

DOUTORAMENTO

CIÊNCIAS MÉDICAS

Qualidade de vida e marcadores bioquímicos na avaliação da caquexia em doentes com cancro da cabeça e pescoço

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D

2021



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**QUALIDADE DE VIDA E MARCADORES BIOQUÍMICOS NA
AVALIAÇÃO DA CAQUEXIA EM DOENTES COM CANCRO DA
CABEÇA E PESCOÇO**

**QUALITY OF LIFE AND BIOCHEMICAL MARKERS IN CACHEXIA
EVALUATION ON HEAD AND NECK CANCER PATIENTS**

Tese de Candidatura ao grau de Doutor em
Ciências Médicas
Programa Doutoral da Universidade do Porto
(Instituto de Ciências Biomédicas de Abel Salazar)

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Para

Sandra, Rita e Pedro,

razão principal para continuar a sonhar

Eles não sabem, nem sonham
que o sonho comanda a vida.
Que sempre que um homem sonha
o mundo pula e avança...

António Gedeão
(Poeta: 1906-1997)

AGRADECIMENTOS

O concluir de um projeto é sempre o momento de maior notoriedade, permitindo aferir a sua relevância e dar sentido ao trabalho realizado.

No entanto, o percurso desenvolvido é o bem mais valioso que está subjacente a cada projeto. Na investigação científica isto é mais evidente uma vez que o próprio conhecimento científico se vem construindo ao longo de um caminho iniciado há muito tempo.

É o caminho desenvolvido, com avanços e recuos, mudanças de perspectiva e constantes descobertas, que nos vai enriquecendo e preparando para melhorarmos todo o trajeto conducente a um resultado que por si só abrirá novos caminhos.

Por outro lado, toda a atividade e progresso humanos estão dependentes de estímulos e novos desafios. Sem a vontade de inovar, de procura incessante de novos conhecimentos e competências, sem a capacidade de sonhar ou de abstração, a civilização humana não teria tido o progresso que conhecemos.

É com este espírito que, chegado ao momento presente deste projeto de investigação, não posso deixar de dedicar umas palavras para quem me acompanhou nesta parte do meu caminho.

Ao Prof. Dr. Eurico Monteiro, meu orientador, quero agradecer toda a disponibilidade, competência e orientação neste projeto. Mas, acima de tudo, agradeço o seu estímulo e incentivo, desde que o conheci em 1998, para manter uma atividade de investigação clínica associada à prática médica. O seu exemplo de dedicação e perseverança na prossecução deste desígnio foram aspetos marcantes para a concretização deste projeto. Sem o seu inestimável contributo e estímulo, este “sonho” não se teria tornado realidade.

Ao Prof. Dr. Lúcio Santos agradeço toda a sua disponibilidade em coorientar esta minha dissertação. A sua competência e experiência foram fundamentais principalmente pela sua capacidade em estabelecer pontes e consensos entre diferentes áreas do conhecimento que foram fulcrais para o sucesso deste projeto. A sua notória capacidade de conciliar e concretizar diferentes projetos nas várias áreas do conhecimento médico é um dos grandes ensinamentos que esta jornada me concedeu e que certamente será relevante para a continuação do meu caminho.

À Prof.^a Dr.^a Rita Ferreira que amavelmente aceitou coorientar este meu projeto de investigação agradeço todo o apoio, disponibilidade e contribuição científica que me dedicou. O seu trabalho e da sua equipa do Departamento de Química da Universidade de Aveiro foi uma parte essencial no conteúdo científico da investigação realizada.

Quero também agradecer à Dr.^a Catarina Cruz e ao Dr. Pedro Valente pela ajuda concedida na recolha e tratamento das amostras clínicas realizadas aos doentes do presente estudo.

De igual forma, não posso deixar de agradecer a toda a equipa de enfermagem do Serviço de ORL do IPOFG, pela colaboração prestada na colheita dos dados da avaliação de qualidade de vida realizada a todos os doentes deste projeto, salientado em particular a Enf. Lurdes Carvalho como coordenadora e as Enf.^{as} Anabela Machado, Aida e Sandrina.

Finalmente, mas não menos importante, agradeço a colaboração voluntária de todos os doentes que participaram no estudo. Só com o seu contributo foi possível conseguir concluir este projeto de investigação. Por outro lado, todo o esforço e trabalho desenvolvidos teve como objetivo último conseguir proporcionar melhores cuidados e resultados para todos os doentes. É para todos os doentes que dedico este trabalho, esperando que esta investigação possa contribuir para melhorar as suas condições de saúde.

Com o compromisso de continuar a desenvolver todos os esforços para ajudar todos os meus doentes, pretendo continuar o caminho depois deste momento, mantendo a vontade de sonhar...

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LIST OF ABBREVIATIONS

BMI	- Body Mass Index
CEORL-HNS	- Confederation of European Otorhinolaryngology-Head and Neck Surgery
CRP	- C Reactive Protein
ENT	- Ear Nose Throat
EORTC	- European Organisation for Research and Treatment of Cancer
HNC	- Head and Neck Cancer
HRQoL	- Health Related Quality of Life
ICC	- Intraclass Correlation Coefficients
IL-6	- Interleukin-6
IPO	- Instituto Português de Oncologia
IPOPFG	- Instituto Português de Oncologia do Porto Francisco Gentil
MIC	- Minimal Important Change
MID	- Minimal Important Difference
MUST	- Malnutrition Universal Screening Tool
NRI	- Nutritional Risk Index
ORL	- Otorhinolaryngology
QLQ	- Quality of Life Questionnaire
QLQ-C30	- Quality of Life Questionnaire Core 30
QLQ-HN35	- Quality of Life Questionnaire Head and Neck 35
QLQ-HN43	- Quality of Life Questionnaire Head and Neck 43
QoL	- Quality of Life
QoLCPIPOPFG	- Quality of Life Computerised Platform of IPOPFG
QoLFUp	- Quality of Life Follow Up
ROC	- Receiver-Operating Characteristics
TNF-α	- Tumour Necrosis Factor α
VP	- Voice Prosthesis

- The abbreviations contained in the original works are referenced in the respective articles.

LIST OF FIGURES

Figure 1 – Graphic output of QLQ-C30's scores from the Quality of life computerised platform of IPOPFPG

Figure 2 – Graphic output of Quality of life follow-up from the Quality of life computerised platform IPOPFPG

- The figures contained in the original works are referenced and captioned in the respective articles.

SUMMARY

Head and neck cancer involves organs and systems that are important for various vital functions as well as for the patients' relationship life. Functions related to swallowing and breathing can be conditioned either by the disease or by the different therapeutic modalities. Likewise, speech, physical appearance or socialization are potentially affected in these patients, causing a negative impact in psychological, social and quality of life aspects. These patients have specific needs that are different from other cancer patients, assuming, in this context, particular relevance the assessment of quality of life.

However, despite the progress made in the treatment of head and neck cancer, the overall survival of patients remained unchanged. In this context, the quality of this survival is an important issue to be considered when deciding on the treatment and, therefore, aspects related to quality of life are fundamental in the decision between treatments, especially when considering similar survival rates.

On the other hand, these patients, due to the limitations imposed by the disease or its treatments or the impact of changes at the molecular level resulting from the evolution of the oncological process, develop states of metabolic deficiency, often leading to cachexia. This multifactorial syndrome is related to unintentional weight loss and loss of muscle mass and fat. Its incidence in head and neck cancer is important and is not only related to deficient food intake due to the disease's impact on vital functions. A complex disturbance in the patient's normal metabolism triggers a persistent inflammatory state and a shift in metabolic balance towards catabolism, primarily affecting skeletal muscle. This leads to severe impairment of the functional, emotional and social status and quality of life of patients, compromising the response to treatment and the prognosis of the disease. The evaluation of these processes through biochemical or molecular markers is important to determine the clinical status related to the oncological disease.

Current scientific evidence confirms these changes related to cachexia in cancer patients, however the relationship between these parameters from a clinical perspective is not evident and the most recent reviews refer a necessity for this assessment.

In order to analyse the importance of quality of life and the determination of biochemical markers in the clinical assessment of cachexia in head and neck cancer patients, this research project was developed.

The study involved three lines of research: 1) importance of quality of life assessment in head and neck cancer patients and the relevance of quality of life questionnaires; 2) role of quality of life assessment on nutritional imbalance in head and neck cancer patients; 3) clinical evaluation of cachexia in head and neck cancer patients considering constitutional,

nutritional, biochemical and quality of life parameters. Different studies were developed in the various phases of the project according to the proposed objectives.

The results obtained by this project showed that biochemical markers and quality of life are important in the assessment and clinical management of cachexia in head and neck cancer patients. The evidence shown by our study allows us to conclude that the development of clinical protocols with the introduction of quality of life evaluation and the determination of biochemical markers is extremely relevant for the assessment and follow-up of these patients. The implementation of the methodology proposed by our project will permit an early identification of cachexia in head and neck cancer patients, promoting clinical interventions for an adequate treatment of patients, improving their global status, prognosis and quality of life.

