 da leitura do texto completo;
- Avaliação criteriosa do risco de viés dos estudos selecionados;
- Síntese qualitativa e quantitativa dos resultados encontrados;
- Inferências a partir dos resultados analisados.

A análise estatística que pode fazer parte de uma RS é a Meta-Análise (MA). Essa análise combina e sumariza os resultados de múltiplos estudos, aumentando assim a precisão e o poder de evidência dos resultados encontrados[29].

O impacto da RS para a pesquisa e atuação clínica é um tópico amplamente discutido. A decisão clínica é feita por meio de vários fatores: preferências e circunstâncias do paciente; recursos disponíveis; conhecimento do profissional da área da saúde e evidências de pesquisa válida e relevante. A prática clínica baseada em evidência auxilia na melhora da qualidade do tratamento disponibilizado[20,32].

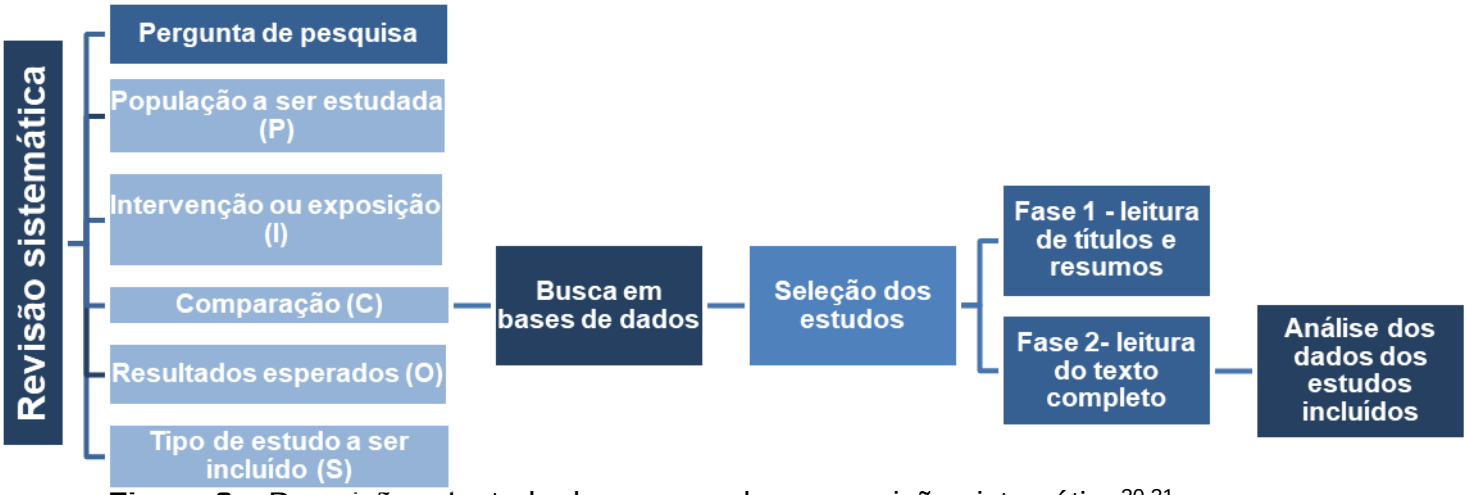

Figura 2 – Descrição adaptada dos passos de uma revisão sistemática[30,31].

3. PROBLEMA DE PESQUISA

A literatura apresenta dados heterogêneos sobre as desordens de deglutição em pacientes com CCP, desde o início da doença, bem como após a finalização do tratamento. A heterogeneidade desses dados pode ser resultante de diversos fatores, como diferentes tipos de CCP, uso de diversas ferramentas para acessar as desordens de deglutição, as várias modalidades terapêuticas, faixa etária da população e estágio em que o câncer foi diagnosticado. Diante desse panorama formulou-se a seguinte pergunta: Qual é a frequência de desordens da deglutição pré e pós-tratamento oncológico em pacientes com CCP?

3.1 HIPÓTESES

Hipótese 1: Há uma alta frequência de desordens de deglutição nos pacientes com câncer em região de cabeça e pescoço desde o diagnóstico da doença.

Hipótese 2: A frequência das desordens aumenta após o tratamento oncológico, quando comparado ao pré-tratamento.

4. OBJETIVOS

4.1 OBJETIVO GERAL

Identificar a evidência disponível na literatura científica sobre as desordens de deglutição pré e pós-tratamento de câncer de cabeça e pescoço.

4.2 OBJETIVOS ESPECÍFICOS

- Coletar artigos científicos que apresentem dados sobre a frequência de desordens de deglutição na população alvo;
- Analisar os dados coletados sobre as desordens de deglutição e alterações associadas dos artigos científicos selecionados;
- Comparar resultados coletados dos estudos sobre as desordens de deglutição e alterações associadas no pré-tratamento com no pós-tratamento oncológico.

5. ARTIGO

Essa revisão sistemática, em formato de artigo, foi submetida para publicação na revista *Head & Neck*, ISSN 1043-3074 (versão impressa), classificada como periódico B1 na Qualis-Capes Medicina II. O registro do envio está sob número HED-17-1459. A escolha da revista foi influenciada pelo escopo da revista, onde se encontram diversas publicações na área de interesse, além de apresentar prévias publicações de revisões sistemáticas.

Deglutition disorders as a consequence of head and neck cancer therapies: a systematic review and meta-analysis

Running title: Frequency of deglutition disorders in HNC patients

Isabela Porto de Toledo, SLP, MSc[1,4]; Leticia Lopes Quirino Pantoja, DDS, MSc[1]; Karen Fontes Luchesi, SLP, MSc, PhD[2]; Daniele Xavier Assad, MD, MSc[1,5]; Graziela De Luca Canto, DDS, MSc, PhD[3,4]; Eliete Neves Silva Guerra*, DDS, MSc, PhD[1]

[1]Laboratory of Oral Histopathology, Health Sciences Faculty, University of Brasília, Brasília, Brazil;

[2]Department of Speech Language Therapy, Federal University of Santa Catarina, Florianopolis, SC, Brazil;

[3]Department of Dentistry, Federal University of Santa Catarina, Florianopolis, SC, Brazil;

[4]Brazilian Centre for Evidence Based Research, Department of Dentistry, Federal University of Santa Catarina, Florianopolis, SC, Brazil;

[5] Hospital Sírio-Libanês, Brasília, Brazil.

* Correspondence Author: Eliete Neves Silva Guerra; elieteneves.unb@gmail.com; Telefax: +55-61-996684988. SQN 2015, Bloco H, apto 201, Asa Norte, Brasília DF, Brazil. Zip Code: 70843-080

ABSTRACT

Objective: The study aims to estimate the frequency of deglutition disorders in patients pre and post-treatment for head and neck cancer (HNC).

Methods: Search strategies were developed for the following databases: LILACS, PubMed, SpeechBITE, LIVIVO, Web of Science and Scopus. Additionally, the grey literature was searched through Google Scholar, Open Grey, and ProQuest. Only studies that performed evaluation of deglutition before and after cancer treatment were included. A proportion of fixed or random effects meta-analysis using MedCalc Statistical Software was conducted.

Results: Sixteen studies were included. Aspiration had a higher frequency between one to six months after treatment, with 27.1% (total sample=478). Penetration of fluids above the vocal cords and reduced laryngeal elevation were also more frequent in the same time period.

Conclusion: The frequency of deglutition disorders and its complications as aspiration appears to be higher in the immediate to six months post-treatment in HNC patients.

Keywords: Deglutition disorders; Head and neck neoplasms; Chemoradiotherapy; Systematic review; Meta-analysis.

INTRODUCTION

According to the World Health Organization Classification of Tumors (WHO), head and neck cancers (HNC) are divided in: oral cavity, larynx, nasopharynx, oropharynx, hypopharynx, nasal cavity and paranasal sinuses, ear, odontogenic, paraganglionic, and salivary glands tumors[1]. Lip and oral cavity tumors had a prevalence of 2.1% worldwide, they were followed by larynx cancer with 1.1%, and nasopharynx cancer with 0.6%[2]. In the United States, oral cavity and pharynx cancers accounted for 34,780 new cases in the male population in 2016[3]. The studies over the incidence of HNC show a trend, this type of tumor occurs more often in males over 40 years old associated to alcohol and tobacco consumption[2-4].

The treatment available for HNC may include: surgery, radiotherapy, chemotherapy or a combination of treatments[5]. The course of treatment is defined based on tumor size, location, resectability, organ preservation approach and metastatic status[6]. Different types of adverse effects are expected from HNC treatments. They differ depending on treatment duration, surgery extension, drug type and radiation location and intensity. Some examples of adverse effects are: pain, weight loss, dry mouth, dysphagia, mucositis, dysgeusia, speech/voice disorders, loss of appetite, changes in physical appearance, social life and in the quality of life in general[7-11].

The frequency of dysphagia in HNC differs when considering different variables such as radiotherapy field size and radicality of surgery. Dysphagia had a higher prevalence, 63.6% right after surgery (<1 year) compared to a longer period (>5 years)[12]. Similarly, dysphagia had a prevalence of 45.9% after cancer treatments (surgery and/or radiotherapy)[13].

Two previous systematic reviews (SR)[14,15] investigate the changes in swallow mechanisms after radiation or drug therapy in HNC. In neither review a quantitative analysis was performed. Therefore, more research on the topic is necessary, because new and more

detailed studies have surfaced over the last 4 years[16-21]. There is also a need for a quantitative analysis of the results found in the literature. Therefore, the aim of this systematic review was to answer the following research question: "What is the frequency of deglutition disorders pre and post treatment in patients that underwent cancer therapy for HNC?"

METHODS

This systematic review was reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[22].

Protocol and registration

The systematic review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42017067837[23].

Eligibility Criteria

- *Inclusion Criteria*

Studies that measured the frequency of deglutition disorders pre and post-treatment in patients with head and neck neoplasms that received any type of therapy for the cancer (surgery, chemotherapy, radiotherapy, or combination of therapies) were included. Only studies with sample over 18 years old and those who had used image exams (i.e. videofluoroscopy swallowing exam) as diagnostic criteria for assessment of deglutition disorders and its complications were included. No language or period restriction was applied.

