JULIANA LOPES DE MORAES

“QUALIDADE DE VIDA DO PACIENTE TRATADO POR CÂNCER AVANÇADO DE LARINGE: REVISÃO SISTEMÁTICA E METANÁLISE DE TRATAMENTO CIRÚRGICO VERSUS QUIMIORADIOTERÁPICO”

“QUALITY OF LIFE IN TREATMENT OF ADVANCED LARYNX CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS”

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Orientador: Prof. Dr. CARLOS TAKAHIRO CHONE

"QUALITY OF LIFE IN TREATMENT OF ADVANCED LARYNX CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS"

Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências Médicas da Faculdade de Ciências Médicas da Universidade de Campinas para obtenção de título de Mestra em Ciências Médicas, área de concentração em Ciências Biomédicas.

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"Reabilitar é despertar o desejo saudável ao retorno, entendendo que, apesar de ter mudado a forma a essência continua a mesma, porque ainda há vida"

Autor desconhecido

Resumo

Objetivo: Comparar a qualidade de vida do paciente tratado cirurgicamente por câncer avançado de laringe com aquele que foi submetido a quimioradioterapia exclusivos.

Método: Revisão sistemática que utilizou, para a seleção dos artigos, 06 bases de dados (PubMed, MedLine, Embase, Web of Science, Cochrane Library e Lilacs) e as palavras-chave "*head and neck cancer*"; *"advanced laryngeal cancer"*; *"laryngeal neoplasm"; larynx cancer"; "quality of life"; "outcomes/functional results";"total laringectomy"; "chemoradiotherapy*". Os critérios de inclusão foram estudos específicos de câncer avançado de laringe, com comparação de modalidades de tratamento e avaliação da qualidade de vida.

Resultados: Foram encontrados 321 artigos. Nove artigos preencheram todos os critérios de inclusão e desses, apenas três possuíam desenho metodológico e instrumento de mensuração de qualidade de vida comparáveis entre si e foram submetidos à metanálise . Os resultados evidenciaram que 90% dos estudos são retrospectivos e não randomizados, que geraram viés quanto à caracterização dos grupos. O tempo pós-tratamento em que os questionários de qualidade de vida foram aplicados mostrou grande variabilidade (3 meses a 11 anos).

Conclusão: A meta-análise dos três estudos comparativos mostraram uma melhor qualidade de vida após o tratamento para indivíduos tratados com quimioradioterapia exlcusiva. No entanto, devido a existência de poucos estudos com dados relevantes na literatura, é necessário realizar pesquisas futuras com as seguintes características de estudo: (a) prospectivos e randomizados, (b)

multicêntrico, com maior número de indivíduos, e (c) enfatizando o funcional seqüelas que ambos os tratamentos acarretam.

Palavras-chaves: câncer de laringe, quimioradioterapia, laringectomia total, qualidade de vida, preservação de órgãos

ABSTRACT

Objective: To compare studies of quality of life in patients undergoing chemoradiotherapy or surgery for advanced laryngeal cancer.

Method: Articles were selected for a systematic review by searching six databases (PubMed, Medline, Embase, Web of Science, Cochrane Library and Lilacs) for keywords “head and neck cancer,” “advanced laryngeal cancer," "laryngeal neoplasm," "larynx cancer," "quality of life," "outcomes and functional results," "total laryngectomy" and "chemoradiotherapy." The included studies must related to advanced larynx cancer, comparisons of treatment modalities and assessment of patient quality of life in validated scales, well defined inclusion and exclusion criteria. Articles with poor methodological evaluation and duplicated results were excluded.

Results: It was found 321 articles. Nine articles fitted to all inclusion criteria and of these, only three observed comparable methodological designs and standardized instruments for measuring quality of life and therefore subjected to meta-analysis. Our analysis observed that 90% of the studies were retrospective and nonrandomized. The time point post-treatment at which the quality of life questionnaires were assessed varied widely (3 months to 11 years).

Conclusion: The meta-analysis of three comparable studies showed improved quality of life after treatment for subjects treated with chemoradiation alone. However, because of few studies with relevant data in literature, it is necessary to conduct future research with the following study characteristics: (a) prospective and randomized; (b) multicentric, with larger numbers of subjects; and (c)

emphasizing the functional sequelae that both treatments entail.

Keywords: larynx cancer, chemoradiotherapy, total laryngectomy, quality of life, organ preservation

LISTA DE ABREVIATURAS

WHOQOL - World Health Organization – Quality of Life Group

TL – Total Laryngectomy

ASCO - American Society of Clinical Oncology

EORTC QLQ - C30 / H & N35 - European Organization for Research and Treatment of Cancer Quality of Life associated with the specific module for head and neck