RESUMO

O cancro da cabeça e pescoço envolve órgãos e sistemas importantes para diversas funções vitais bem como para a vida de relação. Funções relacionadas com a deglutição e a respiração podem ser condicionadas quer pela doença, quer pelas diferentes modalidades terapêuticas. De igual forma, a fala, o aspeto físico ou a socialização são potencialmente afectados nestes doentes, condicionando impacto negativo do ponto de vista psíquico, social e na qualidade de vida. Estes doentes apresentam necessidades específicas e bastantes particulares das de outros doentes oncológicos, assumindo, neste contexto, particular relevância a avaliação da qualidade de vida.

No entanto, apesar das evoluções verificadas no tratamento do cancro da cabeça e pescoço, a sobrevivência global dos doentes tem vindo a manter-se mais ou menos sobreponível. Neste contexto, a qualidade desta sobrevivência é uma questão importante a ser equacionada na decisão do tratamento e, portanto, aspetos inerentes à qualidade de vida são fundamentais na decisão entre tratamentos, principalmente se tivermos em conta taxas de sobrevivência semelhantes.

Por outro lado, estes doentes, pelas limitações impostas pela doença ou seus tratamentos ou, pelo impacto das alterações a nível molecular decorrentes da evolução do processo oncológico, desenvolvem estados de carência metabólica conduzindo muitas vezes a caquexia. Esta síndrome multifactorial está relacionada com perda de peso não intencional, perda de massa muscular e gordura. A sua incidência no cancro da cabeça e pescoço é importante e não está relacionada apenas com a ingestão deficiente de alimentos devido ao impacto da doença nas funções vitais. Um distúrbio complexo no metabolismo normal do doente desencadeia um estado inflamatório persistente e uma mudança no equilíbrio metabólico no sentido do catabolismo, afetando principalmente o músculo esquelético. Isso leva a grave comprometimento do estado funcional, emocional e social e, da qualidade de vida dos pacientes, comprometendo a resposta aos tratamentos e o prognóstico da doença. A avaliação destes processos através de marcadores bioquímicos ou moleculares é importante para determinar o estado clínico referente à doença oncológica.

A evidencia científica atual confirma estas alterações relacionadas com a caquexia nos doentes oncológicos, contudo a relação entre esses parâmetros do ponto de vista clínico não é evidente e as revisões mais recentes referem a necessidade desta avaliação.

Com o objetivo de analisar a importância da qualidade de vida e a determinação dos marcadores bioquímicos na avaliação clínica da caquexia em doentes com cancro da cabeça e pescoço desenvolveu-se o presente projeto de investigação.

O estudo envolveu três linhas de investigação: 1) importância da avaliação da qualidade de vida nos doentes com cancro da cabeça e pescoço e relevância dos questionários da qualidade de vida; 2) papel da qualidade de vida na avaliação e orientação dos distúrbios nutricionais nos doentes com cancro da cabeça e pescoço; 3) avaliação clínica da caquexia nos doentes com cancro da cabeça e pescoço em termos constitucionais, nutricionais, bioquímicos e qualidade de vida. Diferentes estudos foram desenvolvidos nas várias fases do projeto de acordo com os objetivos propostos.

Os resultados obtidos por este projeto mostraram que os marcadores bioquímicos e a qualidade de vida são importantes na avaliação e na orientação clínica da caquexia nos doentes com cancro da cabeça e pescoço. A evidência demonstrada pelo nosso estudo permite concluir que o desenvolvimento de protocolos clínicos, com a introdução da avaliação da qualidade de vida e a determinação de marcadores bioquímicos mostra-se extremamente relevante para a avaliação e seguimento destes doentes. A implementação da metodologia proposta pelo nosso projeto, poderá permitir a identificação precoce da caquexia nestes doentes, promovendo intervenções clínicas para um adequado tratamento dos doentes, melhorando o seu estado global, o prognóstico e a qualidade de vida.

INTRODUCTION

Head and neck cancer is the 6th most common cancer in the world, and it represents 1 to 2% of all cancers. According to *The Global Cancer Observatory* (March 2021), in Portugal, in 2020, over 2500 new head and neck cancer cases were diagnosed (about 4% of all new cancer cases) with an annual incidence of 26/100.000.

Head and neck cancers are mainly squamous cell carcinomas, arising in the mucosa of the superior aerodigestive tract located in the head and neck region, including nose, oral cavity, pharynx and larynx. These areas are important for vital functions like breathing, eating, tasting or smelling that can be compromised by the disease or by treatment. Also, voice and speech, body image, emotional aspects and socialization can be seriously affected, with a negative impact in social and psychic aspects of patients' life. Consequently, head and neck cancer patients have specific needs that are often beyond those of patients with other types of cancers, with relevant impact on the quality of life.

In cancer patients, the most important outcome is survival. In head and neck cancer patients, although treatment options observed in the last decades, overall survival didn't change significantly, namely for larynx cancer and for recurrent or metastatic disease. Overall survival at five years for all sites and stages is about 65%. Considering this, the quality of survival is a major issue in the treatment selection for each patient and so, quality of life aspects are important when deciding between treatments, mainly when similar survival rates are considered.

In this unique context, the evaluation of quality of life has major importance in head and neck cancer patients, particularly if associated in the clinical evaluation of outcomes, in the follow-up and prognosis.

On the other hand, the impact of head and neck cancer on the global status of patients is important, contributing to a progressive worsening of physical, emotional and social conditions with a major impact in the quality of life.

Cachexia is a multifactorial syndrome related with loss of skeletal muscle and fat mass mostly related with cancer. In cancer the incidence of cachexia is important, and more than 50% of patients with advanced disease have important weight loss and cachexia.

The establishment of this syndrome, considerably affects prognosis of the disease and has a negative impact in the response to treatments, increasing toxicities and complications. These aspects conduce to a poor overall survival and cachexia is estimated to be associated to 20% of all-cancer related deaths.

Metabolic changes observed in cancer patients are due not only to the limitations imposed by the disease or treatments that limit an adequate intake of nutrients, but the

disease itself may induce changes at cellular and molecular levels, leading to a state of cachexia. This multi-factorial paraneoplastic syndrome leads to progressive weight loss and to a permanent inflammatory response.

Weight loss is often observed when the first signs of disease appear, and when this loss reaches 30% of the premorbid weight it's generally fatal due to generalised weakness and respiratory muscle failure.

The inflammatory response is related to an accentuated catabolism that is mediated by factors released by the tumour and the host. These mediators seem to induce an imbalance between protein synthesis and degradation, leading to protein depletion and, consequently, loss of muscle mass, the degree of which is inversely correlated with patients' lifespan.

Overall, cancer cachexia is a multifactorial syndrome with impact in physical function, quality of life, treatment response and prognosis.

Cachexia definition has evolved through time, particularly in last years, in relation to increased research in this field. Despite this progression, cachexia definition and its diagnostic criteria are still somewhat controversial. Actual evidence points that assessment of BMI, percentage weight loss, quality of life, biochemical markers, energy expenditure and body composition, are needed to measure cachexia and to implement treatment options. Nevertheless, the specific importance of these factors is not clear in the literature and recent studies report the need for further research.

The present project was designed to characterize cachexia in head and neck cancer and to elucidate the importance of quality of life and biochemical markers in the assessment of head and neck patients with cachexia.

The results of this research may contribute to the elaboration of a clinical protocol for screening the cachexia status in this specific group of patients.

The early identification of cachexia, might promote an early intervention in these patients, initiating clinical strategies to improve patient status, preventing refractory cachexia, leading to a better adhesion and response to treatments and reducing toxicities and complications. If we achieve valid results, by this way we will be able to improve survival outcomes and the quality of life in head and neck cancer patients.

RATIONAL AND AIMS

In the last 25 years I dedicate my clinical practice to treat patients in the medical speciality of otorhinolaryngology. Very early in my specialization, still in the beginning of the otorhinolaryngology residency, I decided that my first purpose was to be involved in the treatment of head and neck oncologic patients. I must state here that the most important influence for this purpose was to have met and had the honour to work, in 1998, during my first oncological internship at the Department of ORL of the IPOPGF, with Prof. Dr. Eurico Monteiro. The opportunity to have a daily experience observing the skills, the dedication and scientific commitment of Prof. Dr. Eurico Monteiro with the head and neck cancer patients was crucial in my decision in pursuing the goal of dedicating my clinical life to head and neck oncological patients.

Another aspect I owe to Prof. Dr. Eurico Monteiro example, is the commitment to develop clinical research along with the clinical practice. A particular topic of my clinical intervention was to develop clinical research that could allow me to understand some aspects of quality of life important for the clinical practice and to achieve better clinical results.

My curiosity and interest in aspects related with quality of life in patients with head and neck cancer begins in 2007. When I began working in the Department of ORL of the IPOPGF, I found a well-structured Department where the introduction of HRQoL evaluation in the clinical practice was already implemented. Different projects were running, particularly the development of a computerised platform, to improve the application of this methodology. Having encountered this context and encouraged by my Director, Professor Doctor Eurico Monteiro, I started developing a lot of projects within the scope of analyse HRQoL in patients with head and neck cancer. Due to this interest, and since 2012 I've integrated the Group of Quality of Life of the EORTC in representation of the Department of ORL of the IPOPGF.

This experience has shown me that patients with head and neck cancer have needs that go beyond the simple treatment of the disease. Disease or its treatments have an important impact in patients, conditioning physical, psychological, family and social aspects that are reflected in their quality of life. On the other hand, changes in the quality of life of patients can highlight changes from the patient's clinical point of view, as an indicator of disease aggravation or as an indicator of response to treatments.