- *Exclusion Criteria*

Studies were excluded for the following reasons: **(1)** Patients without cancer or non-malignant tumors; **(2)** Studies that did not use image exam (i.e. videofluoroscopy swallowing exam or fiberoptic endoscopy evaluation) as diagnose criteria for deglutition disorders before and after treatment for the cancer; **(3)** Patients that did not underwent any type of treatment/ therapy for the cancer; **(4)** Patients that are receiving treatment for the deglutition disorder/ or

only patients with dysphagia; **(5)** Studies that did not report values representative of the deglutition disorders; **(6)** Reviews, letters, conference abstract, personal opinions, case reports, cross sectional; **(7)** Full text not found; **(8)** Duplicated data from other study.

Information Sources

For the search in the literature, an individual strategy was developed for each of the following databases: LILACS, PubMed, SpeechBITE, LIVIVO, Web of Science and Scopus. An additional search of the grey literature was performed in the Google Scholar, OpenGrey, and ProQuest. The search date was March 23th, 2017 in all the databases and grey literature. The search strategies used are described in Appendix 1. The references cited in the included articles were checked for any extra studies that could be included in the analysis as recommended by Greenhalgh and Peacock[24]. The references were collected by the reference manager software (EndNote™ Online Thomson Reuters, Philadelphia, PA). The duplicate references were identified in this software and posteriorly any additional duplicate not identified by EndNote, was found with the help of Rayyan qcri, a free web and mobile app for systematic reviews (Qatar Computing Research Institute, Doha, Qatar)[25].

Study Selection

The process of selection of the references was divided in two phases. The phase 1 was performed by two reviewers (I.P.T and L.Q.P), who independently screened the title and abstract of the collected references. This blind process was ensured and registered as it was carried on the Rayyan qcri platform (Qatar Computing Research Institute, Doha, Qatar). The studies that did not fit in the inclusion criteria were excluded. In the phase 2, the same reviewers (I.P.T and L.Q.P) applied the eligibility criteria for the full text of the studies selected after phase 1. When necessary, a third reviewer (K.F.L) was consulted to provide a consensus between the two reviewers.

Data Collection Process

The first reviewer (I.P.T) collected the required information from the selected studies. The second reviewer (L.Q.P) crosschecked all the collect information for accuracy. The data collected consisted of: study characteristics (authors, year of publication, country, journal of publication, type of study); population characteristics (sample size, age, type of cancer, cancer stage); exposure characteristics (type of cancer treatment, deglutition assessment), and outcome characteristics (occurrence of deglutition disorders pre-treatment and post-treatment).

Risk of Bias in Individual Studies

The risk of bias of the individual studies was assessed by the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data[26]. The first and second reviewers (I.P.T and L.Q.P) performed this assessment independently. Any disagreements were solved by the agreement of the three first reviewers (I.P.T, L.Q.P and K.F.L).

Analysis of subgroups

A subgroup analysis was performed by dividing the main findings by period: Pre cancer treatment, up to 6 months post cancer treatment, and over 6 months post cancer treatment. Also, the parameter aspiration was divided in three groups according cancer treatment modality.

Summary measures

The data collected for the deglutition disorders or its complications (aspiration/penetration) in adult patients with HNC that underwent cancer treatment were expressed by mean percentage and its 95 percentage confidence intervals (95% CI).

Synthesis of results

A meta-analysis was planned within the studies that presented enough data of frequency for deglutition disorders or its complications pre and post cancer treatment. These data were

analyzed by two types of meta-analysis, for fixed and random effects[27]. The calculus was performed with the aid of MedCalc Statistical Software version 14.8.1 (MedCalc Software, Ostend, Belgium). Heterogeneity was calculated by inconsistency indexes (I^2), and a value greater than 50% was considered and indicator of substantial heterogeneity within studies[28]. A significance level was set at 5%.

RESULTS

Study selection

In phase one of this systematic review, 1368 records were screened from the main six databases after removing the duplicates. Added to that, 302 records from the gray literature. After screening all the titles and abstracts, 171 studies were selected for phase two, which consists of full text screening. In the end of this phase, a total of 155 references were excluded (Appendix 2). No additional articles were selected from the reference list. Therefore, sixteen references were included for qualitative and quantitative analysis. All the selection process is described in Figure 1.

Study characteristics

The sixteen[16-21,29-38] articles included were published in ten different journals, a fourth[17,33,36,37] of them being published in the Head & Neck journal, three[18,29,30] studies published in the Dysphagia journal, and other two[32,34] in the Laryngoscope journal. The remaining seven studies were published in different oncology, medical or speech language pathology journals. The total sample varied from 11[32] to 133[20] patients. Twelve[16,19-21,30-34,36-38] of the included studies used the VFSS as diagnostic tool for deglutition disorders, two[18,29] studies used the modified barium swallow (MBS), one[17] study used the Fiberoptic endoscopic evaluation of swallowing (FEES), and one[35] study used the Videofluorographic exam. Almost half[18,31,32,33,35-37] of the studies were from the United States, two[16,19] from Turkey, one from Australia[30], Canada[38], China[34], India[29], Korea[20], The Netherlands[21], and United Kingdom[17].

Because of the nature of the research question of this systematic review, all of the included studies had a convenience sample. A summary of the characteristics of the sixteen studies can be found in Table 1.

Risk of bias within studies

Nine[17,19-21,29,33,36-38] of the included studies were classified as having low risk of bias. Five[18,30-32,34,35] other studies were considered as having moderate risk of bias, with five or six of the ten questions in the assessment tool with "yes" answers. Only one[16] study was assessed as having high risk of bias. Question 2 ("Were study participant recruited in an appropriate way?") was the one where all of the studies answered "no", that is because all of the samples were of convenience nature. Almost half[16,29-31,34,36] of the assessed studies answered "no" in the ninth question ("Are all important confounding factors/ subgroups/ differences identified and accounted for?"), which points out lack of information in the description of the sample and/or selection criteria. All of the classification discrimination can be found in Appendix 3.

Results of included studies

Overall data distribution

All the samples in the included studies presented a higher distribution (at least two thirds) towards the male sex. The most frequent type of cancer presented in the included studies was oropharynx, followed by tongue, larynx, hypopharynx, nasopharynx, tonsil, unknown sites, and others. Most of the studies that presented the data concerning cancers stages had the samples grouped in the stages III-IV. Ten[16,17,29-31,33-37] of the included studies had as main treatment modality for cancer concurrent chemoradiotherapy. Other five[18-20,32,38] studies showed that concerning modalities with surgery, conventional radiotherapy and/or chemotherapy. Only 1[21] of the included studies presented data for the modality treatment of Intensity-modulated radiation therapy (IMRT) combined with chemotherapy.

Pre-cancer treatment

All the sixteen included studies performed swallowing assessment with image exams at the baseline. The type of parameters concerning deglutition was reported in different ways across studies. The common parameter in fourteen[16,17,19-21,29-31,32-36,38] of the included studies was aspiration, a complication of deglutition disorders. The results of the meta-analysis at the pre-cancer treatment showed a frequency of aspiration of 11.3% (Standard deviation (SD), 8.7 to 14.3%; total sample=517) (Figure 2a).

In six[16,30,31] of the included studies was possible to analyze to total occurrence of penetration of food, liquids or saliva above the vocal cords in the pre-cancer treatment period. In the analyses, the frequency of penetration was of 14.7% (SD, 8.9 to 22.3%; total sample=113) (Figure 2b).

Another important parameter that is related to deglutition disorders is the reduction of the elevation of the larynx. The meta-analysis was possible for this parameter in four[20,32,33,37] studies at the baseline. The frequency was established for this parameter at 14.1% (SD, 1.5 to 36.5%; total sample=204) (Figure 2c).

Up to 6 months post-cancer treatment

All the parameters analyzed in the period of time pre-cancer treatment were also assessed from up to 6 months post-cancer treatment. In the meta-analysis of the aspiration, thirteen[16,17,19-21,29-31,32-36] of the fourteen studies included in the meta-analysis at baseline were selected and presented a frequency of 27.1% (SD, 19.0 to 36.0%; total sample=478) (figure 2a). The frequency of penetration was of 37.1% (SD, 23.2 to 52.3%; total sample=113), analyzed from six[16,18,30,31,33,34] studies (figure 2b). Finally, the parameter reduced laryngeal elevation had a frequency of 50.3% (SD, 15.3 to 85.1%; total sample=204), of a total of four[20,32,33,37] studies (figure 2c).

Over 6 months post-cancer treatment

Fewer studies were selected for the meta-analysis of the 3 parameters in the period over 6 months post-cancer treatment. Many of the included studies did not follow the patient over six months after receiving treatment for the cancer. For the analysis of aspiration, a total of seven[16,21,29-31,34,38] studies had data collected, only half as much as the baseline analysis. The frequency of aspiration was of 17.9% (SD, 12.3 to 24.8%; total sample=153) (Figure 2a). Similar to that, in the parameter penetration, only four[16,30,31,34] studies included in the meta-analysis had a prevalence of 33.2% (SD, 11.5 to 59.5%; total sample=80) (Figure 2b). And in the third parameter, the reduction of larynx elevation, the frequency was not calculated because none of the included studies had data for this parameter over six months post-cancer treatment.

Aspiration by treatment modality

In the studies that reported data concerning aspiration up to 6 months post-cancer treatment, nine[16,17,29-31,33-36] used a combination of radiation therapy and chemotherapy as treatment modality. In this group, there was a frequency of 23.8% of aspiration (SD, 14.2 to 35.0%; total sample=301). For the group that combined surgery, radiotherapy and/or chemotherapy, three[19,20,32] studies presented data of aspiration at the same period (up to 6 months post), and had a frequency of aspiration of 39.2% (SD, 22.0 to 57.9%; total sample=138). Only one[21] (16) study included had data concerning aspiration after treatment using the modality IMRT and chemotherapy. This data was of the time period up to six months post-cancer treatment and had a total of 16.3% of the sample of 55 patients with aspiration. All this data is expressed in figure 2d.

Synthesis of results

A proportion meta-analysis was conducted within the 16 included studies. The data of the analysis performed are grouped through figures 2a to 2d. The heterogeneity between the studies varied from 19.8% to 95.4%, therefore a fixed or random model was chosen

depending on the heterogeneity result[27]. The higher frequency of the deglutition complication was found in the period of up to 6 months post-cancer treatment. Aspiration was of 27.1% (SD, 19.0 to 36.0%; total sample=478); penetration the higher frequency was of 37.1% (SD, 23.2 to 52.3%; total sample=113); and 50.3% (SD, 15.3 to 85.1%; total sample=204) for reduced laryngeal elevation.