RNRS - retrospective nonrandomized study

RRS - randomized and retrospective study

PNRS – prospective nonrandomized study

TNM – classificação mundial de estadiamento de tumor

TF/SED – tratamento finalizado / sem evidência de doença

HNQOL - University of Michigan Head and Neck Quality of Life

HSQ – 12 - Health Status Questionnaire – 12

UW – QLQ - University of Washington Quality of Life Instrument

HRQOL - Health-Related Quality of Life

FACT- H & N - Functional Assessment of Cancer Therapy

LT + RTX – tratamento cirúrgico + radioterapia adjuvante

CRT – tratamento quimioterápico exclusivo

SUMÁRIO

1. Introdução

O conceito de qualidade de vida, ainda sem consenso, baseia-se em três aspectos fundamentais: (1) subjetividade; (2) multidimensionalidade; (3) presença de dimensões positivas e negativas. A partir destes elementos, em 1994, a instituição *World Health Organization – Quality of Life Group* (WHOQOL) [1], definiu esse termo sendo "a percepção do indivíduo de sua posição na vida, no contexto da cultura e sistemas de valores nos quais ele vive e com relação aos seus objetivos, expectativas, padrões e preocupações". O reconhecimento da multidimensionalidade do termo fez que tal instituição propusesse, em 1997, a avaliação da qualidade de vida pautada em seis dimensões: (I) saúde física; (II) saúde psicológica; (III) nível de independência; (IV) relações sociais; (V) meio ambiente e (VI) aspectos espirituais/religião/crenças espirituais [2]

O crescente interesse em avaliar a qualidade de vida se deu em todas as esferas nas quais o sujeito se insere e atua. Dentro das ciências humanas e biológicas refere-se a um movimento no sentido de valorizar aspectos mais amplos que o controle da doença, a diminuição da mortalidade ou o aumento da expectativa de vida. Na área da saúde,

> "a oncologia, foi a especialidade que, por excelência, se viu confrontada com a necessidade de avaliar as condições de vida dos pacientes que tinham sua sobrevida aumentada devido aos tratamentos realizados, já que, muitas vezes, na busca de acrescentar anos à vida, era deixada de lado a necessidade de acrescentar vida aos anos" [3].

Sendo assim, os estudos na área de Cirurgia de Cabeça e Pescoço têm valorizado cada vez mais a qualidade de vida do paciente no pós-tratamento [4-8], fato que mobiliza não apenas a equipe médica, mas também as equipes de suporte (enfermeiras e técnicos de enfermagem) e de reabilitação (fonoaudiólogos, psicólogos, fisioterapeutas, terapeutas ocupacionais e nutricionistas).

O câncer de laringe é uma das neoplasias malignas mais frequentes que acomete a via aérea superior. É responsável por 25% dos tumores malignos diagnosticados nessa área e 2% de todas as doenças malignas. Em 2006 houve uma estimativa de 10.000 casos novos nos Estados Unidos e no Brasil, para o ano de 2012 a estimativa foi de 6.110 casos novos. O tipo histológico mais prevalente

de câncer na laringe é o carcinoma espinocelular que apresenta direta relação ao uso de tabaco e álcool e atinge homens e mulheres principalmente a partir da quinta década de vida [9-11].

Durante muitos anos o tratamento padrão para o câncer avançado de laringe consistia na remoção total do órgão, laringectomia total (LT), seguida ou não por radioterapia. Essa abordagem, ainda utilizada, mostra bom controle local da doença, porém com impacto negativo na qualidade de vida do sujeito devido à presença permanente de um estoma além da perda da voz laríngea com consequente dificuldade de comunicação [12-13].

Com o intuito de minimizar sequelas e melhorar a qualidade de vida, tratamentos de preservação de órgãos – cirurgias conservadoras, radioterapia seguida por cirurgias, radioterapia exclusiva e quimioradioterapia exclusivos – foram propostos.

Estudos [14-17], na década de 1990 , mostraram o potencial da quimioterapia no tratamento do câncer avançado de laringe e sugeriram uma possível associação entre quimioterapia e radioterapia como abordagem terapêutica. Entretanto, a difusão dessa modalidade ocorreu, mais enfaticamente, após a publicação de dois estudos [18-19] prospectivos e randomizados em pacientes com câncer de laringe nos estágios III ou IV, submetidos à quimioterapia (cisplatina e fluoracil) seguida por radioterapia.

Os resultados desses estudos mostraram que a quimioterapia de indução seguida por radioterapia não comprometia a sobrevida do paciente, porém o tratamento inicial com quimioradioterapia concomitante evidenciou maiores taxas de preservação do órgão e controle local da doença similar ao da abordagem cirúrgica, porém sem aumento da sobrevida. Entretanto, tais estudos não mencionam os efeitos tóxicos da radioterapia, potencializados pela quimioterapia, sobre a funcionalidade da laringe (voz e deglutição), fato que terá influência direta na qualidade de vida do paciente.

Dado o papel fundamental que a laringe desempenha na comunicação humana e na função deglutição, determinar a melhor condução terapêutica do

câncer avançado de laringe envolve considerar tanto a taxa de sobrevivência quanto as sequelas funcionais próprias de cada abordagem.

Em 2005, a America*n Society of Clinical Oncology* (ASCO) organizou, por meio de um consenso de especialistas na área de cabeça e pescoço, diretrizes de prática clínica para o uso de estratégias de preservação laríngea no tratamento do câncer de laringe. Para tumores em estágios avançados (T3 e T4) não existem marcadores validados capazes de prever consistentemente a eficácia do tratamento de preservação laríngea. Sabe-se que para pacientes com tumores que invadem tecido mole através da cartilagem, a resposta ao tratamento de preservação é muito baixa, devendo, portanto, optar-se pelo procedimento cirúrgico de retirada total do órgão. Sendo assim, a decisão da escolha terapêutica – cirurgia ou preservação de órgãos – a ser adotada em casos de tumores avançados que não tenham invadido a cartilagem ocorre, atualmente, mediante critérios clínicos médicos e da equipe multidisciplinar que acompanha o paciente e/ou opção do paciente e família que, em ambos os casos, preconiza a cura da doença, funcionalidade do órgão e melhor qualidade de vida [20].