Also, head and neck cancer, like many other chronic diseases, conduces to a deterioration of patients' general condition, resulting in weight loss and consequent decline in functions that can progress to cachexia. This status of cachexia, when instituted, affects

negatively the prognosis of the disease and can be a limiting factor for the success of treatments. This multifactorial syndrome also has a negative impact on patients' quality of life.

Literature characterizes and identifies changes related to cachexia in patients, in terms of weight, nutrition, biochemistry and in terms of quality of life. However, the relationship between these parameters from a clinical perspective is not evident and the most recent reviews refer a necessity for this assessment.

In this context, in head and neck cancer, quality of life seems to be determinant to cachexia evaluation and measure. On the other hand, head and neck cancer patients have nutritional impairment due to multiple causes, including deficient intake of food, metabolic changes induced from the disease or comorbidities (hepatic alcoholic disease) conducting to a permanent inflammatory state reflected in biochemical markers levels. The analysis of these two parameters, quality of life and biochemical markers, in the cachexia evaluation in head and neck cancer seems to us of major importance.

In order to analyse the importance of these parameters in the clinical assessment of cachexia in patients with head and neck cancer, an investigation was developed according to the following lines:

1 - Quality of life assessment in patients with head and neck cancer

a) - Beginning with the experience acquired with clinical practice and with some projects in the field of quality of life in head and neck cancer developed in our department, firstly we've studied the assessment of quality of life in head and neck cancer patients.

Laryngeal cancer was selected because is one of the head and neck cancer locations where the impact on quality of life is more evident due to its relationship with voice impairment. Although voice and speech aren't vital functions, they are important to human relationships. The acquisition of language by humans led to development of cognitive functions and socialization, important contributions to the establishment of human civilization.

Head and neck cancer involving larynx often conduce to voice impairment and in most of the patients' treatments imply deterioration or even total loss of voice capacity.

Unfortunately, total laryngectomy is still the standard treatment in most of the patients with laryngeal or pharyngolaryngeal cancers. This radical surgery totally removing the larynx leave patients with total loss of his voice capacity. Different types of voice rehabilitation are available with different outcome rates.

Loss of voice capacity is of major importance in the quality of life of patients and so a good voice rehabilitation is crucial for quality of life improvement. In this context, evaluation of outcomes of patients submitted to total laryngectomy is a good evidence of the importance of quality of life evaluation in head and neck cancer patients.

A retrospective study was designed to evaluate the impact of voice rehabilitation in laryngectomised patients' quality of life.

b) - Analysing this group of patients we feel that a good and actual instrument that evaluate clinical aspects is of major importance to have good clinical perception of quality of life and achieve the better clinical results.

Treatment options has changed in the last years in head and neck cancer with the introduction of new drugs, the implementation of new surgical techniques like laser and robotics or with new radiotherapy techniques. These changes significantly alter the impact on the quality of life of patients. In this field we have the perception that questionnaires of quality of life might need some actualization.

Considering this, the EORTC Quality of Life Group initiated a process of actualization of the specific head and neck cancer module of the EORTC quality of life questionnaires. So, a new questionnaire was developed – the EORTC QLQ–HN43 [Appendix I].

As an active member of the EORTC Quality of Life Group, we developed an international multicentre prospective study in two steps:

1 - Beginning with a list of 60 items, the translation of all items to Portuguese language was done following a standardized forward-backward procedure.

Then, following a prospective international multicentre study protocol, 20 Portuguese patients with head and neck cancer were enrolled. They answer the questionnaire with the 60 new items and the EORTC QLQ-C30. Afterwards, in the same visit, patients were asked about items not completely understandable and how they might address those items, about eventually missing items and enumerating the most important items.

The study has permitted to select 43 items with good accuracy and creating the new module.

2 - The second study, a phase IV study, had the objective to validate the new questionnaire developed in the previous stage: the EORTC QLQ-HN43 [Appendix I]. Following a prospective, international and multicentre protocol, 42 Portuguese patients with head and neck cancer were enrolled. The study protocol intended to test the psychometric properties of the new questionnaire. The patients were divided in two groups. The first one (included 40 Portuguese patients) with patients just about to start treatment and the second

one (included 2 Portuguese patients) with patients with a minimum survival of 24 months and disease free. All locations, stages and treatments were included.

The first group of patients were evaluated at 3 different time points, before treatment, 3 and 6 months after treatment to test the questionnaire's response to change. The second group of patients were evaluated twice, with the second evaluation time taking place one week after the first one, to measure test-retest reliability.

These studies provided an actual and accurate questionnaire for evaluation HRQoL in head and neck cancer patients that were applied in the next steps of this present work.

2 - Quality of life and assessment of nutritional imbalance in patients with head and neck cancer

Nutritional impairment is frequently seen in head and neck cancer patients at first clinical presentation. This condition is determinant in patients' treatment and quality of life results. Early identification of the patients at risk is crucial in improve outcomes and patients' HRQoL.

A retrospective study enrolled 114 head and neck cancer patients grouped according to nutritional index defined by the score of the MUST and HRQoL evaluated using the EORTC QLQ-C30.

This study aimed to demonstrate the role of quality of life evaluation in the screening of nutritional impairment in head and neck cancer patients and as potential use in the clinical follow-up of these patients.

3 - Clinical evaluation of cachexia in patients with head and neck cancer considering weight, nutritional, biochemical and quality of life parameters

Malnutrition in head and neck cancer is a condition related to a cachexia status with impact in disease prognosis and quality of life of the patients. The importance of different parameters in the assessment of cachexia is already studied and described in the literature. Nevertheless, the relationship between all these parameters and their specific usefulness in the cachexia evaluation hasn't yet been clear, namely in head and neck cancer.

Our purpose in this research was to determinate and clarify the relevance and importance both of quality of life and biochemical markers in patients with cachexia.

A prospective study was done trying to understand the inter-relations of these parameters (weight, nutritional, biochemical and quality of life) on a clinical basis. Head and neck cancer patients were enrolled and grouped according to the presence or not of cachexia. All clinical, nutritional, biochemical and quality of life were considered and compared between groups. A medium follow-up of 48 months was considered to evaluate overall survival.

RESULTS

The results of the different steps of this dissertation originated different scientific papers. The following papers are presented as they were published:

- Quality of Life Assessment in Total Laryngectomized Patients Rehabilitated with Voice Prosthesis.

Published:

Silva J. C., Reis S., Viana R., Monteiro E.

Quality of Life Assessment in Total Laryngectomized Patients Rehabilitated with Voice Prosthesis.

J Otolaryngol ENT Res. 2017;6(5): 00178.<https://doi.org/10.15406/joentr.2017.06.00178>

- Measuring quality of life in patients with head and neck cancer: Update of the EORTC QLQ-H&N Module, Phase III.

Published:

Singer S., Araújo C., Arraras J. I., Baumann I., Boehm A., Herlofson B.B., Castro Silva J, Chie WC, Fisher S, *et al.*

Measuring quality of life in patients with head and neck cancer: Update of the EORTC QLQ-H&N Module, Phase III.

Head & Neck. 2015;1358-1367. <https://doi.org/10.1002/hed.23762>

- International validation of the revised European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43: Phase IV.

Published:

Singer S., Amdal C. D., Hammerlid E., Tomaszewska I.M., Castro Silva J., Mehanna H., Santos M., *et al.*

International validation of the revised European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43: Phase IV.

Head & Neck. 2019;1–13. <https://doi.org/10.1002/hed.25609>

- Head and Neck Cancer Early Identification of Malnutrition High Risk Patients and Quality of Life Optimization.

Published:

Silva, J.C., Silveira, A., Sacau, A., Monteiro, E. and Sequeira, T.

Head and Neck Cancer Early Identification of Malnutrition High Risk Patients and Quality of Life Optimization.

International Journal of Otolaryngology and Head & Neck Surgery. 2019;8, 204-216.

<https://doi.org/10.4236/ijohns.2019.86023>

- Health Related Quality of Life and Biochemical markers for Cachexia evaluation in Head and Neck Cancer patients.

Published:

Castro Silva, J., Tavares, P., Ferreira, R., Santos, L.L., Monteiro, E.

Health Related Quality of Life and Biochemical markers for Cachexia evaluation in Head and Neck Cancer patients

International Journal of Otolaryngology and Head & Neck Surgery. 2021;10, 320-335.

<https://doi.org/10.4236/ijohns.2021.104029>

Quality of Life Assessment in Total Laryngectomized Patients Rehabilitated with Voice Prosthesis

ABSTRACT:

To correlate voice prosthesis devices (VP) with voice intelligibility and quality of life in laryngectomized patients (QoLLP).

Methods: C30 and H&N35 quality of life questionnaires *European Organization for Research and Treatment of Cancer* (EORTC) and Harrinson Robillard-Schultz Rating Scale for tracheoesophageal voice were used to evaluate 61 patients submitted to total laryngectomy or pharyngolaryngectomy and rehabilitated with primary or secondary voice prosthesis (VP).

Results: A moderate but statistically significant correlation between the regular use of VP and voice intelligibility was verified. No statistically significant differences for major rating/items of assessment questionnaires of Quality of Life (QoL) according to the use of VP neither for the existing patients who have placed primary/secondary VP.