Level of evidence

The grading of recommendation, assessment, development, and evaluation system (GRADE) for evaluating quality of evidence was adapted for the analysis of observational studies and applied on three groups, according the meta-analysis performed for the deglutition parameters before and after cancer treatment. The aspiration outcomes were evaluated as moderate quality at baseline, low quality at up to 6 months post treatment, and as moderate quality of evidence at over 6 months post treatment for HNC. The outcome penetration of fluids above the vocal cords had a moderate quality of evidence at baseline and low quality at 1 to 6 months and over 6 months post cancer treatment. Reduced laryngeal elevation was the only outcome that had moderate quality of evidence in both the baseline data and the up to 6 months post treatment. GRADE table of findings is shown on Appendix 4.

DISCUSSION

Approximately 30% of patients with HNC present with early disease (stage I or II)[39]. In general, these patients are treated with either primary surgery or definitive radiation therapy (RT)[40]. Locoregionally advanced (stage III/IV) HNC is associated with a high risk of both local recurrence and distant metastases and requires combined modality approaches (surgery, RT, and/or chemotherapy) for long-term disease control[41]. Radiotherapy is a crucial part of HNC treatment, unfortunately it can cause several toxicities[42].

Toxicity from cancer therapy is classified as acute or late based upon its temporal relationship to treatment. Acute toxicity develops during or shortly after the completion of

treatment and is usually temporary. Late toxicity presents months to years after the completion of treatment and is often permanent[43]. The most common long-term complication of radiation therapy (RT) and chemoradiotherapy for HNC is xerostomia[44]. Late complications may include lymphedema, carotid artery injury, trismus, thyroid disease and dysphagia, among others[44].

The objective of this systematic review (SR) was to assess the frequency of deglutition disorders in the population of head and neck cancer patients. It was investigated deglutition disorders parameters and complications that were diagnosed through image exams for the swallowing function. The results found indicated a higher frequency of deglutition complications in the period right after cancer treatments, from its completion up to six months. It was also found a higher frequency of aspiration in the group of patients that went through surgery, radiotherapy and/or chemotherapy as treatment for the HNC.

The data found in this SR, when compared to previous performed ones[14,15] is complementary and also sheds a different perspective in the swallowing complications in HNC patients. The heterogeneity of the methodology of the studies published in the literature was a common factor found in all three SR. However, the computing of key complications of the swallowing process was possible to be analyzed in this review, showing when some swallowing complications are more frequent.

Different types of swallowing impairments can be found in patients with HNC previous and after cancer treatment. In the study by Lalla et al.[45], it was reported through quality of life questionnaire (OH-QOL), low scores towards the swallowing function, with the aspect “chocking when swallowing” being worse at six months post treatment.

Some studies in the literature discuss that swallowing disorders, as dysphagia, has a prevalence of 50.6%[12] in the HNC population. Rinkel et al.[46], with a sample of 50 patients, of them 30 with oropharyngeal cancer, 79.0% presented swallowing problems after receiving

chemoradiation. In the USA, a population-based study found that over 9 million north Americans reported swallowing problems, and that the third most common cause was HNC, with 4.9%, in 2012[47].

A long term follow up of HNC patients after cancer treatment referred late dysphagia for a median of nine years, with tube feeding present in 21.0% of the cases[48]. In a study of over five years follow up of HNC survivors, 53.5% of patients treated with non-IMRT modality and 22.0% in the IMRT treated group referred dysphagia[49].

The findings in this systematic review points out that there is a higher prevalence of the complication aspiration in the population that underwent surgery for the cancer and had radiation and/or chemotherapy combined. In the study of Lindblom et al.[50], 47% of the 108 patients analyzed through videoflouroscopic exam, aspirated. Of these patients, six had pneumonia. For Mortensen et al.[51], 18 out of 324 of the patients analyzed developed aspiration pneumonia, more than half of that, 11 patients had been also diagnosed with dysphagia.

LIMITATIONS

This systematic review had some limitations. The data collected for the parameters analyzed were not from the same exact amount of studies or the exact period of time after cancer treatment. This is even more evidenced when concerning the lack data for the parameter reduced laryngeal elevation for the period over six months post cancer treatments. Additionally, the parameter aspiration analyzed by different treatment modalities was performed with different number of studies. For the modality IMRT there was only data from one study, which makes the comparison more tenues.

CONCLUSIONS

The frequency of parameters or complications associated to deglutition disorders was higher in the period immediate after cancer treatments (up to 6 months post-cancer treatment).

One of the most serious complications of deglutition disorders, the aspiration, had a frequency of 27.1% in that period. The most frequent parameter was reduced laryngeal elevation, with 50.3%, in the same period of time as the aspiration one. However, for this parameter the sample was smaller when compared to baseline and no study evaluated this elevation reduction in the period over six months post-cancer treatment. This evidence presented in the literature highlights the need for more longitudinal studies, which follow the patient for periods longer than 12 months, with assessment of deglutition parameters through image exams, and comparing these parameters through the different modalities of cancer treatment.

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FIGURES LEGENDS

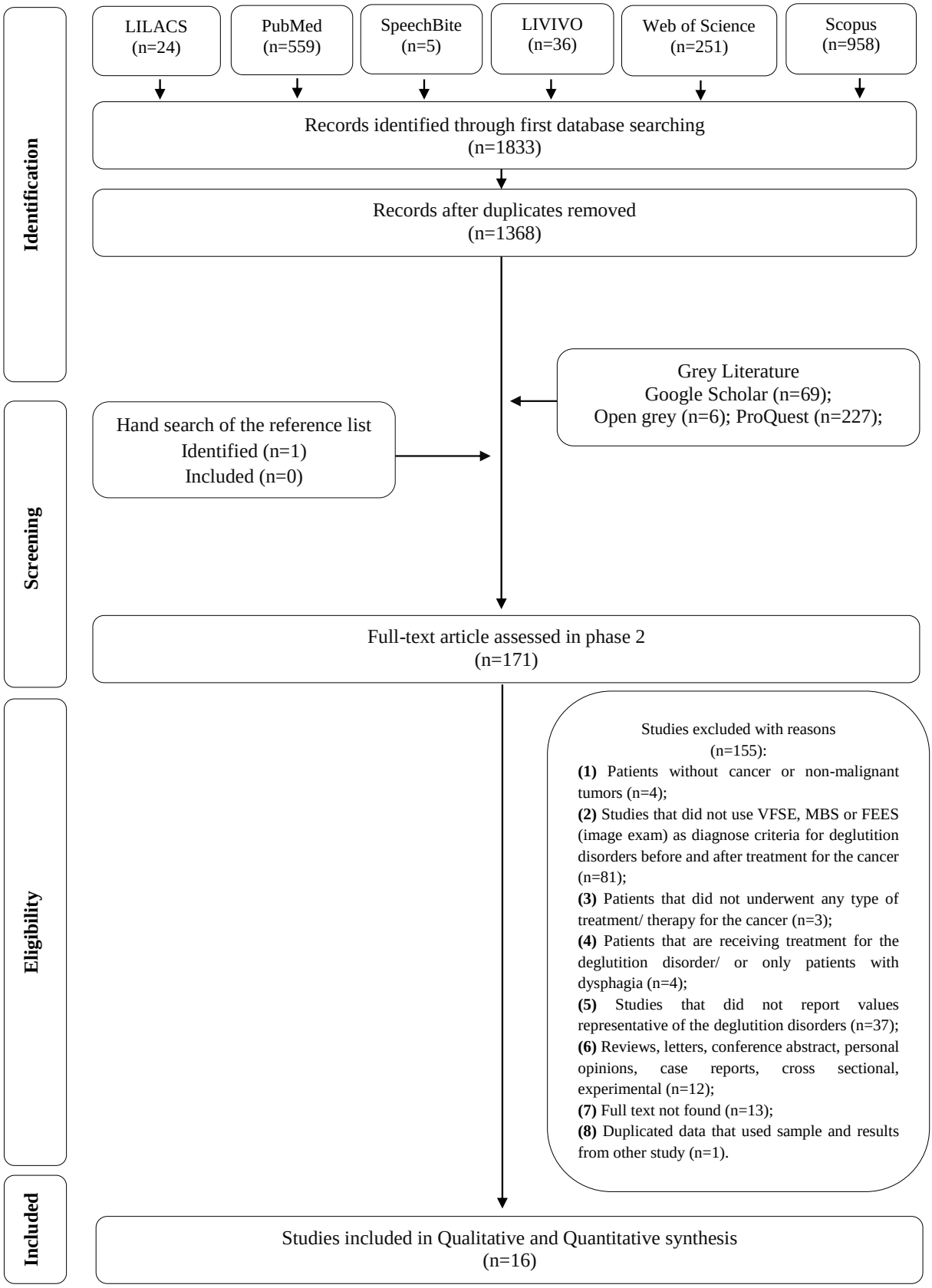
Figure 1. Flow diagram of literature search and selection criteria adapted from PRISMA[22].

Figure 2a. Meta-analysis graphs and data for aspiration in three different periods.

Figure 2b. Meta-analysis graphs and data for penetration in three different periods.

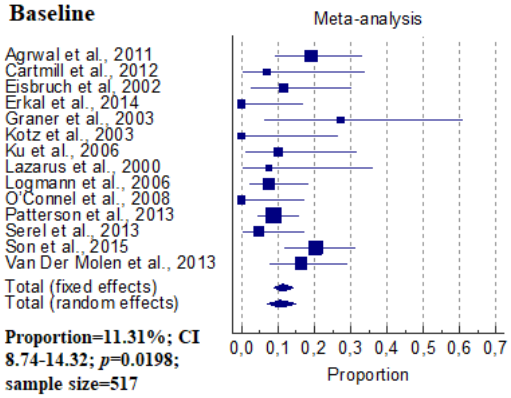
Figure 2c. Meta-analysis graphs and data for reduced laryngeal elevation in two different periods.

Figure 2d. Meta-analysis graphs and data for aspiration by type of cancer treatments.