Independente da escolha, o tratamento para o câncer avançado de laringe acarretará em mudanças que afetam não apenas o sujeito em si, mas toda a dinâmica ao seu redor. A privação total da comunicação oral e/ou da alimentação via oral, durante ou após o tratamento, gera desconforto para o paciente, que muitas vezes se isola socialmente, e acarreta dúvidas e receios para quem o acompanha.

Entender como se encontra a qualidade de vida do paciente que teve câncer avançado de laringe pode influenciar diretamente a escolha da abordagem terapêutica, por parte da equipe médica, bem como o processo de reabilitação.

Poucos estudos na literatura comparam a qualidade de vida de pacientes tratados por câncer avançado de laringe, aptos a ambas as abordagens terapêuticas – cirurgia ou quimioradioterapia exclusivos.

Dessa forma, esta tese é composta por um artigo que apresenta os resultados, qualitativos e estatísticos, de uma revisão sistemática de estudos que comparam qualidade de vida de pacientes com câncer avançado de laringe

tratado cirurgicamente com aquele que foi submetido ao tratamento quimioradioterápico exclusivo. Esse artigo foi submetido à publicação internacional.

2. Objetivo

2.1 **- Objetivo geral:**

Comparar a qualidade de vida do paciente tratado cirurgicamente por câncer avançado de laringe com aquele que foi submetido a quimioradioterapia exclusivos.

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3.Capítulo

QUALITY OF LIFE IN TREATMENT OF ADVANCED LARYNX CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Objective: To compare studies of quality of life in patients undergoing chemoradiotherapy or surgery for advanced laryngeal cancer, using data collected by questionnaire.

Data Sources: Articles were selected for a systematic review by searching six databases (PubMed, Medline, Embase, Web of Science, Cochrane Library and Lilacs).

Review Methods: The keywords “head and neck cancer,” “advanced laryngeal cancer," "laryngeal neoplasm," "larynx cancer," "quality of life," "outcomes and functional results," "total laryngectomy" and "chemoradiotherapy." Were combined in various ways to maximize the results. The included studies must related to advanced larynx cancer, comparisons of treatment modalities and assessment of patient quality of life in validated scales, well defined inclusion and exclusion criteria. Articles with poor methodological evaluation and duplicated results were excluded.

Results: It was found 321 articles. Nine articles fitted to all inclusion criteria and of these, only three observed comparable methodological designs and standardized instruments for measuring quality of life and therefore subjected to meta-analysis. Our analysis observed that 90% of the studies were retrospective and nonrandomized. The time point post-treatment at which the quality of life questionnaires were assessed varied widely (3 months to 11 years).

Conclusion: The meta-analysis of three comparable studies showed improved quality of life after treatment for subjects treated with chemoradiation alone. However, because of few studies with relevant data in literature, it is necessary to

conduct future research with the following study characteristics: (a) prospective and randomized; (b) multicentric, with larger numbers of subjects; and (c) emphasizing the functional sequelae that both treatments entail.

Keywords: larynx cancer, chemoradiotherapy, total laryngectomy, quality of life

Introduction

Quality of life is a multidimensional term that was defined by the World Health Organization Quality of Life Group (WHOQOL) as an individual perception of their position in life in the context of culture and value systems in which live and in relation to goals, expectations, standards and concerns[1]. Interest in evaluating quality of life—despite the complexity of its abstract and subjective nature—is growing in all areas in which it has a significant role. In medicine, oncology is one of the specialties in which it is important to assess the quality of life of patients undergoing different treatment modalities because merely having survived the disease does not guarantee satisfaction with respect to emotional, physical and social functioning, which directly influence the way an individual will overlooks socially after treatment[2,3,4].

Laryngeal cancer is one of the most common malignancies affecting the upper airway. It accounts for 25% of malignant tumors diagnosed in this area and for 2% of all malignancies. The most prevalent histological type of is squamous cell carcinoma, which has a direct relationship with the use of tobacco and alcohol and mainly affects men and women in the fifth decade of life and later[5,6,7].

When diagnosed late, laryngeal cancer requires more aggressive approaches that will inevitably impact quality of life. For many years, the standard treatment for advanced laryngeal cancer has consisted of total laryngectomy (TL), followed in select cases by radiotherapy with great impact in voice production. Thus, impairment of quality of life can occur in multiple ways, including physical and psychological aspects as well as level of independence and social

relationships[8].

To minimize treatment sequelae and improve quality of life, organ preservation treatments, including conservative surgery (partial laryngeal surgery) or concomitant radiotherapy and chemoradiotherapy without surgery, have been proposed. Among these methods, concomitant chemotherapy and radiation therapy have been shown to be effective, with high rates of survival and organ preservation. However, the action of chemotherapy increases the toxicity of radiotherapy and its functional sequelae. Indeed, poor voice quality and swallowing are observed during and after treatment, and these symptoms can also impact breathing functions and are a major cause of odynophagia[9,10].

In 2005, the American Society of Clinical Oncology (ASCO)[11] issued clinical practice guidelines for the use of larynx-preservation strategies in the treatment of laryngeal cancer based on the consensus opinions of experts in head and neck cancer. However, for tumors in late stages (T3 and T4), validated markers are not able to consistently result on effective treatment for laryngeal preservation. Patients with tumors that invade soft tissue through the cartilage, would have a low rate of complete response to non surgical treatments and TL would be more appropriate.