Conclusion: Patients who present a more intelligible speech are the ones who usually use VP. QoL items constipation, taste and smell, speech, social contact and sexuality showed significantly better levels in those patients who used more frequently VP. Voice rehabilitation using VP considerably improves QoL and social reintegration of laryngectomized patients and so we consider this method as an effective option for the rehabilitation of our patients

Quality of Life Assessment in Total Laryngectomized Patients Rehabilitated with Voice Prosthesis

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Keywords: Quality of life; Laryngectomies; Voice prosthesis; VP; EORTC; QoL; TL; HRQoL; TEV; Provox

Research Article

Volume 6 Issue 5 - 2017

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Received: November 05, 2016 | Published: April 12, 2017

Abbreviations: EORTC: European Organization for Research and Treatment of Cancer; VP: Voice Prosthesis; QoL: Quality of Life; TL: Total Laryngectomy; TEV: Tracheo Esophageal Voice

Introduction

Total laryngectomy (TL) is a traditional surgical procedure directed to patients with larynx and/or hypopharynx tumors in advanced stage, and is associated to deep anatomical and physiological modifications, that include loss of laryngeal voice, swallowing problems, loss of nasal function with changes in smell and taste, loss of cough reflex and several other changes in pulmonary functions. Moreover, this procedure has important psychological consequences for all patient's life [1]. TL can be applied in the treatment of laryngeal tumors, or may be associated with radiotherapy or chemoradiotherapy treatments. These treatments options are usually associated with several secondary effects, with important physical and psychological impact, and consequent alterations in the well-being and socialization [2]. Laryngectomies patients have profound changes in the verbal capacity that affects in a large scale their communication abilities [3].

Vocal rehabilitation of these patients has been a vital subject over the last decades, tending the actual interest in QoL related questions [3]. Nowadays, professionals who work in oncologic institutions try to give to the patients a similar quality of life they

had before the disease, based in patterns of QoL evaluation. This tendency is also applied to laryngectomies patients. For these patients, factors such as phonation, swallowing, breathing and aesthetics are relevant questions.

QoL is a relatively new concept in oncology practice, however not a common concept in assessing head and neck oncologic treatment results in Portuguese patients [4]. According to the World Health Organization, QoL is expressed by the individual perception of their position in life, in the context of cultural systems and values, in relation to their goals, expectations, standards and concerns. When applied to the health context, this concept is defined as "Health-Related Quality of Life (HRQoL)", translating the impact of the disease and treatments in patient's personal, professional and sociocultural domains. The QoL and HRQoL concepts are related but the latter is directly related to the disease and its treatment [5]. There are several organizations addressing this theme and some of them responsible for the creation of QoL assessment scales in oncology. EORTC is one of these organizations focused to oncologic diseases trying to correlate patients' survival patterns with their QoL.

In order to attain the above mentioned objectives, this organization has developed several QoL assessment scales, such as QLQ-C30 (applied to all cancer types) and QLQ-H&N35 (specific module for head and neck tumors) [5].

Over the years, several methods of vocal rehabilitation for laryngectomies have been developed, such as oesophageal voice, electrolarynx and, more recently, tracheoesophageal voice (TEV) (Jongmans et al. 2006). Overall methods, TEV is the one that shows better results in terms of voice quality, with low rate of complications, so that currently many oncological centers use this option for vocal rehabilitation opposed to oesophageal voice [1].

TEV is the combination of three factors: expiratory air flux directed to the phonatory prosthesis, neoglottis and/or effects of the remaining structures vibration and physiologic aspects of the upper respiratory system.

Success rate of these devices is between 50% and 90% (Jongmans et al. 2006; Bussu et al. 2011). Insertion of VP may be done during the laryngectomy (primary) or in a second time (secondary), usually after the end of complementary treatment [1]. After the placement of the VP, patients are generally referred to Speech Therapists, in order to achieve or improve their vocal quality, so that they can reach an acceptable and intelligible speech, achieving a way to make themselves be orally understood.

Voice generated by non-laryngeal structures is characterized by changes in the acoustic basis, which brings implications on perception. These changes reduce intelligibility patterns and are also a limitative aspect to psychosocial and communicative levels. Another factor which generally influences communication is the regularity of the VP use, associated with some factors such as the diameter and shape of tracheostomy hole, presence of respiratory problems and the ability to do an effective occlusion of the stoma [6].

The results of VP use may be assessed through the Harrinson Robillard-Schultz Rating Scale for tracheoesophageal voice that divides this parameter in 5 items, from the non-use to the use of the VP as the elective communication mean [7].

Methodology

The objective of the analysis is to collect information about QoL of total laryngectomies rehabilitated with VP, relating the results with the utilization regularity, voice intelligibility patterns and the timing of placement of the device. So all the patients selected were rehabilitated with VP and a control group wasn't needed.

This study include 61 total laryngectomy patients from the Otolaryngology Department of the Portuguese Institute of Oncology Francisco Gentil in Porto, Portugal (IPOPPG, EPE), rehabilitated in terms of voice and who frequent Speech Therapy and Otolaryngology periodic consultations. From these 61 patients, two were excluded, one that abandoned Speech Therapy regular follow-up and the other due to the deterioration of health conditions because of tumor relapse. All the participants were rehabilitated through the placement of a model Provox® VP.

This analysis includes patients submitted to total laryngectomy or pharyngolaryngectomy with an average time of use of the VP equal or superior to three months. Patients under 18 years of age were excluded (ethical reasons/0 patients), as well as those who had physical limitations with implications in participating in the study and those who were rehabilitated in other institutions.

Sample characteristics are shown in Table 1.

Table 1: Sample characterization.

Qualitative Variables	n (%)	Quantitative Variables	Average ± Divert -Pattern
Sex		Age	63.07 ± 10.20
Male	53 (89.83%)	Time (months) after VP placement until the applying of measurement instruments	29.98±31.43
Female	6 (10.17%)	Number of sessions of Speech Therapy	14.17±9.68
Tumor Location			
Larynx	51 (86.44%)		
Hipopharynx	6 (10.17%)		
Oropharynx	2 (3.39%)		
Surgery Type			
Total Laryngectomy	46 (77.97%)		
Total Pharyngolaryngectomy	13 (23.03%)		
Additional Treatment			
Yes	45 (76.27%)		
No	14 (23.73%)		
VP Placement			

Primary Puncture	41 (69.49%)		
Secondary Puncture	18 (30.51%)		
Type of Occlusion of the Tracheostomy			
Digital Occlusion	16 (27.12%)		
Simple Fenestrated cannula Portex®	3 (5.08%)		
Simple fenestrated cannula Provox® with heat and moisture exchanger (HME)	35 (59.32%)		
Adhesive with HME Provox®	4 (6.78%)		
Larybatton with HME Provox®	1 (1.69%)		
Tumor Relapse			
Yes	4 (6.78%)		
No	55 (93.22%)		

Assessment Instruments used in this study were QLQ-C30 (version 3), QLQ-H&N35 (version 4) and for items of intelligibility and use of the device the Harrinson Robillard-Schultz Rating Scale.

QLQ-C30 (version 3) incorporates five functional scales (physical, performance, cognition, emotional and social), three symptoms scales (fatigue, pain, nausea and vomits), the global status of QoL, health and six simple items to assess symptoms and other problems (dyspnea, loss of appetite, insomnia, financial difficulties, constipations and diarrhoea).

QLQ-H&N35 adds seven symptoms scales (pain, swallowing, taste and smell, speech, eating in public, social contact and sexuality) and 11 simple items.

Both QoL questionnaires used are translated into European Portuguese, and QLQ-C30 is certified for the same language [8].

Harrinson Robillard-Schultz Rating Scale for tracheoesophageal prosthesis is defined for its success rate in three parameters: use (level in which TEV is used as first mean of communication), intelligibility (ease to produce TEV and its effects in speech intelligibility) and hygiene care (patient's autonomy and professional help in the maintenance of fistula and VP). This scale is translated into Portuguese, but not certificated [7].

After approval by the Ethics Commission of IPOPPG, EPE, the project was implemented in the ORL Department. At first, patient's clinical processes were analysed, and the following information was collected: age, sex, tumor location, type of surgery, complementary treatments, VP placement opportunity, mean time of use of VP, number of speech therapy sessions and current health stage of the patients.

In order to apply QoL questionnaires and, to assess intelligibility and use of VP items and the method of tracheostomy occlusion, a Speech Therapy appointment was scheduled. An authorization was requested to all patients, through an informed consent about the extent, framework, objectives and relevance of the study.

QoL questionnaires were filled by the patients, without any supervision, and in a few cases they were sent by e-mail. In cases in

which patients had eye and/or motor difficulties, or in cases they denied to answer alone, the researchers filled the questionnaires after the patient's answer to each question.

The rating scale and QoL questionnaires were scored according to the application manual of each instrument.

The analysis software used for analysis was SPSS version 20.0. Spearman correlation was calculated to correlate the variables of use and the intelligibility of VP. Anova was applied in a number of independent samples, as well as the Kruskal-Wallis test, depending on whether the assumptions were accomplished or not, with the objective of verifying whether the level of QoL was different on the basis of VP utilization. Some items and ratings were under multiple comparisons. U Mann-Whitney test were used to collect information between the placement of VP and QoL. In all statistic procedures a significance level of 0.05 was used.