Identification
Screening
Eligibility
Included
LILACS (n=24)
PubMed (n=559)
SpeechBite (n=5)
LIVIVO (n=36)
Web of Science (n=251)
Scopus (n=958)
Records identified through first database searching (n=1833)
Records after duplicates removed (n=1368)
Grey Literature
Google Scholar (n=69);
Open grey (n=6); ProQuest (n=227);
Hand search of the reference list
Identified (n=1)
Included (n=0)
Full-text article assessed in phase 2 (n=171)
Studies excluded with reasons (n=155):
(1) Patients without cancer or non-malignant tumors (n=4);
(2) Studies that did not use VFSE, MBS or FEES (image exam) as diagnose criteria for deglutition disorders before and after treatment for the cancer (n=81);
(3) Patients that did not underwent any type of treatment/ therapy for the cancer (n=3);
(4) Patients that are receiving treatment for the deglutition disorder/ or only patients with dysphagia (n=4);
(5) Studies that did not report values representative of the deglutition disorders (n=37);
(6) Reviews, letters, conference abstract, personal opinions, case reports, cross sectional, experimental (n=12);
(7) Full text not found (n=13);
(8) Duplicated data that used sample and results from other study (n=1).
Studies included in Qualitative and Quantitative synthesis (n=16)

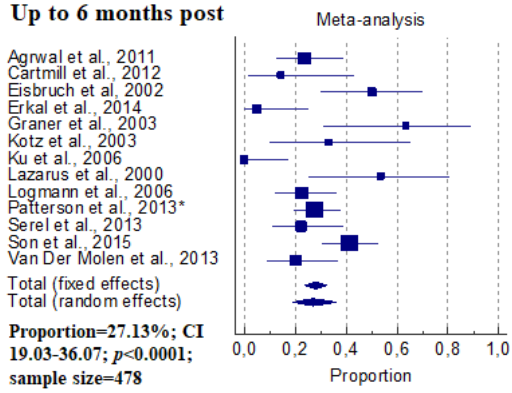
ASPIRATION

Baseline



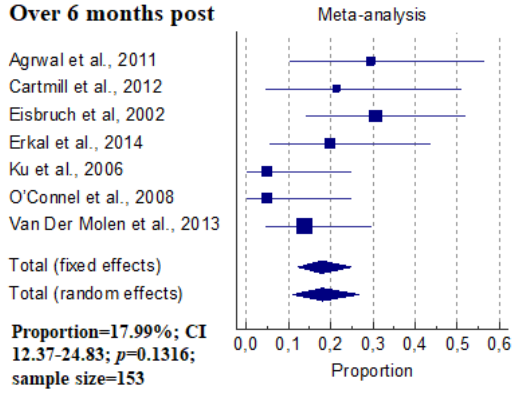
Proportion=11.31%; CI 8.74-14.32; *p*=0.0198; sample size=517 Inconsistency=49.01%

Up to 6 months post



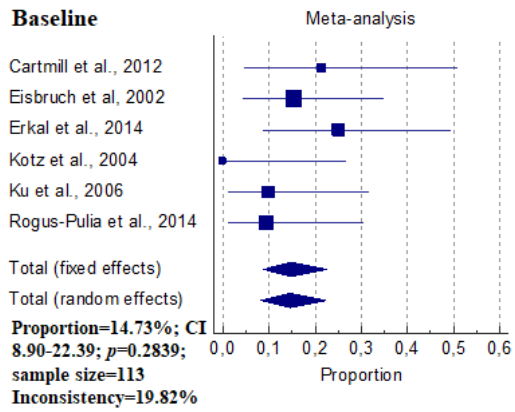
Proportion=27.13%; CI 19.03-36.07; *p*<0.0001; sample size=478 Inconsistency=76.22%

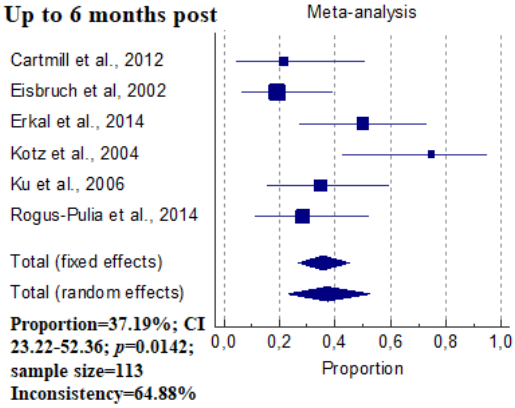
Over 6 months post

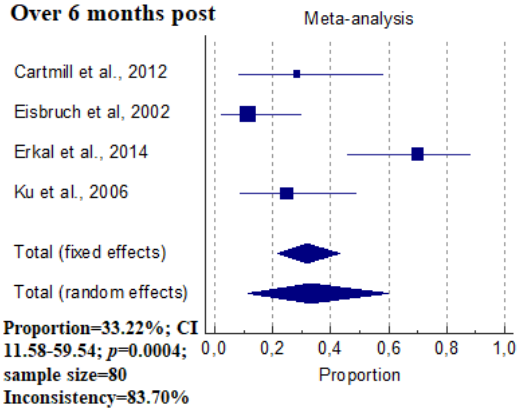


Proportion=17.99%; CI 12.37-24.83; *p*=0.1316; sample size=153 Inconsistency=39.02%

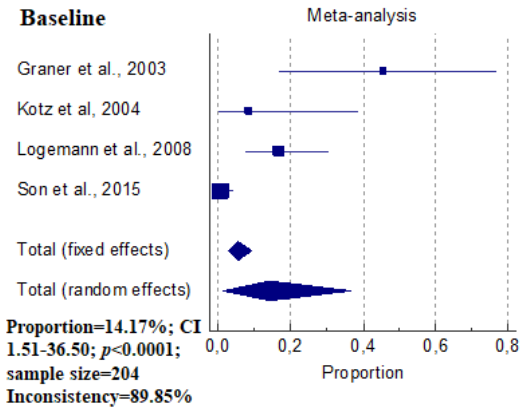
PENETRATION



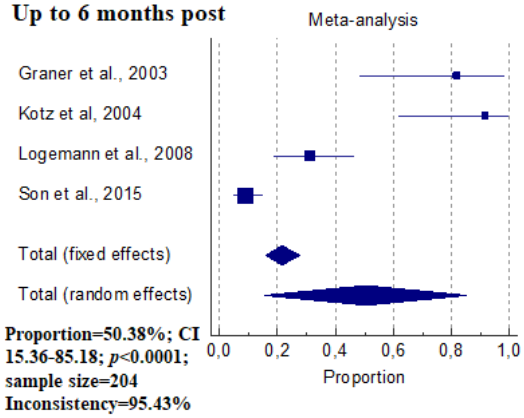




REDUCED LARYNGEAL ELEVATION



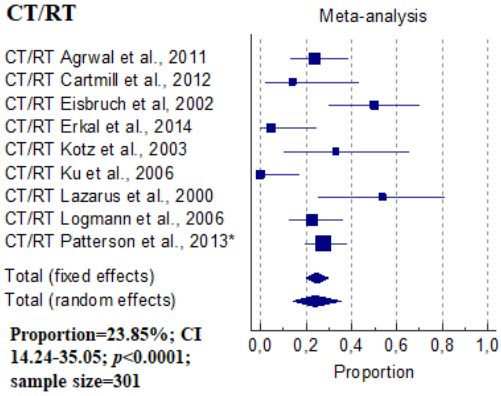
Proportion=14.17%; CI 1.51-36.50; p<0.0001; sample size=204 Inconsistency=89.85%



Proportion=50.38%; CI 15.36-85.18; p<0.0001; sample size=204 Inconsistency=95.43%

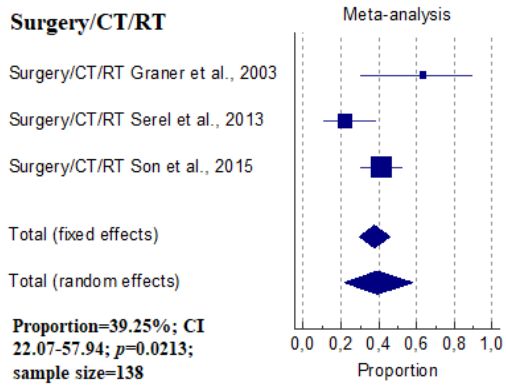
ASPIRATION BY TYPE OF TREATMENT

CT/RT



Proportion=23.85%; CI 14.24-35.05; p<0.0001; sample size=301 Inconsistency=76.52%

Surgery/CT/RT



Proportion=39.25%; CI 22.07-57.94; p=0.0213; sample size=138 Inconsistency=74.03%

Table 1. Summary of study descriptive characteristics of included studies (n=16).

Author, year, country	Type of study	Sample size (M:F)	Mean age or age range (years)	Type of cancer (n)	Tumor stages (n)	Type of cancer treatment (n)	Deglutition assessment (period)	Occurrence of deglutition disorders (n)		
								Pretreatment	< 6 months of treatment	>6 months of treatment
Agarwal et al., 2011, India	Cohort	47 (40:7)	40-65	Oropharynx (25*) Hypopharynx (16*)	I/II (11) III/IV (36)	-Conventional RT 66-70 Gy/33-35 fractions (40) -Conformal RT (7) -Concurrent CT cisplatin (40)	MBS (before and up to 12 months posttreatment)	-Aspiration=9 of 47 -PAS=0	2 months post: -Aspiration=11 of 46 -PAS=13 of 34 -6 months after: -Aspiration=11 of 38 -PAS=9 of 30	12 months post: -Aspiration= 5 of 17 -PAS=10 of 14
Cartmill et al., 2012, Australia	Cohort	14 (12:2)	53-82	Tonsil (9) Supraglottis (3)	I (2*) II (4*) III (5*) IV (3*)	-AFRT-CB 66 Gy/35 fractions (14)	VFSS (before and up to 6 months posttreatment)	-Aspiration on fluids/solids = 0/1 -Penetration on fluids/solids = 1/ 3 -PAS=5 events	4-6 weeks post = -Aspiration on fluids/solids = 1/1 -Penetration on fluids/solids = 3/ 3 -PAS=8 events	6 months post = -Aspiration on fluids/solids = 1/2 -Penetration on fluids/solids = 1/ 4 -PAS=8 events
Eisbruch et al., 2002, USA	Cohort	26 (NA)	NA	Oropharynx (14) Nasopharynx (4) Oral cavity (2) Larynx (2) Hypopharyngeal (1) Thyroid (1) Paranasal sinus (1) External ear (1)	III/IV (26)	-Conventional RT 70 Gy/35 fractions for Primary tumor; 50-54 Gy or 58-64 Gy for metastasis or previous to surgery (26) -Concurrent QT gemcitabine (26)	VFSS (before and up to 12 months posttreatment)	-Base of tongue weakness=9 -Pharyngeal residue=5 -Reduced larynx/hyoid elevation=4 -Reduced epiglottic inversion=3 -Swallow reflex delay=8 -	1-3 months post: -Base of tongue weakness=11 -Pharyngeal residue=15 -Reduced larynx/hyoid elevation=7 -Reduced epiglottic inversion=10 -Swallow reflex	6-12 months post: -Base of tongue weakness=11 -Pharyngeal residue=10 -Reduced larynx/hyoid elevation=6 -Reduced epiglottic inversion=7 -Swallow reflex