Thus, the choice between surgery and organ preservation in cases of advanced tumors that have not invaded the cartilage is currently determined by clinical criteria as interpreted by the physicians and multidisciplinary teams that follow the patient. For both treatments, patients and families report that their goals are the survival, maintaining organ function and preserving quality of life[12].

Few studies are available comparing the quality of life of patients following

surgical treatment with that of those treated with chemoradiation alone for advanced laryngeal cancer. Thus, the goal of this systematic review and meta-analysis was to determine which of these two treatment options results in less impairment of quality of life following treatment for advanced laryngeal cancer.

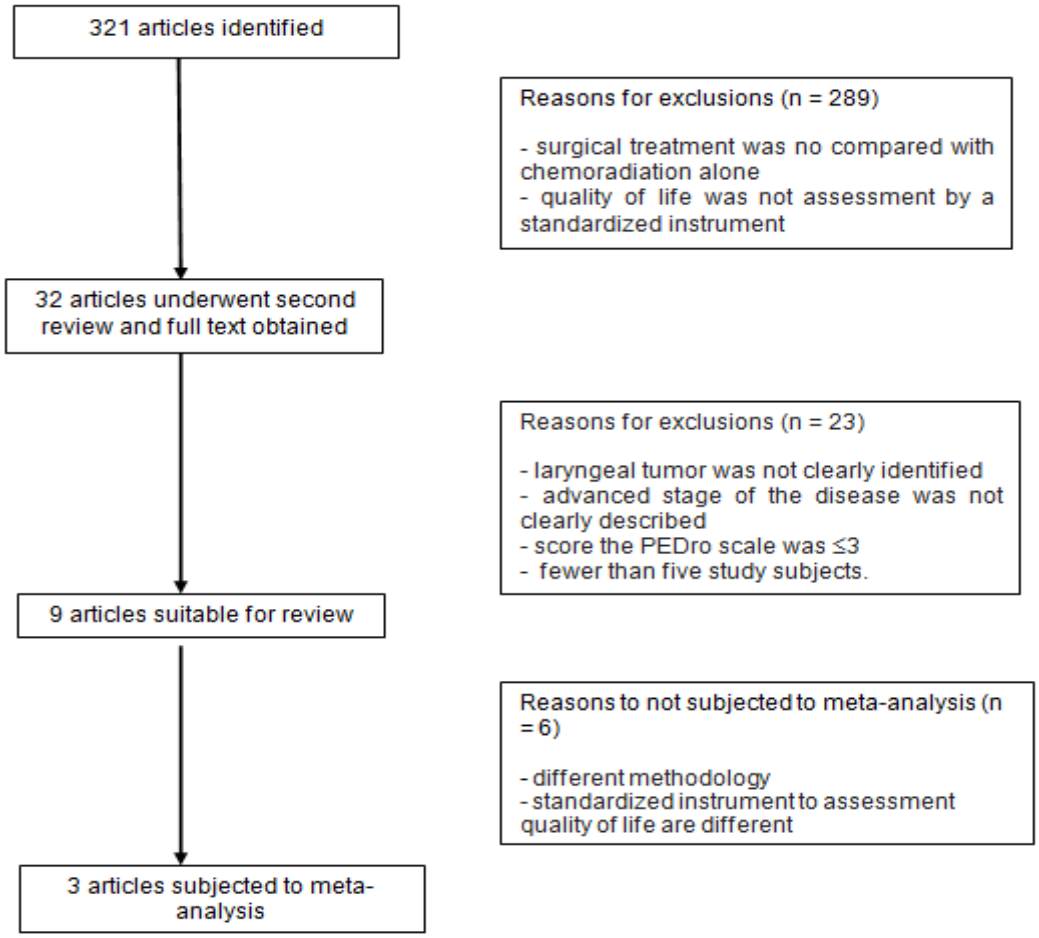
Material and Methods

Search method: The search for this systematic review was conducted in September 2012 and updated periodically until June 2013. Two independent researchers systematically reviewed the following databases: PubMed, Medline, Embase, Web of Science, Cochrane Library and Lilacs. The search strategy, modified according to the criteria of each database, was formulated from the following descriptors in English combined in various ways to maximize the results: "head and neck cancer," "advanced laryngeal cancer," "laryngeal neoplasm," "larynx cancer," "quality of life," "outcomes and functional results," "total laryngectomy" and "chemoradiotherapy." The search was limited to human research articles published in English between January 1990 and June 2013.

Inclusion and exclusion criteria: The studies selected for this systematic review met the following inclusion criteria: (1) compared surgery versus a conservative approach with chemoradiotherapy for advanced laryngeal cancer without invasion of the cartilage, (2) evaluated quality of life between the two treatment groups using a standardized instrument, (3) clearly described the advanced stage of the tumor, (4) clearly described the location of the laryngeal tumor, (5) assessed the methodological quality using the PEDro Scale and reported a score >3 and (6) included at least five studied subjects. We excluded studies in which (1) non-surgical treatment was not related to chemoradiation, (2) patients did not undergo assessment of quality of life using equal standardized instrument, (3) the site of larynx cancer was not clearly identified, (4) the advanced stage of the disease was

not clearly described, (5) the methodological quality score, as assessed using the PEDro scale, was ≤3 and there were fewer than five studied subjects. The references in all the selected articles were checked and read to increase the sensitivity of this systematic review. After the manual search, the articles were imported into the Endnote reference manager to delete duplicate references. The studies included in this analysis were reviewed in their complete form, and the most relevant data were entered into an Excel spreadsheet for further analysis. The various steps of the systematic review of the abstracts and full-text studies, as well as the reasons for exclusion, are described in Figure 1.