Results

Table 2 depicts the results of the correlation between the use of TEV (U1: never uses the TEV; U2: uses TEV less than 50% of the time; U3: Uses TEV between 50% and 80% of communication opportunities; U4: uses TEV as the main communication mean) and voice intelligibility (I1: incapable of producing sound; I2: voice too tense or too blowing, being impossible to use in conversation; I3: the stoma is often poorly occluded resulting in a air leakage, which interferes with the intelligibility of speech; I4: the voice is mildly tense or gently blown, but it is possible to use in conversation, the stoma occlusion is generally good, and the speech is intelligible; I5: voice is easily produced, with good stoma occlusion and intelligible voice).

The Spearman coefficient was statistically significant ($p = 0.000$). I.e., the level of TEV intelligibility rises with the use of VP. Most part of the patients who produce voice easily uses VP as elective mean of communication.

Spearman correlation value is moderate and positive, $r (59) = 0.677$, $p < 0.05$, which means a high dependency level between the variables.

Tables 3-6 present the results of the comparison between the level of QoL and the use of TEV. It was reported that the QoL level is similar for major scales/items of questionnaires QLQ C30 and QLQ H&N35, independently of the use of VP. Nevertheless, it was also observed that for items: Constipation ($p=0.028$), Taste and Smell ($p=0.012$), Speech ($p=0.000$), Social contact ($p=0.007$), and Sexuality ($p=0.034$) patients who use VP have a higher level of QoL, comparing to those who use the device less often.

Tables 7 & 8 show the results of the comparison of QoL levels between the patients who placed primary/ secondary VP. The results of the Mann-Whitney and U test show there are no statistical significant differences between both groups.

Table 2: Use and Intelligibility of TEV.

Intelligibility	U1	U2	U3	U4	Total
Use of TEV					
I1	5	0	0	0	5
I2	0	1	0	0	1
I3	2	1	1	0	4
I4	2	4	3	7	16
I5	0	2	5	26	33
Total	9	8	9	33	

Table 3: EORTC-QLQ C30 questionnaire on the basis of the use of TEV.

EORTC-QLQ C30/Use of TEV		U1 (n=9)			U2 (n=8)			p
		A±DP	Aver.	AIQ	A±DP	Aver.	AIQ	
Functional Rating	Physical	64.6±20.9	67.0	37	76.5±23.8	80.0	40	0.068
	Performance	83.3±27.5	100.0	25	81.3±24.3	91.5	33	0.512
	Social	70.3±26.1	67.0	50	95.8±7.9	100.0	13	0.063
	Emotional	75.0±23.0	75.0	38	80.3±19.5	87.5	38	0.809
	Cognitive	79.6±24.7	83.0	42	95.8±7.9	100.0	13	0.499
Symptoms Rating	Fatigue	35.3±29.2	42.0	33	15.1±16.6	11.0	28	0.104
	Pain	35.1±34.7	33.0	75	22.9±36.7	0.0	46	0.167
	Nausea and Vomit	5.6±11.7	0.0	9	12.5±35.4	0.0	0	0.985
	Global Status of health	54.6±22.5	58.0	21	66.8±33.3	75.0	56	0.111
Simple Items	Dyspnea	18.3±17.4	33.0	33	8.3±15.3	0.0	25	0.137
	Loss of appetite	14.8±24.2	0.0	33	12.5±35.4	0.0	0	0.546
	Insomnia	22.2±37.3	0.0	50	20.9±39.7	0.0	50	0.963
	Financial Difficulties	22.1±23.6	33.0	33	8.4±23.7	0.0	0	0.409
	Constipation	33.3±44.1	0.0	84	25.0±38.9	0.0	59	0.028
	Diarrhoea	7.4±22.3	0.0	0	4.1±11.7	0.0	0	0.823

Table 4: EORTC-QLQ C30 questionnaire on the basis of the use of TEV.

EORTC-QLQ C30/Use of TEV		U3 (n=9)			U4 (n=33)			p
		A±DP	Aver.	AIQ	A±DP	Aver.	AIQ	
Functional Rating	Physical performance	81.6±14.1	87.0	17	81.8±15.0	87	17	0.068
	Social	87.0±27.3	100.0	17	90.4±19.6	100.0	9	0.512
	Emotional	88.9±33.3	100.0	0	85.8±20.5	100.0	17	0.063
	Cognitive	82.3±13.6	83.0	21	82.4±21.4	92.0	29	0.809
	Social	88.9±14.3	100.0	25	83.8±31.3	100.0	17	0.499

Symptoms Rating	Fatigue	15.9±16.6	22.0	28	15.4±21.5	11.0	22	0.104
	Pain	16.1±23.6	0.0	33	11.1±20.2	0.0	17	0.167
	Nausea and Vomit	5.6±11.7	0.0	9	3.1±6.7	0.0	0	0.985
Simple Items	Global Status of health	74.1±18.3	75.0	33	75.8±17.4	75.0	21	0.111
	Dyspnea	14.7±17.4	0.0	33	7.0±16.1	0.0	0	0.137
	Loss of appetite	18.4±24.2	0.0	33	12.1±27.4	0.0	0	0.546
	Insomnia	14.8±24.2	0.0	33	18.1±25.1	0.0	33	0.963
	Financial Difficulties	25.8±32.4	33.0	33	20.2±31.2	0.0	33	0.409
	Constipation	33.3±37.3	33.0	67	6.0±15.5	0.0	0	0.028
	Diarrhoea	N.A.	N.A.	N.A.	2.0±8.0	0.0	0	0.823

N.A. = Not available in data, once the sample in these groups was zero.

Table 5: EORTC-QLQ H&N35 questionnaire on the basis of the use of TEV.

EORTC-H&N35/ Use of TEV		U1 (n=9)			U2 (n=8)			p
		A ± DP	Aver.	AIQ	A±DP	Aver.	AIQ	
Symptoms Rating	Pain	29.7±36.1	17.0	59	10.5±14.8	4.0	17	0.385
	Swallowing	43.4±33.3	33.0	55	21.9±33.3	4.0	61	0.111
	Taste and Smell	74.1±33.4	100.0	59	60.4±23.6	58.5	42	0.012
	Speech	53.2±13.7	56.0	29	43.0±24.3	44.0	42	0.000
	Eating in public	35.2	25.0	51	13.6±10.0	17.0	21	0.079
	Social contact	31.0±29.7	33.0	44	15.1±15.5	13.5	27	0.007
	Sexuality	51.8±38.6	50.0	75	52.0±44.0	58.0	92	0.034
Simple Items	Teeth problems	40.8±43.5	33.0	84	8.3±15.3	0.0	25	0.257
	Trismus	22.1±23.6	33.0	33	8.3±15.3	0.0	25	1.00
	Xerostomia	25.9±27.9	33.0	50.0	16.5±17.6	16.5	33	0.784
	Thick saliva	33.3±37.3	33.0	67.0	16.6±35.6	0.0	25	0.380
	Cough	29.7±39.0	0.0	67	41.6±34.6	33.0	59	0.576
	Discomfort	26.0±32.5	0.0	67	12.5±24.9	0.0	25	0.119
	Analgesic consumption	22.2±44.1	0.0	50	25.0±46.3	0.0	75	0.479
	Food supplement	33.3±50.0	0.0	100	12.5±35.4	0.0	0	0.091
	Feeding tube	22.2±44.1	0.0	50	N.A.	N.A.	N.A.	0.162
	Weight loss	44.4±52.7	0.0	100	25.0±46.3	0.0	75	0.192
	Weight gain	22.2±44.1	0.0	50	50.0±53.5	50.0	100	0.500

Table 6: EORTC-QLQ H&N35 questionnaire on the basis of the use of TEV.

EORTC-H&N35/ Use of TEV		U3 (n=9)			U4 (n=33)			p
		A ± DP	Aver.	AIQ	A ± DP	Aver.	AIQ	
Symptoms Rating	Pain	7.3±13.5	0.0	8	6.8±10.6	0.0	13	0.385
	Swallowing	15.8±17.1	8.0	34	16.9±19.6	8.0	25	0.111
	Taste and Smell	51.8±29.4	50.0	42	35.9±28.0	33.0	50	0.012
	Speech	29.4±21.5	33.0	33	16.8±18.9	11.0	22	0.000
	Eating in public	17.7±16.0	17.0	30	12.1±16.6	8.0	17	0.079
	Social contact	14.1±12.2	13.0	24	7.9±13.1	0.0	7	0.007
	Sexuality	42.7±40.9	50.0	84	19.7±25.8	0.0	33	0.034
Simple Items	Teeth problems	11.1±23.6	0.0	17	18.2±32.4	0.0	33	0.257
	Trismus	7.3±14.6	0.0	17	7.1±18.2	0.0	0	1.00
	Xerostomia	25.8±32.4	33.0	33	17.1±22.2	0.0	33	0.784
	Thick saliva	18.4±33.8	0.0	33	23.1±21.2	33.0	33	0.380
	Cough	22.2±29.0	0.0	50	25.2±30.1	33.0	33	0.576
	Discomfort	3.7±11.0	0.0	0	5.0±12.0	0.0	0	0.119
	Analgesic consumption	44.4±52.7	0.0	100	18.2±39.2	0.0	0	0.479
	Food supplement	N.A.	N.A.	N.A.	6.1±24.2	0.0	0	0.091
	Feeding tube	N.A.	N.A.	N.A.	3.0±17.4	0.0	0	0.162
	Weight loss	22.2±44.1	0.0	50	12.1±33.1	0.0	0	0.192
	Weight gain	33.3±50.0	0.0	100	24.2±43.5	0.0	50	0.500

Table 7: EORTC-QLQ questionnaire on the basis of VP placement.