								Velopharyngeal incompetence=1 -Cricopharyngeal m. dysfunction=0 -Upper esophageal stricture=2 -Penetration=4 -Aspiration=1 -Silent aspiration=2	delay=6 -Velopharyngeal incompetence=5 -Cricopharyngeal m. dysfunction=1 -Upper esophageal stricture=7 -Penetration=5 -Aspiration=10 -Silent aspiration=3	delay=8 -Velopharyngeal incompetence=2 -Cricopharyngeal m. dysfunction=1 -Upper esophageal stricture=6 -Penetration =3 -Aspiration =5 -Silent aspiration=3
Erkal et al., 2014, Turkey	Cohort	20 (17:3)	30-76	Nasopharynx (10) Supraglottic larynx (10)	NA	-3DCRT 70 Gy for the primary tumor; 66-70 Gy involved cervical lymph nodes; 50-60 Gy uninvolved cervical lymph nodes; 46-50Gy supraclavicular lymph nodes/ daily fractions 2 Gy (8) -3DCRT with Concomitant CT (12)	VFSS (before and up to 6 months posttreatment)	-Impaired lingual movement=1 -Base of tongue weakness=10 -Pharyngeal residue=7 -Reduced laryngeal elevation=2 -Reduced epiglottic inversion=0 -Swallow reflex delay=0 -Cricopharyngeal muscle dysfunction=0 -Proximal esophageal stricture=3	At 3 months post: -Impaired lingual movement=4 -Base of tongue weakness=15 -Pharyngeal residue=11 -Reduced laryngeal elevation=2 -Reduced epiglottic inversion=6 -Swallow reflex delay=1 -Cricopharyngeal muscle dysfunction=2 -Proximal	At 6 months post: -Impaired lingual movement=2 -Base of tongue weakness=12 -Pharyngeal residue=10 -Reduced laryngeal elevation=3 -Reduced epiglottic inversion=5 -Swallow reflex delay=1 -Cricopharyngeal muscle dysfunction=2 -Proximal esophageal

								-Penetration=5 -Aspiration=0	esophageal stricture=5 -Penetration=10 -Aspiration=1	stricture=6 -Penetration =14 -Aspiration =4
Graner et al., 2003, USA	Cohort	11 (7:4)	37-78	Oropharynx (5) Larynx (3) Hypopharynx (3)	III-IV (11)	-CT 150 mg/m^2 of cisplatin for 4 weeks (11) -Concomitant RT 72 Gy, 6 weeks for primary tumor (11) -Surgery (select, modified or radical neck dissection= 7)	VFSS (before and up to 5 months posttreatment)	-Oral residue=0 -Nasal regurgitation=0 -Diffuse falling over tongue base=1 -Delayed pharyngeal response=3 -Reduced tongue base retraction=5 -Reduced Laryngeal elevation=5 -Laryngeal vestibule, thin liquid=6 -Laryngeal vestibule, thick liquid=6 -Laryngeal vestibule, pureed=1 -Aspiration=3 -Valleculae residue, thin liquid=3 -Valleculae residue, thick liquid=6 -Valleculae residue, pureed=3 -Pyriform sinus	At 5 months post: -Oral residue=1 -Nasal regurgitation=1 -Diffuse falling over tongue base=0 -Delayed pharyngeal response=4 -Reduced tongue base retraction=9 -Reduced Laryngeal elevation=9 -Laryngeal vestibule, thin liquid=9 -Laryngeal vestibule, thick liquid=9 -Laryngeal vestibule, pureed=5 -Aspiration=7 -Valleculae residue, thin liquid=7 -Valleculae residue, thick liquid=10 -Valleculae residue,	NA

								residue, thin liquid=1 -Pyriform sinus residue, thick liquid=3 -Pyriform sinus residue, pureed=3 -Tight cricopharyngeal segment=2 Backflow to pharynx=1	pureed=7 -Pyriform sinus residue, thin liquid=8 -Pyriform sinus residue, thick liquid=8 -Pyriform sinus residue, pureed=4 -Tight cricopharyngeal segment=4 Backflow to pharynx=1	
Kotz et al., 2004, USA	Cohort	12 (9:3)	31-72	Oropharynx (7) Larynx (3) Oral cavity (1) Unknow (1)	III-IV (12)	-Induction CT 2-3 cycles -CT Docetaxel during 4 weeks of RT and 3 weeks of Hyperfractionated RT (5) -CT Carboplatin 6-7 weeks and once-a-day RT (7)	VFSS (before and 1-4 weeks posttreatment)	-Reduced tongue base to posterior pharyngeal wall=1* -Reduced laryngeal elevation=1* -Reduced laryngeal vestibule closure=1* -Reduced upper esophageal sphincter opening=0	-Reduced tongue base to posterior pharyngeal wall=12* -Reduced laryngeal elevation=10* 3ml/ 11* 5ml -Reduced laryngeal vestibule closure=9* 3ml/ 8* 5ml -Reduced upper esophageal sphincter opening=2* -Laryngeal aspiration=4 -Penetration=9	NA
Ku et al., 2007, China	Cohort	20 (14:6)	33-62	Nasopharyngeal carcinoma (20)	I-II (9) III-IV (11)	-RT 66 Gy (20) -RT boost of 20 Gy for	VFSS (before and up to 12 months	-Impaired lingual control=0	At 6 months post: -Impaired	At 12 months post: -Impaired

						pharyngeal extension (17) -Concurrent CT cisplatin (11)	posttreatment)	-Impaired oral transfer food=0 -Stasis in Vallecula=0 -Stasis in pyriform fossa=0 -Impaired pharyngeal peristalsis=3* -Impaired tongue propulsion=1* -Penetration=2* -Aspiration=2*	lingual control=8* -Impaired oral transfer food=9* -Stasis in Vallecula=17* -Stasis in pyriform fossa=12* -Impaired pharyngeal peristalsis=12* -Impaired tongue propulsion=3* -Penetration=7* -Aspiration=0	lingual control=8* -Impaired oral transfer food=8* -Stasis in Vallecula=20* -Stasis in pyriform fossa=12* -Impaired pharyngeal peristalsis=12* -Impaired tongue propulsion=6* -Penetration=5* -Aspiration =1*
Lazarus et al., 2000, USA	Cohort	13 (10:3)	38-72	Tongue base (6) Floor of the mouth (3) Tonsil (4)	I (1) IV (12)	-RT high dose ≥7000 cGy (13) -Concomitant CT cisplatin (12)	VFG (before and up to 2 months posttreatment)	-Aspiration=1	At 2 months post: -Aspiration=7	NA
Logemann et al., 2006, USA	Cohort	53 (41:12)	NA	Oropharynx (22) Larynx (14) Hypopharynx (4) Nasopharynx (3) Unknown (10)	T1 (2) T2 (11) T3 (16) T4 (19) IV (42-53*)	-TFHX, Taxol infusion (13) -TFHX, Taxol bolus (16) -TFHX, bolus, induction (15) -RADPLAT (9) -RT dose range 6700-7275 cGy (53)	VFSS (before and up to 3 months posttreatment)	-Reduced Tongue base retraction=26* -Reduced tongue strength=20* -Delayed laryngeal vestibule closure=10* -Reduced tongue control=9* -Delayed	At 3 months post: -Reduced Tongue base retraction=47* -Reduced tongue strength=27* -Delayed laryngeal vestibule closure=16* -Reduced lateral/anterior	NA

								pharyngeal swallow=8* -Reduced laryngeal elevation=7* -Reduced propulsion of bolus=6* -Reduced tongue stabilization=3* -Bilateral pharyngeal weakness=3* -Reduced vertical tongue movement=2* -Reduced cricopharyngeal opening=1* -Visible cricopharyngeal bar=1* -Unilateral pharyngeal weakness=1* -Gastrostomy or jejunostomy=8 -Aspiration=4	tongue Stabilization=2* -Incomplete laryngeal vestibule Closure=2* -Reduced velopharyngeal closure=2* -Reduced vertical tongue movement=1* -Reduced glottic closure=0* -Gastrostomy or jejunostomy=21 -Aspiration=12	
Logemann et al., 2008, USA	Cohort	48 (38:10)	38-76	Oropharynx (21) Laryngeal (21) Nasopharynx (3) Hypopharynx (3)	I (1) II (7) III-IV (40)	-CT (36) -Concurrent RT dose range from 6500 to 7920 cGy (36) -Induction CT (6) -RT dose range from 6500 to 7920 cGy (12)	VFSS (before and up to 12 months posttreatment)	-Reduced tongue base retraction=32* -Reduced tongue strength=24* -Delay in triggering the pharyngeal swallow=19*	At 3 months post: -Reduced tongue base retraction=43* -Reduced tongue strength=29* -Delay in triggering the	At 12 months post: -Reduced tongue base retraction= 41* -Reduced tongue strength= 27* -Delay in triggering the

								-Slowed/delayed vestibule closure=13* -Reduced tongue control=16* -Reduced Anterior-Posterior tongue movement=12* -Reduced laryngeal elevation=8* -Reduced tongue stabilization=7* -Bilateral pharyngeal weakness=4* -Reduced cricopharyngeal opening=4* -Visible cricopharyngeal bar=5* -Incomplete laryngeal vestibule closure=3	pharyngeal swallow=27* -Slowed/delayed vestibule closure=29* -Reduced tongue control=22* -Reduced Anterior-Posterior tongue movement=22* -Reduced laryngeal elevation=15* -Reduced tongue stabilization=6* -Bilateral pharyngeal weakness=11* -Reduced cricopharyngeal opening=11* -Visible cricopharyngeal bar=6* -Incomplete laryngeal vestibule closure=6*	pharyngeal swallow= 20* -Slowed/ delayed vestibule closure=26* -Reduced tongue control=18* -Reduced Anterior-Posterior tongue movement=27* -Reduced laryngeal elevation= 17* -Reduced tongue stabilization=7* -Bilateral pharyngeal weakness= 10* -Reduced cricopharyngeal opening= 10* -Visible cricopharyngeal bar=7* -Incomplete laryngeal vestibule closure=6*
O'Connell et al., 2008, Canada	Cohort	20 (14:6)	44-70	Base of tongue (20)	II (2) III (8) IV (10)	-Primary Surgery and reconstruction with beavertail modification of the radial forearm	VFSS (before and at 12 months posttreatment)	-Mild pharyngeal residue During=17 -Moderate pharyngeal	NA	At 12 months post: -Mild pharyngeal residue During=6