Figure 1: Steps of the systematic review



Data collected: Comparison of patient quality of life after surgery with radiotherapy or after chemoradiation treatment alone for advanced laryngeal cancer was the primary aim of the current review. This approach was based on the anatomical and functional changes that both treatment methods bring about in patients as well as their families and social relationships.

Aspects related to the time after treatment when the quality of life instrument was subset and correlation between organ preservation and laryngeal functioning as well as the above mentioned inclusion and exclusion criteria were analyzed.

Assessment of methodological quality: The studies that met the inclusion criteria were assessed for methodological quality using the PEDro scale[13], based on the Delphi list. This scale has a score of zero to 10 points, and studies of low methodological quality (PEDro score ≤3) were removed from the analysis. The itens of assessment of methodological quality using the PEDro scale are described in Figure 2.

Figure 2. Assessment of methodological quality using the PEDro scale

1. Eligibility criteria specified.*
2. Subjects randomly distributed between groups.
3. Subjects blinded to their group allocation.
4. Groups initially similar with respect to the most important prognostic factors.
5. All subjects participated in blinded studies.
6. All therapists administered therapy blindly.
7. All assessors who measured at least one key outcome did so blindly.
8. Measurements of key outcomes were obtained in over 85% of the subjects initially distributed between the groups.
9. All subjects for whom results were available received treatment or a control condition according to their allocation or, if this was not the case, analysis of the data was carried out for at least one of the key results in an "intention to treat" analysis.
10. The results of statistical comparisons between the groups were reported for at least one key outcome.
11. The study presented both accuracy measures as measures of variability for at least one key outcome.

Yes = 1, No = 0

* This item did not receive a score

Qualitative analysis: To summarize and evaluate the data from the studies included in this systematic review, qualitative, descriptive analyses were performed on the data collected.

Statistical analysis: From the systematic review, we selected comparable studies that used the same measurement instrument (EORTC QLQ–C30/H&N35) and combined these results in a meta-analysis. This technique allowed us to obtain a

more accurate estimation of quality of life in patients undergoing surgical treatment compared with chemoradiotherapy alone.

The included studies measured quality of life with respect to five variables: overall quality of life, social functioning, cognitive functioning, emotional well-being and physical well-being. The result of the meta-analysis represented the combination of this mean difference and the 95% confidence interval, taking into account the weight assigned to each study.

Results

The search strategy identified 321 studies by searching all the databases and reviewing the references of the selected studies. Only three[14,15,16] of the included studies observed comparable methodological designs and standardized instruments for measuring quality of life and were therefore subjected to meta-analysis.

Of the nine studies reviewed and included in this systematic review, seven [14,15,16,17,18,19,20] were described as retrospective nonrandomized (ERNR), one[21] as prospective nonrandomized and one[22] as randomized and retrospective (ERR). In the assessment of the methodological quality using the PEDro scale, eight studies[14,15,16,17,18,19,20,21] received grade four and one[22] received a score of seven. The choice of treatment modality and the selection of subjects for the assessment of instruments to measure quality of life are summarized in Table 1.

TABLE 1. General Characteristics of the Sample

Author	Year	Quality Score	Method	Decision therapy	Selection subject
Terrel et al[22]	1998	7	ERR	Randomized	TF/SED
Major et al[17]	2001	4	ERNR	No mention	TF/SED
Nordgren et al[21]	2003	4	EPNR	TNM	T0 – all T1/2/3/6/12 – survivors
Hanna et al[14]	2004	4	ERNR	Patient	TF/ SED
LoTempio et al[18]	2005	4	ERNR	Patient	TF/SED
El-Deiry et al[19]	2005	4	ERNR	TNM	TF/SED
Boscolo-Rizzo et al[15]	2008	4	ERNR	TNM/Patient	TF/SED
Trivedi et al[20]	2008	4	ERNR	TNM/Patient	TF/SED
Guibert et al[16]	2011	4	ERNR	multidisciplinary team	TF/SED

ERR - randomized retrospective study; ERNR - retrospective nonrandomized study; EPNR - a prospective and nonrandomized study; TNM - World tumor staging classification, TF / SED - Treatment finalized / no evidence of disease

Assessment of quality of life

A large variety of instruments for measuring quality of life were used. Four[14,15,16,21] of the nine included studies used the European Organization for Research and Treatment of Cancer Quality of Life associated with the specific module for head and neck (EORTC QLQ - C30 / H & N35), whereas the other instruments used were only once each: University of Michigan Head and Neck Quality of Life (HNQOL); Health Status Questionnaire - 12 (HSQ - 12), University of Washington Quality of Life Instrument (UW - QLQ), Health-Related Quality of Life (HRQOL) and Functional Assessment of Cancer Therapy (FACT- H & N). Table 2 indicates which instruments were used in the studies, the composition of each group within these studies and the average time interval (in retrospective studies) between the end of the treatment and the assessment of the instruments. Six[15,16,17,20,21,22] of these

studies revealed statistically significant differences between the chemoradiotherapy group and the surgery plus radiotherapy group with respect to specific items on the measurement scales, whereas other studies[14,18,19] detected no significant differences or trends or improved scores on specific items. Analysis of the study findings revealed that of the nine included studies, two[15,22] found that long-term quality of life was better in the chemoradiotherapy group. The other studies reported that long-term overall quality of life differed between the two groups based on the effects of each treatment on anatomical structures and function. Table 2 presents the included studies that reported significant differences between the two treatment groups and the authors related conclusions.