EORTC-QLQ C30/ Time of Surgery		A ± DP		Aver.		AIQ		p
		1 st Surgery n=41	2 nd Surgery n=18	1 st Surgery n=41	2 nd Surgery n=18	1 st Surgery n=41	2 nd Surgery n=18	
Functional Rating	Physical	77.1±18.8	81.4±15.6	80.0	83.5	23	26	0.455
	Performance	85.3±23.0	92.6±20.7	100.0	100.0	25	0	0.120
	Social	85.7±21.0	84.2±28.3	100.0	100.0	17	25	0.737
	Emotional	82.1±20.8	78.3±18.8	83.0	79.0	25	29	0.327
	Cognitive	83.3±26.9	90.7±24.4	100.0	100.0	25	4	0.167
Symptoms Rating	Fatigue	18.3±22.5	18.9±22.3	11.0	16.5	28	35	0.969
	Pain	20.2±29.4	10.3±17.4	0.0	0.0	33	17	0.448
	Nausea and vomit	6.5±17.4	1.9±5.5	0.0	0.0	0	0	0.365
Global Status of health		67.9±22.6	78.2±18.5	67.0	83.0.00	33	35	0.112

Simple Items	Dyspnea	12.9±18.0	3.7±10.7	0.0	0.0	33	0	0.059
	Loss of appetite	13.0±26.7	14.8±28.5	0.0	0.0	17	33	0.855
	Insomnia	19.4±29.8	16.7±26.2	0.0	0.0	33	33	0.765
	Financial Difficulties	19.5±28.9	20.3±30.6	0.0	0.0	33	33	0.980
	Constipation	20.3±32.4	9.2±25.0	0.0	0.0	33	0	0.175
	Diarrhoea	3.24±12.5	1.83±7.8	0.0	0.0	0	0	0.895

Table 8: EORTC-QLQ H&N35 questionnaire on the basis of surgical type variable.

EORTC-H&N35/ Type of surgery		M±DP		Aver.		AIQ		p
		1 st surgery n=41	2 nd surgery n=18	1 st surgery n=41	2 nd surgery n=18	1 st surgery n=41	2 nd surgery n=18	
Symptoms Rating	Pain	10.8±16.9	11.1±23.6	0.0	0.0	17	17	0.894
	Swallowing	24.0±27.0	15.7±19.8	17.0	8.0	38	25	0.334
	Taste and Smell	50.8±30.3	39.8±33.4	0.0	33.0	34	54	0.219
	Speech	31.4±22.6	19.7±24.6	33.0	11.0	39	44	0.054
	Eating in public	16.9±18.0	16.2±25.5	17.0	8.0	25	19	0.442
	Social contact	14.8±19.1	10.1±16.0	7.0	0.0	27	14	0.327
	Sexuality	33.7±36.6	29.7±33.6	33.0	17.0	67	50	0.842
Simple Items	Teeth problems	19.5±29.8	18.5±38.3	0.0	0.0	33	8	0.465
	Trismus	9.7±18.6	9.2±19.1	0.0	0.0	17	8	0.957
	Xerostomia	20.2±24.6	18.4±23.5	0.0	0.0	33	33	0.875
	Thick saliva	21.9±28.5	25.8±26.9	0.0	33.0	33	33	0.461
	Cough	30.9±32.0	20.3±30.6	33.0	0.0	67	33	0.203
	Discomfort	11.3±20.6	3.7±15.8	0.0	0.0	33	0	0.104
	Analgesic consumption	22.0±41.9	27.8±46.1	0.0	0.0	0	100	0.742
	Food supplement	12.2±33.1	5.6±23.6	0.0	0.0	0	0	0.656
	Feeding tube	4.9±21.8	5.6±23.6	0.0	0.0	0	0	1.00
	Weight loss	19.5±40.1	22.2±42.8	0.0	0.0	0	25	1.00
	Weight gain	24.4±43.5	38.9±50.2	0.0	0.0	50	100	0.350

Discussion

The concept of QoL comprises diverse fundamental domains in physical, psychological and social domains. Head and neck cancer patients are vulnerable to many psychosocial problems, once social interactions and emotional expressions depend mainly on structural and functional integrity of important areas. The impact of the diagnoses of head and neck cancer, as well as treatment

consequences, has relevant influence in their lives, affecting their well-being and the QoL.

TL is an adequate treatment option for patients with malignant tumours of larynx and hypopharynx in advanced stages. However, the resulting functional limitations (physical, psychological, social and emotional alterations) influence patient's perception about his/her own QoL. The way each patient deals with the diagnoses of

a malignant tumour, the surgical procedure and its consequences depends on factors such as age, sex, economic condition, familiar support, psychological strategies, as well as the time elapsed after the surgery [9]. Collected data from our patients show that those who use TEV as first mean of communication have a more intelligible speech. Speech Therapy after TL has the objective to help vocal rehabilitation of patients, improving their phonatory performance and speech intelligibility, providing fluency and intelligibility to the voice, contributing to the improve the communication and QoL [3].

From the three voice rehabilitation methods, TEV is the most similar to laryngeal voice in its acoustic and perceptive characteristics. So, using VP in all communicative contexts, laryngectomies patients will improve their verbal ability and improve speech intelligibility.

Results obtained between the level of TEV use and QoL reveal that, for the major part of the applied questionnaires, QoL was not influenced by the use of VP.

The inability of oral expression, the presence of a permanent tracheostomy and the fear of a tumor relapse are the most devastating consequences of TL, and all these contribute in a significant way to the inadequate perception of QoL by these patients. People's life suffers a drastic change. Breathing becomes affected by the tracheostomy, raising the risk of pulmonary infections, besides inhering in social interaction patterns. Taste and smell also suffer many changes, once the lack of larynx limits the airway through upper areas, influencing these senses. In terms of social contact and interaction, patients experiment communicative difficulties, both with people they known or with strangers. Thus, the loss of laryngeal voice causes invariably many disadvantages in psychological, social and economic levels.

It has been found that some patients who have good speech intelligibility refer not to use VP with regularity, aspect that we would not expect and consequently will induce a decrease in the perception of QoL. According to the patients and our evaluation, the less use of TEV as first mean of communication is due to the difficulty of occlusion of the tracheostomy owing to its shape (eg: large, deep or irregular tracheostomy), the presence of chronic obstructive pulmonary pathology, side effects of complementary treatments as radiotherapy or chemoradiotherapy, financial problems that enable the acquisition of support systems, and absence of communication interest as a result of social isolation, aspects that are in agreement with the literature.

Nevertheless, it was verified that for the items: constipation, taste and smell, sexuality, speech and social contact, patients who use TEV as preferential means of communication have higher QoL level. These differences in appreciation of QoL, notwithstanding the small relevance of this study, may be based on several factors. With regard to the communication ability, the fact that patients who use usually TEV find it easier to communicate [10]. Considering the social contact aspects, differences may occur because patients who use TEV more often, do not isolate themselves, and so don't allow that the presence of a TL and consequent voice deprivation as a limitative factor. Regarding the taste and smell, while training for acquisition of TEV, patients suffered vocal resonant cavities activation, causing a predictable

impact in olfactory rehabilitation. This fact may explain the differences observed. About constipation, differences are not clinically explained by the results obtained. Finally, differences verified on the sexuality item, may be explained by the lack of interest and sexual pleasure conditioned by oncologic treatments and by the disease itself, but we can predict some greater interest due to the best communication skills of patients [10].

Actually, it was not found in literature any study analysing the relation between TEV and QoL. However, many studies show that VP is an invaluable help for these patients, insofar as it promotes their self-confidence and social interaction. Furthermore, laryngectomies feel much more satisfied with TEV, and all are unanimous in considering that VP has improved their QoL. In this context, vocal rehabilitation has many positive effects at the emotional level, as well as in social interaction, being a benefit aspect in their QoL [10].

Regarding to the results of QoL in patients who have placed primary versus secondary VP, no significant differences were identified between both groups.

Over the last years, surgery for tracheoesophageal puncture with the insertion of VP is considered an effective intervention with low complication rates. TEV is characterized by adequate voice intensity, better speech intelligibility and an increase in the level of patient's satisfaction in comparison to other methods of vocal rehabilitation.

Analyzing other published studies, VP placement in first or second option has achieved high success rates on vocal rehabilitation (65-85% e 69-83%, respectively) [7].

The results obtained in this study, confirm what was mentioned above, significant differences between patients who have placed primary VP compared with those who have placed the device in a second surgical time [7]. Some authors highlight a high success rate tendency when the VP is primary placed. According to our results, either primary or secondary tracheoesophageal puncture with Provox® VP are safe and efficient procedures, providing in patients similar satisfaction levels.

Possible reasons for this fact, may be due to our careful patients selection criteria, namely for secondary prosthesis placement, which are supported on the results of the insufflation test, sometimes in fluoroscopy and, in patient's determination and motivation to acquire voice [11-16].

Conclusion

Laryngectomized patients who use VP to speak normally are the ones who show more intelligibility in verbal communication and better QoL indicators.