						free flap (20) -Postoperative RT (20) -Primary CT and RT (5)		residue=3 -Aspiration=0		-Moderate pharyngeal residue=6 -Severe pharyngeal residue=8 -Aspiration= 1
Patterson et al., 2014, United Kingdom	Cohort	112 (90:22)	42-77	Oropharynx (59) Hypopharynx (22) Larynx (16) Nasopharynx (5) Unknown (10)	NA	-RT 3D conformal, dose 63Gy in 30 fractions over 6 weeks (112) -Combined CT Cisplatin 40mg/m^2 in 6 cycles or Mitomycin C 15mg/m^2 in 2 cycles (112)	FEES (before and at 3 months posttreatment)	-Aspiration=10 of 112 patients	At 3 months post: -Aspiration=27* of 97 patients -Silent aspiration=8* of 97 patients	NA
Rogus-Pulia et al., 2014, USA	Cohort	21 (17:4)	36-80	Base of tongue (8) Tonsil (6) Nasopharynx (3) Hypopharynx (1) Tongue (1) Vocal Fold (1) Unknown (1)	T0 (2) T1 (6) T2 (9) T4 (4) I-IV (21)	-RT dose of 66 to 70 Gy over a mean of 7 weeks (21) -Concurrent CT (21) -Induction CT (6) -Tonsillectomy (4) -Neck dissection (3) -Partial Glossectomy (1) -Tumor debulking (1)	MBS (before and mean of 5 months posttreatment)	-Penetration during swallow=2	Mean of 5 months post: -Penetration during swallow=6	NA
Serel et al., 2013, Turkey	Cohort	40 (33:7)	20-65	Larynx (20) Nasopharynx (5) Tongue (5) Tonsil (3) Retromolar trigone	I (5) II (1) IIA (2) IIB (1) III (20)	-RT dose from 5400 cGy to 7000 cGy (40) -Concomitant CT (33)	VFSS (before and up to 3 months posttreatment)	-Aspiration with liquid=2 -Aspiration with pudding=0 -Aspiration	At 1 month post: -Aspiration with liquid=8 -Aspiration	NA

				(2) Parotid (2) Lips (1) Tongue base (1) Hypopharynx (1)	IVA (11)	-Surgery for the primary tumor (2) -Surgery for the primary tumor and neck dissection (24)		with biscuit=0	with pudding=7 -Aspiration with biscuit=7 At 3 months post: -Aspiration with liquid=9 -Aspiration with pudding=7 -Aspiration with biscuit=7	
Son et al., 2015, Korea	Cohort	133 (85:48)	53.5±15	Tongue (133)	T1 (38) T2 (40) T3 (3) T4 (52)	-Hemiglossectomy (16) -Wide resection (82) -Partial glossectomy (23) -Total glossectomy (5) -Supraomohyoid neck dissection (61) -Modified radical neck dissection (59) -Reconstruction surgery (81) -RT (70) -CT (57)	VFSS (was administered to 87 patients after surgery and to 74 patients prior to surgery - before and mean of 4 months posttreatment)	-Inadequate lip movement=0 -Inadequate tongue control=18 -Inadequate chewing=5 -Delayed oral transit time=3 -Aspiration or penetration=8 -Fluid aspiration=15 -Solid aspiration=5 -Nasal regurgitation=0 -Vallecular pouch residue=6 -Pyriform sinus residue=3 -Inadequate laryngeal elevation=1	At mean of 4 months post: -Inadequate lip movement=3 -Inadequate tongue control=64 -Inadequate chewing=25 -Delayed oral transit time=28 -Aspiration or penetration=26 -Fluid aspiration=36 -Solid aspiration=15 -Nasal regurgitation=4 -Vallecular pouch residue=39 -Pyriform sinus residue=16 -Inadequate laryngeal elevation=12	NA
Van der	Cohort	55	32-79	Oral	III (17)	CT-IMRT	VFSS (before	-Aspiration	At 10 weeks	At 12 months

Molen et al., 2013, The Netherlands	t	(44:11)	cavity/Oropharynx (29) Laryngo/hypopharynx (19) Nasopharynx (7)	IV (38)	Cisplatin 100mg/m^2 (40 minutes for 3 non-consecutive days); 70 Gy in 35 daily fractions of 2Gy – total of 7000 cGy over 7 weeks plus sequential boost of IMRT (55).	– 55 patients/ at 10 weeks- 48 patients/ at 12 months-36 patients)	and/or penetration=9 of 55	post: -Aspiration and/or penetration=8 of 39	post: -Aspiration and/or penetration=5 of 36

Legend: MBS = modified barium swallow; M = male; F = female; RT = radiotherapy; CT = chemotherapy; CRT = chemoradiation; AFRT-CB = altered fractionation radiotherapy with concomitant boost; IMRT = intensity-modulated radiotherapy; VFSS = videofluroscopy; VFG = Videofluorographic; FEES=Fiber-optic endoscopic evaluation of swallowing; PAS= penetration-aspiration scale (only values with grade 3 or over); Events = number of events of penetration/aspiration; RADPLAT= intraarterial cisplatin radiation; TFHX, Taxol infusion= hydroxyurea, 5-fluorouracil, and paclitaxel infusion for 1 week; TFHX, Taxol bolus= hydroxyurea, 5-fluorouracil, and paclitaxel 1-hour bolus; TFHX, bolus, induction= induction chemotherapy with carboplatin and paclitaxel followed by concurrent chemoradiation with hydroxyurea, 5-fluorouracil, and paclitaxel 1-hour bolus; NA = Not Available.
*Values calculated by the author

Appendix 1. Search strategy and date that was performed in the chosen Databases.

Database	Search (March 23, 2017)
LILACS	(tw:(Cancer OR câncer OR neoplasia OR Neoplasm OR tumor)) AND (tw:(Disfagia OR dysphagia OR "alteração de deglutição" OR "swallowing disorders" OR "disfunción de deglución")) AND (tw:(Quimioterapia OR chemotherapy OR radioterapia OR radiotherapy OR quimioradioterapia OR chemoradiotherapy OR quimiorradioterapia))
PubMed	#1: "Neoplasms"[Mesh] OR cancer OR cancers OR neoplasm OR "neoplasms" OR tumor OR tumors OR tumour OR tumours OR neoplasia OR "malignant neoplasm" OR "malignant tumour" OR "malignant tumor" OR "malignant tumors" OR "malignant tumours" OR carcinoma OR carcinomas #2: "Deglutition Disorders"[Mesh] OR "Respiratory Aspiration"[Mesh] OR aspiration OR "food aspiration" OR "liquid aspiration" OR "Aspiration Pneumonia" OR "Aspiration Pneumonias" OR dysphagia OR "swallowing disorders" OR "swallowing problems" OR "swallowing difficulties" OR "swallowing impairment" OR "deglutition disorder" OR "deglutition disorders" OR "swallowing disorder" OR "oropharyngeal dysphagia" OR "esophageal dysphagia" OR "mechanical dysphagia" #3: "clinical examination" OR "clinical exam" OR "clinical assessment" OR "swallowing exam" OR "swallowing assessment" OR "video fluoroscopic" OR "VFSE" OR "VFSS" OR "VSF" OR "videofluoroscopy" #4: "Radiotherapy"[Mesh] OR "Chemoradiotherapy"[Mesh] OR surgery OR chemotherapy OR chemotherapies OR "radiotherapy" OR radiotherapies OR "radiation therapy" OR "radiation therapies" OR "targeted radiotherapy" OR "targeted radiotherapies" OR "targeted radiation therapy" OR "targeted radiation therapies" OR chemoradiotherapy OR chemoradiotherapies OR "radiochemotherapy" OR "radiochemotherapies" OR "combination therapy" OR "tumor removal" OR "cancer therapy" OR "cancer treatment" OR "tumor resection" OR "tumour resection" OR "tumour removal" #5: #1 AND #2 AND #3 AND #4
Scopus	*TITLE-ABS-KEY (cancer OR cancers OR neoplasm OR "neoplasms" OR tumor OR tumors OR tumour OR tumours OR neoplasia OR "malignant neoplasm" OR "malignant tumour" OR "malignant tumor" OR "malignant tumors" OR "malignant tumours" OR carcinoma OR carcinomas) AND TITLE-ABS-KEY ("Respiratory aspiration" OR aspiration OR "food aspiration" OR "liquid aspiration" OR "Aspiration Pneumonia" OR "Aspiration Pneumonias" OR dysphagia OR "swallowing disorders" OR "swallowing problems" OR "swallowing difficulties" OR "swallowing*

	impairment" OR "deglutition disorder" OR "deglutition disorders" OR "swallowing disorder" OR "oropharyngeal dysphagia" OR "esophageal dysphagia" OR "mechanical dysphagia") AND TITLE-ABS-KEY ("clinical examination" OR "clinical exam" OR "clinical assessment" OR "swallowing exam" OR "swallowing assessment" OR "video fluoroscopic" OR "VFSE" OR "VFSS" OR "VSF" OR "videofluoroscopy") AN D TITLE-ABS-KEY (surgery OR chemotherapy OR chemotherapies OR "radiotherapy" OR r adiotherapies OR "radiation therapy" OR "radiation therapies" OR "targeted radiotherapy" OR "targeted radiotherapies" OR "targeted radiation therapy" OR "targeted radiation therapies" OR chemoradiotherapy OR chemoradiotherapies OR "radiochemoth erapy" OR "radiochemotherapies" OR "combination therapy" OR "tumor removal" OR "cancer therapy" OR "cancer treatment" OR "tumor resection" OR "tumour resection" OR "tumour removal") AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "sh") OR LIMIT-TO (DOCTYPE , "ip"))
Web of Science	#1: TS=(cancer OR cancers OR neoplasm OR "neoplasms" OR tumor OR tumors OR tumour OR tumours OR neoplasia OR "malignant neoplasm" OR "malignant tumour" OR "malignant tumor" OR "malignant tumors" OR "malignant tumours" OR carcinoma OR carcinomas) #2: TS=("Respiratory aspiration" OR aspiration OR "food aspiration" OR "liquid aspiration" OR "Aspiration Pneumonia" OR "Aspiration Pneumonias" OR dysphagia OR "swallowing disorders" OR "swallowing problems" OR "swallowing difficulties" OR "swallowing impairment" OR "deglutition disorder" OR "deglutition disorders" OR "swallowing disorder" OR "oropharyngeal dysphagia" OR "esophageal dysphagia" OR "mechanical dysphagia") #3: TS=("clinical examination" OR "clinical exam" OR "clinical assessment" OR "swallowing exam" OR "swallowing assessment" OR "video fluoroscopic" OR "VFSE" OR "VFSS" OR "VSF" OR "videofluoroscopy") #4: TS=(surgery OR chemotherapy OR chemotherapies OR "radiotherapy" OR radiotherapies OR "radiation therapy" OR "radiation therapies" OR "targeted radiotherapy" OR "targeted radiotherapies" OR "targeted radiation therapy" OR "targeted radiation therapies" OR chemoradiotherapy OR chemoradiotherapies OR "radiochemotherapy" OR "radiochemotherapies" OR "combination therapy" OR "tumor removal" OR "cancer therapy" OR "cancer treatment" OR "tumor resection" OR "tumour resection" OR "tumour removal") #5: #1 AND #2 AND #3 AND #4
LIVIVO	TI=((cancer OR cancers OR neoplasm OR "neoplasms" OR tumor OR tumors OR tumour OR tumours OR neoplasia OR "malignant neoplasm" OR "malignant tumour" OR "malignant tumor" OR "malignant tumors" OR "malignant tumours" OR carcinoma OR carcinomas)) AND TI=(("Respiratory aspiration" OR aspiration OR "food aspiration" OR "liquid aspiration" OR "Aspiration Pneumonia" OR "Aspiration Pneumonias" OR dysphagia OR "swallowing disorders" OR