TABLE 2. Specific characteristics of the studies

Autor	n total	T3+T4	Treatment performed	Instruments	Mensuration (months)	Results	Conclusion
Terrel et al[22]	46	33 / 13	LT + RTX / CRT	HNQOL; SF-36	1, 2, 4, 8		
Major et al[17]	24	6 / 15	LT + RTX / CRT	HSQ-12	42.8 / 30.7		
Nordgren et al[21]	86	13 / 73	LT + RTX / CRT	EORTC QLQ C-30/H&N35	0, 1, 2, 3, 6, 12, 60		
Hanna et al[14]	42	27 / 15	LT + RTX / CRT	EORTC QLQ C-30/H&N35	36		
LoTempio et al[18]	49	34 / 15	LT + RTX / CRT	UW-QLQ	40 / 6		
El-Deiry et al[19]	54	7 / 9	LT + RTX / CRT	HRQOL	32.1 / 28.9		
Boscolo-Rizzo et al[15]	67	39 / 28	LT + RTX / CRT	EORTC QLQ C-30/H&N35	30 / 29		
Trivedi et al[20]	40	29 / 11	LT + RTX / CRT	FACT-H&N	22 / 20		
Guibert et al[16]	63	46 / 17	LT + RTX / CRT	EORTC QLQ C-30/H&N35	41 / 50		

Grey shade representing a statistically significant difference; clear shade is no statistically significant difference

Laryngeal organ preservation and function

The studies included in this review considered organ preservation and laryngeal function as synonymous with successful treatment for patients undergoing chemoradiation.

Statistical analysis

The results of the meta-analysis of the studies by Hanna et al[14], Bocolo-Rizo et al[15] and Guibert et al[16], given in Figures 3-8, demonstrate favorable results for the CRT group with respect to the overall quality of life as well as the social, functional and

physical quality of life as measured by the EORTC QLQ C - 30 / H & N35. The study by Boscolo-Rizo et al.[15] was given more weight in the meta-analysis (> 60% for all variables), which ultimately determined the outcome of the meta-analysis. This weight was calculated based on the study size and the precision of the estimates.