QoL items constipation, taste and smell, speech, social contact and sexuality showed significantly better levels in those patients who used more frequently VP. These indicators apparently are not influenced by the timing of placement of VP. Voice rehabilitation using VP considerably improves QoL and social reintegration of laryngectomized patients.

Our study shows improved quality of life in laryngectomized patients rehabilitated with VP, particularly those patients who

actively use it. We consider this method as an effective option for the rehabilitation of our patients. The treatment of these patients should include multidisciplinary teams in the care of rehabilitation, including otolaryngologists, speech therapists and nurses. Particular attention should be given to clinical protocols that can encourage the use of VP by these patients.

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Measuring quality of life in patients with head and neck cancer: Update of the EORTC QLQ-H&N Module, Phase III.

ABSTRACT:

Background. The objective of this study was to pilot test an updated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N60).

Methods. Patients with head and neck cancer were asked to complete a list of 60 head and neck cancer-specific items comprising the updated EORTC head and neck module and the core questionnaire EORTC QLQC30. Debriefing interviews were conducted to identify any irrelevant items and confusing or upsetting wording.

Results. Interviews were performed with 330 patients from 17 countries, representing different head and neck cancer sites and treatments. Forty-one of the 60 items were retained according to the predefined EORTC criteria for module development, for another 2 items the wording was refined, and 17 items were removed.

Conclusion. The preliminary EORTC QLQ-H&N43 can now be used in academic research. Psychometrics will be tested in a larger field study.

ORIGINAL ARTICLE

Measuring quality of life in patients with head and neck cancer: Update of the EORTC QLQ-H&N Module, Phase III

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Accepted 7 May 2014

Published online 21 July 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.23762

ABSTRACT: Background: The objective of this study was to pilot test an updated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N37).

Methods: Patients with head and neck cancer were asked to complete a list of 60 head and neck cancer-specific items comprising the updated EORTC head and neck module and the core questionnaire EORTC QLQ-C30. Debriefing interviews were conducted to identify any irrelevant items and confusing or upsetting wording.

Results: Interviews were performed with 330 patients from 17 countries, representing different head and neck cancer sites and

treatments. Forty-one of the 60 items were retained according to the predefined EORTC criteria for module development, for another 2 items the wording was refined, and 17 items were removed.

Conclusion: The preliminary EORTC QLQ-H&N43 can now be used in academic research. Psychometrics will be tested in a larger field study. © 2014 Wiley Periodicals, Inc. *Head Neck* 37: 1358–1367, 2015

KEY WORDS: head and neck neoplasms, larynx, pharynx, oral cavity, multimodal therapies, chemoradiation, quality of life

INTRODUCTION

Over the past 30 years, the European Organization for Research and Treatment of Cancer (EORTC) Quality of

Life Group (QLG) has developed numerous self-reported questionnaires to assess quality of life (QOL) in oncology.¹ These tools generally use a modular approach, with a 30-item core questionnaire² and additional modules for different cancer sites or treatments covering specific symptoms, treatment side-effects, and functional problems. One of the first site-specific modules was the 37-item head and neck cancer module (EORTC QLQ-H&N37), published in 1992.³ It was subsequently shortened into the QLQ-H&N35 and validated⁴ and finally tested in a European field study.⁵ Since that time, numerous researchers and clinicians have used the QLQ-

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Contract grant sponsor: This project was kindly supported by a grant from the EORTC Quality of Life Group.

H&N35, and it has been administered in at least 19 different languages in 26 countries,⁶ 8 phase III trials, 10 phase II trials, 42 cohort studies, 2 case-control studies, and 72 cross-sectional studies.⁶

A recent systematic review demonstrated that the QLQ-H&N35 scales possessed robust psychometric characteristics and that it has achieved good acceptance by patients throughout the world.⁶ It also revealed, however, that some methodological improvements had been suggested by the users of the QLQ-H&N35, for example, to reduce the relatively high percentage of missing values on the speech (7%) and sexuality (11.5%) scale, or to improve the internal consistency of the speech scale,⁶ indicating a need for updating and revising the module. In addition, standard treatments of head and neck cancer have evolved during the past decades, now including induction or simultaneous concomitant chemotherapy and/or targeted therapies more frequently, and it was considered that the H&N35 did not sufficiently cover the side-effects of these treatments.^{7,8}

As a consequence, the EORTC Quality of Life Group together with the EORTC Head and Neck Cancer Group including the principal investigator of the QLQ-H&N35 discussed whether or not to revise the QLQ-H&N35. On the one hand, it would be desirable to have a module sensitive to detect QOL issues of current therapy regimens. On the other hand, changing a well-established and widespread questionnaire has the disadvantage that comparisons between studies using different versions would be hindered. Moreover, investigators and clinicians may be in doubt about which version to use in new studies.

Therefore, it was decided to first systematically investigate whether an update of the QLQ-H&N35 was indeed really necessary. After a literature review identifying potentially relevant new issues, we conducted interviews with 137 patients and 96 health care professionals finding that 26 issues relevant for patients' QOL were not part of the current head and neck module,⁹ for example, rash and neurological problems, yielding a list of 60 issues. This confirmed that an update of the QLQ-H&N35 would be useful, both from a clinical and a research point of view. This was agreed between the EORTC Quality of Life Group and the EORTC Head and Neck Cancer Group.

Consequently, the new issues were reformatted into items and the EORTC item bank¹⁰ was consulted for consistency. The response format conforms with the EORTC recommendations ranging from 1 = not at all to 4 = very much. The resulting provisional updated module QLQ-H&N60 then needed pilot-testing with respect to understanding, comprehensiveness, and applicability (phase III according to the EORTC Module Development Guidelines),¹¹ which was the primary purpose of the current study. A secondary purpose was to condense/shorten the module as much as possible without compromising its validity and comprehensiveness.

MATERIALS AND METHODS

Translations

The items were translated from English into Danish, Dutch, French, German, Greek, Hebrew, Italian, Japanese, Mandarin, Norwegian, Polish, Portuguese, Spanish, and Swedish following a standardized forward-backward pro-

cedure.¹¹ After the translation report was approved by the Translation Unit of the EORTC Quality of Life Department, and after native speakers with a clinical background had checked the translation, data collection commenced.

Data collection

Patients were enrolled from 21 collaborating hospitals via members of the EORTC QLQ. Patients with head and neck cancer with disease affecting the following tumor sites were eligible: larynx, hypopharynx, nasopharynx, oropharynx, parotid gland, nose, and oral cavity. Exclusion criteria included thyroid and eye cancer, insufficient command of any of the languages that the H&N60 was translated into, and severe cognitive dysfunction. Patients could have had any of the following treatments: surgery alone, surgery with radiotherapy, surgery with (radio) chemotherapy, (radio) chemotherapy alone, radiation alone, and biological therapy with and without any other treatment. Patients could be on or off treatment.

The procedure for patient interviews followed the EORTC QLQ Module Development Guidelines.¹¹ Eligible patients were approached and invited to participate in this study. They received information about this project and could ask the study personnel any questions about the study. Once they had provided written informed consent, they were asked to complete the core questionnaire QLQ-C30 and the updated provisional head and neck module QLQ-H&N60.

After the patient had completed the questionnaire, a brief structured interview was conducted asking if there were any questions that were difficult to understand or perceived as upsetting. If patients found an item difficult to understand or confusing, they were asked to indicate how they would word this question. The interview ended with gaining their opinions on which were the 15 most relevant items, any irrelevant items, and any important items that were not included yet, addressing the entire questionnaire. Questionnaire completion and interview were conducted within one single patient visit.

Data on age, sex, education, tumor site, stage of disease, treatment, and performance status was collected using a Case Report Form to be completed by the interviewer. Data entry was done manually in Leipzig, Germany.

The study protocol was approved by the local ethical committees according to the national requirements. Informed consent was obtained before administration of the provisional module and interviews. Questionnaires were mailed to Leipzig, with no personal identifiable information.

Data analysis

Data analysis was performed in accordance with the EORTC QLQ Module Development Guidelines.¹¹ To retain an item in the module, it should fulfil certain pre-defined criteria.

Criterion 1, relevance

The item mean value is >1.5 (on a scale of 1–4).

Criterion 2, relevance

More than 50% of the patients rate this item as 3 ("quite a bit") or 4 ("very much").

TABLE 1. Demographic characteristics of the sample (n = 330).

Category	No. of patients	(%)
Sex		
Female	92	(27.9)
Male	232	(70.3)
Unknown	6	(1.8)
Age, y		
< 50	39	(11.8)
50–59	96	(29.1)
60–69	115	(34.9)
70–79	61	(18.5)
≥ 80	15	(4.6)
Unknown	4	(1.2)
School education		
Compulsory school education or less	133	(40.3)
Post compulsory school education	117	(35.5)
University level	77	(23.3)
Not specified	3	(0.9)
Country		
Chile	9	(2.7)
Denmark	8	(2.4)
France	13	(3.9)
Greece	9	(2.7)
Germany	66	(20.0)
Israel	22	(6.7)
Italy	37	(11.2)
Japan	5	(1.5)
Norway	25	(7.6)
Poland	13	(3.9)
Portugal	20	(6.1)
Spain	15	(4.6)
Sweden	25	(7.6)
Taiwan	18	(5.5)
The Netherlands	19	(5.8)
United Kingdom	11	(3.3)
United States	15	(4.6)

Criterion 3, neither floor nor ceiling effects

More than 10% of the patients rate this item with a score of 1 or 2; >10% rate this item as 3 or 4.