	"swallowing problems" OR "swallowing difficulties" OR "swallowing impairment" OR "deglutition disorder" OR "deglutition disorders" OR "swallowing disorder" OR "oropharyngeal dysphagia" OR "esophageal dysphagia" OR "mechanical dysphagia")) AND TI=(("clinical examination" OR "clinical exam" OR "clinical assessment" OR "swallowing exam" OR "swallowing assessment" OR "video fluoroscopic" OR "VFSE" OR "VFSS" OR "VSF" OR "videofluoroscopy")) AND TI=((surgery OR chemotherapy OR chemotherapies OR "radiotherapy" OR radiotherapies OR "radiation therapy" OR "radiation therapies" OR "targeted radiotherapy" OR "targeted radiotherapies" OR "targeted radiation therapy" OR "targeted radiation therapies" OR chemoradiotherapy OR chemoradiotherapies OR "radiochemotherapy" OR "radiochemotherapies" OR "combination therapy" OR "tumor removal" OR "cancer therapy" OR "cancer treatment" OR "tumor resection" OR "tumour resection" OR "tumour removal"))
Speech BITE	Keyword(s): *cancer AND dysphagia* Practice Area: *Dysphagia* Within population: *Cancer* Research Design: *Non Randomised Controlled Trial*
Google Scholar	Search 1: tudonotítulo: cancer swallowing radiotherapy chemotherapy Search 2: tudonotítulo: cancer swallowing radiotherapy Search 3: tudonotítulo: cancer swallowing chemotherapy
Opengrey	Cancer AND Swallowing
ProQuest	TI,AB(cancer OR cancers OR neoplasm OR "neoplasms" OR tumor OR tumors OR tumour OR tumours OR neoplasia OR "malignant neoplasm" OR "malignant tumour" OR "malignant tumor" OR "malignant tumors" OR "malignant tumours" OR carcinoma OR carcinomas) AND TI,AB("Respiratory aspiration" OR aspiration OR "food aspiration" OR "liquid aspiration" OR "Aspiration Pneumonia" OR "Aspiration Pneumonias" OR dysphagia OR "swallowing disorders" OR "swallowing problems" OR "swallowing difficulties" OR "swallowing impairment" OR "deglutition disorder" OR "deglutition disorders" OR "swallowing disorder" OR "oropharyngeal dysphagia" OR "esophageal dysphagia" OR "mechanical dysphagia") AND TI,AB(("clinical examination" OR "clinical exam" OR "clinical assessment" OR "swallowing exam" OR "swallowing assessment" OR "video fluoroscopic" OR "VFSE" OR "VFSS" OR "VSF" OR "videofluoroscopy") AND TI,AB(surgery OR chemotherapy OR chemotherapies OR "radiotherapy" OR radiotherapies OR "radiation therapy" OR "radiation therapies" OR "targeted radiotherapy" OR "targeted radiotherapies" OR "targeted radiation therapy" OR "targeted radiation therapies" OR chemoradiotherapy OR chemoradiotherapies OR "radiochemotherapy" OR "radiochemotherapies" OR "combination therapy" OR "tumor removal" OR "cancer therapy" OR "cancer treatment" OR "tumor resection" OR "tumour resection" OR "tumour removal")

Appendix 2. Excluded articles and reasons for exclusion (n=155).

Author, year	Reason for exclusion
Al-Othman et al., 2003(1)	2
Andrade et al., 2017(2)	2
Angelis et al., 2003(3)	2
Aplak et al., 2007(4)	2
Archontaki et al., 2010(5)	2
Arrese et al., 2017(6)	5
Atkins et al., 2006(7)	1
Barringer et al., 2009(8)	5
Barros et al., 2007(9)	7
Batth et al., 2014(10)	6
Bergquist et al., 2007(11)	2
Bodin et al., 2004(12)	5
Borggreven et al., 2007(13)	2
Brookes et al., 2006(14)	5
Bruijn et al., 2013(15)	6
Bumber et al., 1990(16)	5
Caglar et al., 2007(17)	7
Caliceti et al., 2004(18)	5
Campbell et al., 2004(19)	2
Carnaby et al., 2014(20)	2
Cartmill et al., 2011(21)	7
Celedon et al., 2008(22)	2
Chan et al., 2009(23)	7
Chang et al., 2003(24)	2
Chone et al., 2011(25)	5
Christianen et al., 2016(26)	5
Cintra et al., 2005(27)	2
Coia et al., 1993(28)	2
Collan et al., 2011(29)	5
Crombie et al., 2015(30)	5
Dale et al., 2016(31)	2
Del Bon et al., 2012(32)	6
Deng et al., 2009(33)	2
Deng et al., 2016(34)	6
Dracini et al., 2013(35)	2
Eisbruch et al., 2004(36)	8
Eisbruch et al., 2011(37)	2
Fang et al., 2004(38)	2
Ford et al., 2009(39)	2
Frowen et al., 2010(40)	5
Frowen et al., 2016(41)	5
Garcia-Peris et al., 2007(42)	2
Gaspar et al., 2000(43)	2
Gluck et al., 2010(44)	5
Haderlein et al., 2014(45)	2
Halczy-Kowalik et al., 2015(46)	2
Hara et al., 2003(47)	2
Hartl et al., 2010(48)	5

Hey et al., 2013(49)	2
Higo et al., 2011(50)	6
Hughes et al., 2000(51)	2
Hunter et al., 2013(52)	2
Hunter et al., 2014(53)	5
Hutcheson et al., 2015(54)	6
Itoh et al., 2015(55)	2
Jacob et al., 1998(56)	2
Jensen et al., 2007(57)	2
Jung et al., 2011(58)	3
Kato et al., 2007(59)	5
Kendall et al., 1998(60)	5
Knox et al., 2010(61)	2
Kolh et al., 1998(62)	7
Kraaijenga et al., 2015(63)	2
Kreeft et al., 2012(64)	5
Kreuzer et al., 2000(65)	2
Kumar et al., 2014(66)	2
Kurnatowski et al., 2014(67)	2
Kurosu et al., 2011(68)	4
Langendijk et al., 2009(69)	2
Lazarus et al., 1996(70)	2
Lazarus et al., 2007(71)	5
Leder et al., 1998(72)	2
Lee et al., 2016(73)	2
Leu et al., 2005(74)	2
Lewin et al., 2008(75)	2
Lindblom et al., 2016(76)	2
Logemann et al., 1992(77)	3
Logemann et al., 2002(78)	5
Maruo et al., 2014(79)	2
Mercadante et al., 2015(80)	2
Moerman et al., 2003(81)	1
Montesi et al., 1990(82)	7
Muz et al., 1987(83)	2
Muz et al., 1991(84)	6
Nasef et al., 2016(85)	2
Nguyen et al., 2009(86)	2
Nikbakhsh et al., 2012(87)	2
Nilsson et al., na(88)	7
Nonoshita et al., 2010(89)	2
Oeken et al., 2001(90)	2
Ohba et al., 2016(91)	4
Ottosson et al., 2014(92)	2
Oursin et al., 1998(93)	2
Panchal et al., 1996(94)	6
Patterson et al., 2011(95)	5
Patterson et al., 2014(96)	2
Pauloski et al., 1993(97)	5
Pauloski et al., 1994(98)	5

Pauloski et al., 1995(99)	5
Pauloski et al., 1998(100)	5
Pauloski et al., 2000(101)	6
Pauloski et al., 2002(102)	5
Pauloski et al., 2006(103)	5
Pauloski et al., 2009(104)	5
Pauloski et al., 2015(105)	5
Paya et al., 2001(106)	1
Pearson et al., 2016(107)	5
Pedersen et al., 2016(108)	5
Peretti et al., 2006(109)	2
Peretti et al., 2013(110)	2
Piazza et al., 2016(111)	2
Pillon et al., 2004(112)	2
Portas et al., 2009(113)	7
Portas et al., 2011(114)	2
Posio et al., 2006(115)	7
Prgomet et al., 2002(116)	2
Queija et al., 2009(117)	2
Rahman et al., 2015(118)	2
Rhodus et al., 1995(119)	7
Roe et al., 2015(120)	2
Rutten et al., 2011(121)	2
Salama et al., 2008(122)	2
Samuels et al., 2016(123)	5
Santini et al., 2015(124)	4
Schache et al., 2009(125)	2
Silver et al., 2014(126)	6
Simonelli et al., 2010(127)	2
Smet et al., 2014(128)	2
So et al., 2014(129)	2
Soderstrom et al., 2017(130)	2
Sonoi et al., 2016(131)	2
Stachler et al., 1996(132)	6
Starmer et al., 2014(133)	2
Starmer et al., 2015(134)	2
Stecewicz et al., 2006(135)	7
Stephens et al., 2015(136)	2
Strasser et al., 2000(137)	1
Sugahara et al., 1996(138)	7
Szczesniak et al., 2014(139)	2
Szczesniak et al., 2015(140)	5
Takashima et al., 2010(141)	7
Teguh et al., 2008(142)	5
Tei et al., 2012(143)	4
Ursino, 2016(144)	3
Vainshtein et al., 2016(145)	2
Wall et al., 2016(146)	2
Wall et al., 2016(147)	2
Walther et al., 1990(148)	5

Walther et al., 1991(149)	5
Weber et al., 1991(150)	2
Wilson et al., 2011(151)	2
Yoo et al., 2012(152)	2
Yuceturk et al., 2005(153)	6
Zhang et al., 2016(154)	5
Zuydam et al., 2000(155)	2

(1) Patients without cancer or non-malignant tumors (n=4); **(2)** Studies that did not use VFSE, MBS or FEES (image exam) as diagnose criteria for deglutition disorders before and after treatment for the cancer (n=81); **(3)** Patients that did not underwent any type of treatment/ therapy for the cancer (n=3); **(4)** Patients that are receiving treatment for the deglutition disorder/ or only patients with dysphagia (n=4); **(5)** Studies that did not report values representative of the deglutition disorders (n=37); **(6)** Reviews, letters, conference abstract, personal opinions, case reports, cross sectional, experimental (n=12); **(7)** Full text not found (n=13); **(8)** Duplicated data Used sample and results from other study (n=1).