FIGURE 3. Meta-analysis – Global Quality of Life

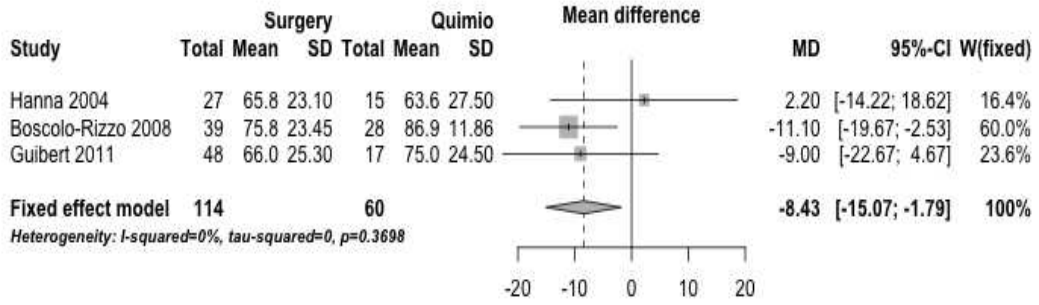


FIGURE 4. Meta-analysis – Social functioning

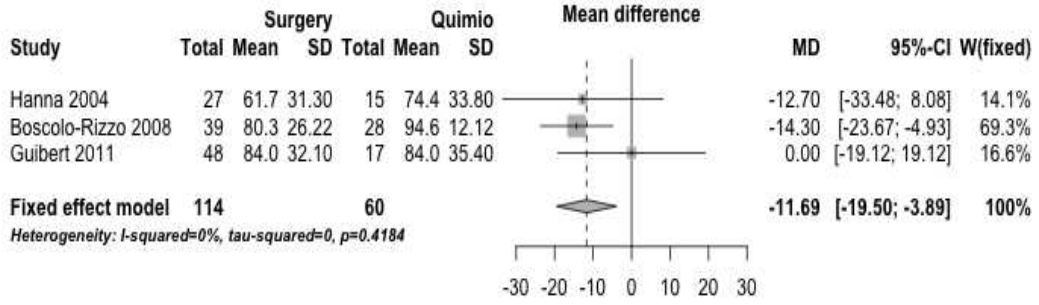


FIGURE 5. Meta-analysis – Cognitive functioning

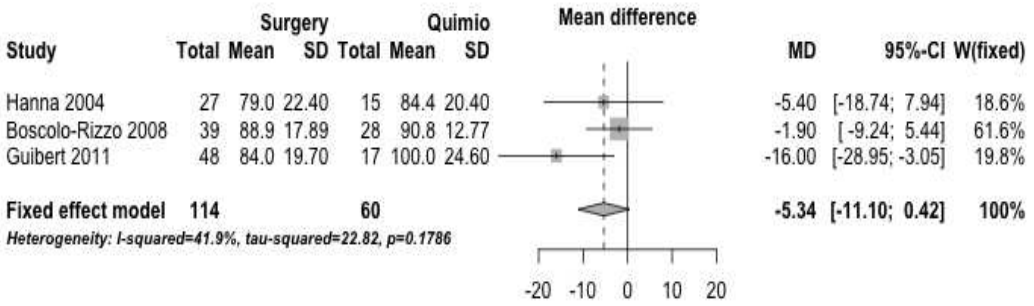


FIGURE 6. Meta-analysis – Emocional functioning

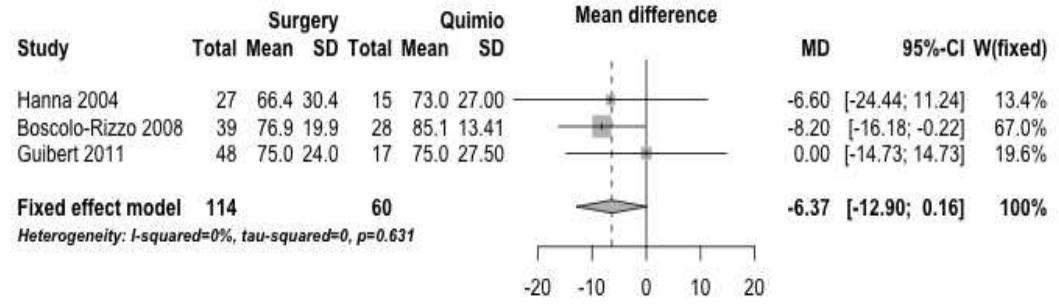


FIGURE 7. Meta-analysis – Role functioning

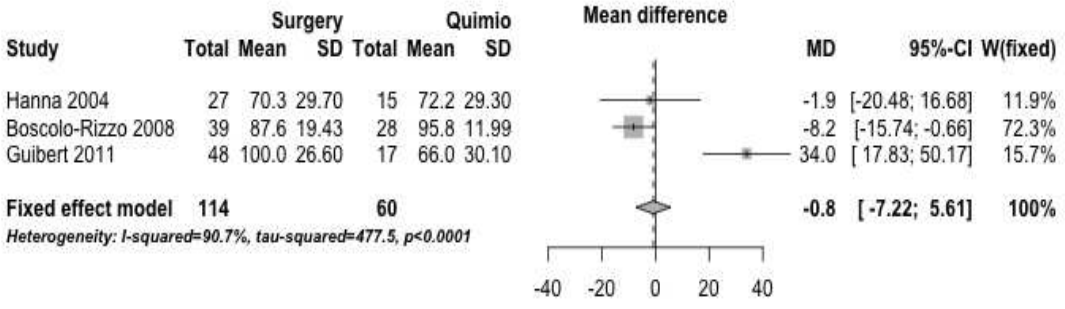
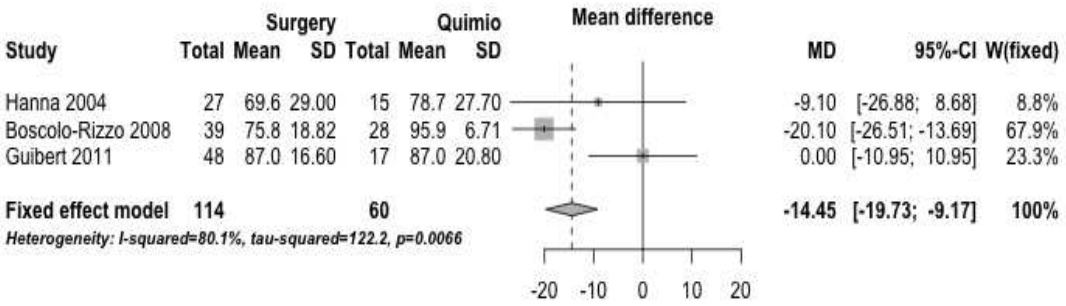


FIGURE 8. Meta-analysis – Physical functioning



Discussion

Regardless of the treatment modality, our systematic review demonstrates that treatment for advanced laryngeal cancer will impact quality of life due to the anatomical and functional sequelae of both treatment options. The meta-analysis of the quality of life study suggested that chemoradiotherapy may represent a more favorable approach because organ preservation eliminates the visual impact of surgery and allows the social functions and autonomy that are enabled by communication. However, some relevant points of this review should be considered before assuming that the quality of life following treatment for advanced laryngeal cance is tied only to the choice of therapeutic approach.

The limitations of this systematic review with meta-analysis include variations in methodological quality and the use of different standardized instruments to measure quality of life. The main drawback of this study is that of the nine studies reviewed, seven [14, 15, 16, 17, 18, 19, 20] were nonrandomized retrospective studies, which analyzed the medical records and databases of patients treated for advanced laryngeal cancer to identify individuals to invite to participate in the research by answering questionnaires specific to quality of life. One[21] study employed a prospective nonrandomized study design; as described above, this study did not use random allocation of the subjects, and the treatment decision was made by the clinical criteria of the medical staff or, if given the option, by the family and the patient. Only one[22] study used a randomized retrospective design, where subjects were randomly distributed between two therapeutic groups that were initially similar in their prognostic indicators and previous therapies at the time

of the study. Additionally, all retrospective articles reported that the subjects who answered to the questionnaires of quality of life had achieved therapeutic success, thereby generating a bias in the analysis of the results; the lack of data from patients with treatment failure could mascarade the final analysis of overall quality of life. For these reasons, we observed low scores on the PEDro scale, indicating poor methodological quality of the included studies, and therefore it is not advisable to reproduce these studies to compare the quality of life between treatment modalities.