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Appendix 3 - Risk of bias assessed in the included studies (n=16) by The Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data. Risk of bias was categorized as High when the study reaches up to 49% score "yes", Moderate when the study reached 50% to 69% score "yes", and Low when the study reached more than 70% score "yes".

Author, Year	**Q1***	**Q2***	**Q3***	**Q4***	**Q5***	**Q6***	**Q7***	**Q8***	**Q9***	**Q10***	**Score/Risk** (the Not Applicable (NA) items were excluded from the sum).
Agarwal et al., 2011(1)	Y	N	Y	Y	Y	Y	Y	Y	N	NA	77.7%/Low
Cartmill et al., 2012(2)	Y	N	N	Y	Y	Y	N	Y	N	NA	55.5%/Moderate
Eisbruch et al., 2002(3)	Y	N	N	Y	Y	Y	Y	Y	N	NA	66.6%/Moderate
Erkal et al., 2014(4)	Y	N	N	N	Y	Y	N	Y	N	NA	44.4%/High
Graner et al., 2003(5)	Y	N	N	Y	Y	Y	N	Y	Y	NA	66.6%/Moderate
Kotz et al., 2004(6)	Y	N	N	Y	Y	Y	Y	Y	Y	NA	77.7%/Low
Ku et al., 2007(7)	Y	N	N	Y	Y	Y	Y	Y	N	NA	66.6%/Moderate
Lazarus et al., 2000(8)	Y	N	N	Y	Y	Y	N	Y	Y	NA	66.6%/Moderate
Logemann et al., 2006(9)	Y	N	Y	Y	Y	Y	Y	Y	N	NA	77.7%/Low
Logemann et al., 2008(10)	Y	N	Y	Y	Y	Y	Y	Y	N	NA	77.7%/Low
O'Connell et al., 2008(11)	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	88.8%/Low
Patterson et al., 2014(12)	Y	N	Y	N	Y	Y	Y	Y	Y	NA	77.7%/Low
Rogus-Pulia et al., 2014(13)	Y	N	N	Y	Y	Y	N	Y	Y	NA	66.6%/Moderate
Serel et al., 2013(14)	Y	N	Y	Y	Y	Y	N	Y	Y	NA	77.7%/Low
Son et al., 2015(15)	Y	N	Y	Y	Y	Y	N	Y	Y	NA	77.7%/Low
Van der Molen et al., 2013(16)	Y	N	Y	Y	Y	Y	Y	Y	N	NA	77.7%/Low

Q1*: Was the sample representative of the target population?
Q2*: Were study participant recruited in an appropriate way?
Q3*: Was the sample size adequate?
Q4*: Were the study subjects and the setting described in detail?
Q5*: Was the data analysis conducted with sufficient coverage of the identified sample?
Q6*: Were objective, standard criteria used for the measurement of the condition?
Q7*: Was the condition measured reliably?
Q8*: Was there appropriate statistical analysis?
Q9*: Are all important confounding factors/ subgroups/ differences identified and accounted for?
Q10*: Were subpopulations identified using objective criteria?

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Appendix 4. Quality of the studies assessed with an adaptation for observational studies of the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system.

Quality assessment						Summary of findings	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Impact	Quality
Subgroups							
Aspiration - Pretreatment							
14	observational studies	serious [a]	not serious	not serious	not serious	Proportion=11.31 %; CI 8.74-14.32; p=0.0198; sample size=517; Inconsistency=49.01%	⊕⊕⊕○ MODERATE
Aspiration - 1 to 6 months posttreatment							
13	observational studies	serious [a]	serious [b]	not serious	not serious	Proportion=27.3 %; CI 19.03-36.07; p<0.0001; sample size=478; Inconsistency=76.22%	⊕⊕○○ LOW
Aspiration - over 6 months posttreatment							
7	observational studies	serious [a]	not serious	not serious	not serious	Proportion=17.99 %; CI 12.37-24.83; p=0.1316; sample size=153; Inconsistency=39.02%	⊕⊕⊕○ MODERATE
Penetration above the vocal cords - Pretreatment							
6	observational studies	serious [a]	not serious	not serious	not serious	Proportion=14.73 %; CI 8.90-22.39; p=0.2839; sample size= 113; Inconsistency=19.82%	⊕⊕⊕○ MODERATE
Penetration above the vocal cords - 1 to 6 months posttreatment							
6	observational studies	serious [a]	serious [b]	not serious	not serious	Proportion=37.19 %; CI 23.22-52.36; p=0.0142; sample size=113; Inconsistency=64.88%	⊕⊕○○ LOW
Penetration above the vocal cords - over 6 months posttreatment							

Quality assessment						Summary of findings	
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Impact**	**Quality**
Subgroups							
4	observational studies	serious [a]	serious [b]	not serious	not serious	Proportion=33.22 %; CI 11.58-59.54; p=0.0004; sample size=80; inconsistency=83.70%	⊕⊕○○ LOW
Reduced laryngeal elevation - Pretreatment							
4	observational studies	not serious	serious [b]	not serious	not serious	Proportion=14.17 %; CI 1.51-36.50; p<0.0001; sample size=204; Inconsistency=89.85%	⊕⊕⊕○ MODERATE
Reduced laryngeal elevation - 1 to 6 months posttreatment							
4	observational studies	not serious	serious [b]	not serious	not serious	Proportion=50.38 %; CI 15.36-85.18; p<0.0001; sample size=204; Inconsistency=95.43%	⊕⊕⊕○ MODERATE

CI: Confidence interval

Explanations

a. One of the study included in this analysis was classified as high risk of bias.

b. Inconsistency in the meta-analysis over 50%

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

6. CONSIDERAÇÕES GERAIS

Os objetivos desse estudo consistiam em coletar, analisar e comparar os resultados encontrados na literatura sobre a frequência de desordens de deglutição e alterações associadas, em pacientes com CCP pré e pós-tratamento oncológico. Observou-se que há maior frequência de complicações no pós-tratamento imediato (1 a 6 meses), quando comparado ao pré-tratamento e aos períodos mais longos após finalização das terapias (>6 meses). Esse resultado encontrado é semelhante a outros estudos. No período imediato pós-tratamento de CCP com a modalidade IMRT, disfagia foi referida por 75% da amostra, reduzindo para 14% após 6 meses da finalização do tratamento[33].

Dos estudos incluídos na RS, nenhum deles apresentou acompanhamento do paciente por período acima de um ano. Dados coletados por períodos mais longos podem trazer informações relevantes quanto à qualidade de vida e prognóstico desses pacientes. Numa amostra acompanhada por uma média de 21 meses pós-tratamento, foram observados que 35% dos participantes possuíam modificação na consistência da dieta (pastosa) e 20% faziam uso de alimentação por via alternativa[34]. Similarmente, num acompanhamento médio de 44 meses pós-tratamento em pacientes com CCP, 57% apresentaram alterações na deglutição avaliada por videofluoroscopia[35]. A presença de disfagia a longo tempo após tratamento oncológico também pode ser um dos indicadores para recorrência da doença[36].

No que concerne às limitações desse estudo, foi observado uma heterogeneidade quanto às formas de avaliação e classificação das desordens e alterações relacionadas à deglutição. A avaliação, identificação e tratamento das sequelas orais/orofaríngeas geradas pelo CCP apresentam desafios e falta de métodos sistemáticos adotados mundialmente. Para a avaliação de deglutição, alguns exemplos são os exames objetivos: videofluoroscopia e videoendoscopia da deglutição[37]. Além deles a coleta do histórico e sintomatologia do paciente também é de suma importância, assim como avaliação clínica.

A variação nos períodos de acompanhamento dos pacientes nos estudos incluídos, também foi uma das limitações encontradas. Esse fator influenciou a análise realizada, pois, o número de estudos incluídos na análise na fase pré-tratamento (14 estudos[38-50] na análise de aspiração) foi maior que a quantidade

incluída nas análises das fases pós-tratamento oncológico (7[38-41,43,46,50] estudos na análise de aspiração até 12 meses). Outra variação que influencia na consideração dos dados analisados são as diferentes modalidades de tratamento oncológico empregadas nos estudos. Quase todos os estudos incluídos[38-49,51,52] apresentaram amostras que foram tratadas por radioterapia e quimioterapia associadas ou não à cirurgia. Adicionalmente, apenas um estudo[50] apresentou dados de pacientes tratados com a modalidade IMRT associada a quimioterapia.

O tratamento de radioterapia com uso de IMRT, associado ao não a imagem guiada, para pacientes com CCP vem se propagando. A IMRT associada à técnica para poupar glândulas salivares pode auxiliar na diminuição de sequelas como a xerostomia [53,54]. A longo tempo (1 a 2 anos), apenas 18% e 21% dos pacientes com CCP tratados com esse tipo de radioterapia, apresentavam xerostomia e disfagia, respectivamente[55].

7. CONCLUSÃO

A partir dos objetivos estabelecidos e resultados encontrados, pode-se concluir que:

- Na literatura há poucos estudos que analisem desordens de deglutição com exames objetivos comparando dados do pré e pós-tratamento oncológico do CCP;
- A frequência de desordens da deglutição é alta na população com CCP;
- Observou-se uma frequência mais alta de alterações no pós-tratamento oncológico imediato quando comparado ao pré-tratamento e períodos mais longos (até 12 meses);
- Há ainda lacuna na literatura para estudos longitudinais, com acompanhamento do paciente de CCP num período superior a 12 meses. Também é necessário a realização de avaliação da deglutição com exames objetivos e estabelecendo classificação padronizada para as alterações encontradas.

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