A variety of instruments for measuring quality of life used in the included studies precluded the comparison and analysis of the scores of overall quality of life and specific items of each instrument. The only instrument that was used in more than one of the studies was the EORTC QLQ - C30 / H & N35, and items were comparable only if they were common to all studies. The use of only common items introduces other biases, as the items in the particular part of the instrument (EORTC - H & N35) that could describe more specific alterations of the functions of speech, voice, chewing and swallowing were not reported in all studies and thus were not analyzed. Another disadvantage of this systematic review identified as a bias in all the included studies was the time interval between the end of treatment and the assessment of instruments for measuring quality of life. In our clinical practice, we observed that the major sequelae of surgical treatment, including adaptations to the new conditions, breathing patterns, communication difficulties and changes in smell and taste, are more pronounced in the first months after surgery; with length of time, the individual finds strategies to overcome these

changes, reducing their impact on quality of life. Treatment with organ preservation suggests that the toxic effects of radiation therapy added by chemotherapy affect the quality of life of the patient throughout treatment and may persist for up to 24 months after completion. The most common complaint of patients undergoing chemoradiation was xerostomia which often leads to a condition of intense mucositis in the oral and oropharyngeal region associated with laryngeal edema. Sore throat and respiratory disorders are the most frequent sequelae witch lead to enteral nutrition with feeding tube and tracheostomy, which can also lead to dysphagia and communication difficulties. Thus, the greater the length of time between the treatment and the quality of life assessment, the more the individual is able to adapt to his new living conditions and the less harm to his quality of life. Studies report that functional alterations of speech and swallowing were minimized through the rehabilitation process. The use of tracheoesophageal prostheses as a method of voice rehabilitation is considered effective to meet communication challenges. For changes in swallowing, studies report quotations from a speech therapist but do not specify which therapeutic techniques were used. Additionally, the time and frequency of rehabilitative therapy is not specified. The ASCO consensus (2005)[11] recognizes that speech and swallowing are highly complex neuromuscular functions that can be interrupted by either the presence of disease or the therapeutic modality, thereby justifying the involvement of a multidisciplinary team. Surgical sequelae are visual and are thus more easily identified and addressed, whereas chemoradiotherapeutic sequelae are silent and difficult for the patient to convey. Therefore, careful evaluation and timely intervention are

necessary for chemoradiotherapeutic patients. A multidisciplinary approach can minimize many of the sequelae of these treatments, and the increasingly participation of these professionals will result in a better quality of life for their patients.

Functionality and laryngeal preservation

Laryngeal preservation and laryngeal function are two different concepts that are often used synonymously. Preserving the body does not necessarily imply preservation of function. According to the ASCO consensus (2005)[11], the presence of persistent dysphagia, tracheostoma and tracheal aspiration failures are not considered functional organ preservation therapy because the vital functions of breathing and swallowing are altered such that other clinical complications or death may occur. However, our clinical practice suggests that the concept of laryngeal function may be as subjective as quality of life and that one may be crucial to the other. The definition of function may differ between patients and between a patient and his therapist. For some patients, the fact that only food of specific consistencies may be taken orally indicates treatment failure, as this restriction will result in significant changes in the patient eating habits that will ultimately influence his oquality of life. Furthermore, clinically, we do not include voice quality scores in the evaluation of laryngeal function, although for some patients, vocal quality or vocal fatigue and stress may directly impact quality of life.

CONCLUSION

Although the meta-analysis of this systematic review suggests that chemoradiation treatment is the best therapeutic option for patients with respect to quality of life, further prospective randomized studies that include data on patient rehabilitation are in need to conclude that the therapy, in itself, influences the overall quality of life of patient. Understanding patients quality of life and their post-treatment organ function is necessary for multidisciplinary teams to better define their goals and interventions in the search for better quality of life for patients treated for advanced laryngeal cancer.

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4.Conclusões Gerais

Conclusões Gerais

Com essa revisão sistemática concluímos que poucos estudos nas áreas de cirurgia de cabeça e pescoço, oncologia e fonoaudiologia abordam qualidade de vida pós tratamento para câncer avançado de laringe comparando abordagem cirúrgica e quimioradioterápica. Nesse contexto, a realização de metanálise torna-se desafiante devido aos diferentes desenhos metodológicos dos estudos e à diversidade de instrumentos de mensuração de qualidade de vida.

Apesar da metanálise desta revisão sistemática ter sido favorável para o tratamento quimioradioterápico nota-se a necessidade de realização de estudos prospectivos randomizados que incluam dados da reabilitação dos pacientes para então concluirmos que a escolha terapêutica, de forma isolada, influencia na qualidade de vida global do paciente. O entendimento do que é preservação e funcionalidade do órgão também se faz necessário para que a equipe multidisciplinar tenha mais claro seus objetivos na busca e intervenção por uma melhor qualidade de vida ao paciente tratado por câncer avançado de laringe.

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