Criterion 4, range

The responses to the item include the full range of the scale from 1 to 4.

Criterion 5, not upsetting

Less than 5% of the patients find the item upsetting.

Criterion 6, not difficult

Less than 5% of the patients find the item difficult to understand.

Criterion 7, compliance

More than 95% of the patients complete the item.

Criterion 8, priority

More than 10% of the patients rate the item as relevant.

The aim was to include items fulfilling 5 of the first 7 criteria or criterion 8. Additional items could be added if the particular issue was mentioned by at least 5 patients.

Also, items were added to scales according to a hypothesized scale structure and the internal consistency (Cronbach's Alpha) of this scale was calculated. This information was used as an additional "Criterion α " indicating that the item can meaningfully be combined with other items to form a multi-item scale (ie, Cronbach's Alpha is ≥ 0.70) and the Alpha decreases if the item is removed.

All these criteria were tabulated together with the results of the methodological review⁶ and the results discussed with a multiprofessional expert group at the EORTC QLQ Spring Meeting 2013. This group decided, based on the results, their clinical experience, and the results of the review,⁶ whether to keep the item as is, to remove the item, or change the wording.

RESULTS**Sample**

Between August 2011 and February 2013, a total of 333 patients were enrolled. Three patients were excluded because they had thyroid (n = 1) or eye cancer (n = 2), resulting in 330 eligible participants. Patients came from 21 institutions in 17 countries, distributed over Central Europe (n = 66), Southern Europe (n = 81), Northern Europe (n = 58), Eastern Europe (n = 13), Western Europe (n = 43), Asia (n = 45), Northern America (n = 15), and Southern America (n = 9). Seventy percent of the patients were men, and the average age was 61 years (range, 25–89 years). The most frequent tumor site was oral cavity (n = 94), followed by oropharynx (n = 80), and larynx (n = 79). Full demographic and clinical sample characteristics are shown in Tables 1 and 2.

Module administration

The time needed to complete the H&N60 was less than 10 minutes in 30% of all cases, 41% needed 11 to 15 minutes, 18% needed 16 to 20 minutes, 8% needed 21 to 30 minutes, and 3% needed more than 30 minutes.

Sixty-eight percent completed the module on their own, 25% needed assistance from the interviewer, and 7% from relatives or friends.

Preliminary module

Based on the predefined thresholds, 47 of the 60 items had a mean > 1.5 and therefore fulfilled criterion 1, none had $> 50\%$ responses of "quite a lot" or "very much" (criterion 2), 55 had neither floor nor ceiling effects (criterion 3), all had a range of 1 to 4 (criterion 4), 58 were not upsetting for more than 5% (criterion 5), 58 were not difficult to understand for more than 5% (criterion 6), and 56 were completed by $> 95\%$ of the patients (criterion 7). Fifty-two items fulfilled at least 5 of these 7 criteria. Fifteen items were prioritized by $> 10\%$ of the patients (criterion 8). All of the highly prioritized items fulfilled at least 5 of the first 7 criteria.

Considering these criteria and the preliminary scale structure, the expert group decided to retain 41 items as they were, to amend the wording of 2 items, and to remove 17 items. Details are shown in Table 3. The wording of item 46 was changed from "Have you had problems because of losing some teeth (as part of your

TABLE 2. Clinical characteristics of the sample (n = 330).

Category	No. of patients	(%)
Tumor site		
Larynx	79	(23.9)
Hypopharynx	19	(5.8)
Oropharynx	80	(24.2)
Nasopharynx	18	(5.5)
Oral cavity	94	(28.5)
Parotid gland	6	(1.8)
Nasal cavity and sinuses	19	(5.8)
Unknown primary	5	(1.5)
Other	8	(2.4)
Unknown	2	(0.6)
Karnofsky performance score		
< 50	7	(2.1)
60	36	(10.9)
70	60	(18.2)
80	86	(26.0)
90	105	(31.8)
100	54	(16.4)
Unknown	2	(0.6)
Recurrent disease		
No	279	(84.6)
Yes	47	(14.2)
Unknown	4	(1.2)
Tumor stage (UICC 2005)		
I	41	(12.4)
II	55	(16.7)
III	62	(18.8)
IV	148	(44.9)
Unknown	24	(7.3)
Treatment		
OP alone	58	(17.6)
RT alone	35	(10.6)
CT alone	6	(1.8)
RCT without OP	67	(20.3)
OP + RCT	77	(23.3)
OP + CT	3	(0.9)
OP + RT	78	(23.6)
Other	3	(0.9)
Unknown	2	(0.6)
Targeted therapy		
No	295	(89.4)
Yes	32	(9.7)
Unknown	3	(0.9)
Stage of treatment		
Before treatment	11	(3.3)
During treatment	132	(40.0)
< 6 mo after end of treatment	49	(14.9)
≥ 6 mo after end of treatment	63	(19.1)
≥ 12 mo after end of treatment	71	(21.5)
Unknown	4	(1.2)

Abbreviations: UICC, Union for International Cancer Control; OP, surgery; RT, radiotherapy; CT, chemotherapy; RCT, radiochemotherapy.

treatment?" into "Have you had problems because of losing some teeth?" and item 71 from "Have you been hoarse?" into "Have you had problems with hoarseness?"

There were 44 additional items suggested by patients. The most frequently mentioned issues were doctor-patient-relationship (4×), mental well-being (3×), and information about the disease or treatment (2×). However, none was mentioned 5 times or more. In addition, these issues are covered by the QLQ-C30 and the EORTC

information module.¹² Therefore, no new items were added to the questionnaire and the resulting preliminary module contains 43 items.

DISCUSSION

The EORTC QLQ-H&N43 is an updated and revised version of the EORTC QLQ-H&N35, measuring QOL in patients with head and neck malignancies excluding eye and thyroid cancers. Patients representing different tumor sites, tumor stages, treatment options, and treatment phases were included in this update to ensure that the module is applicable in a broad variety of clinical studies.

Traditionally, the EORTC H&N module has followed the concept of targeting a heterogeneous group of patients. This is in contrast to other EORTC QOL modules. For example, the modules for patients with gynecological malignancies were developed separately for cervical,¹³ endometrial,¹⁴ and ovarian cancer,¹⁵ and a module for vulval cancer is currently under development. That approach has certain advantages. For example, the module can be shorter as the variety and number of QOL issues relevant to the patients is smaller because the disease and the treatment-specific side effects are similar. Shorter questionnaires are usually preferred by clinicians and researchers. However, as many clinical trials in head and neck oncology enroll patients with different tumor sites, it was decided after discussion within the EORTC Quality of Life Group and the EORTC Head and Neck Cancer Group to continue with the previous concept of having one single module for all types of head and neck malignancies (except eye and thyroid cancer, which are specific entities with their own profile of QOL experience). This ensures that within one trial one module can be used instead of needing to include two or more different modules. As a consequence, the module is somewhat longer than other EORTC questionnaires. Compared to the previous version, QLQ-H&N35, it contains additional questions regarding skin problems, a typical symptom after targeted therapy,¹⁶ neurological side-effects, and shoulder problems, whereas some issues that can be assessed more reliably by other means were removed (for example, weight or pain medication). However, the QLQ-H&N43 contains many scales of the QLQ-H&N35, thus, data from studies using the 2 different versions of the EORTC head and neck module will be comparable to some extent. We also tried to harmonize the QLQ-H&N43 with the newly developed EORTC oral health module OH-17.¹⁷ However, although there are some overlapping issues across both modules, they do not focus on the same QOL areas. The OH-17 targets oral health issues in a variety of cancer diagnoses whereas the head and neck module is for head and neck cancer only.

The patients in our sample can be considered representative of a wider head and neck cancer population. The male/female ratio, as well as the distribution of tumor sites, mirrors the incidence data of head and neck malignancies. The educational level is probably skewed to a higher educational level than the general head and neck cancer population, although we can state that participants

	crit α	crit 1	crit 2	crit 3	crit 4	crit 5	crit 6	crit 7	crit 8											
Item Nr	wording	α of hypothesized scale	α if item removed	decreased α if item removed?	mean	mean proportion of scores 3/4 > 1.57	proportion of scores 3/4 > 50%	proportion of scores 1/2 of scores 1/2 > 50%	indifer for	% upscaling	<5% upscaling	<5% difficult	% complete	proportion > 95% complete	size of CRT 1 to 7	min. 5 of CRT 1 to 7	proportion > 10% relevant	Decision		
q 31	Have you had a swelling in your neck?	W01	n.a.	n.a.	1	1.7	1	0.20	0	0.79	1	1-4	1	0.00	1	6	1	0.08	0	keep
q 32	Have you had problems with your head?	W01	0.45	n.a.	0	1.4	0	0.14	0	0.84	1	1-4	1	0.00	1	5	1	0.04	0	keep
q 33	Have you had skin problems e.g itching, dry?	S06	0.62	0.75	1	1.6	1	0.23	0	0.77	1	1-4	1	0.00	1	6	1	0.08	0	keep
q 34	Has dryness of your skin bothered you?	S06	0.62	0.74	1	1.6	1	0.15	0	0.82	1	1-4	1	0.00	1	6	1	0.06	0	remove
q 35	Have you had itching or numbness in your hands or feet?	W01	0.48	n.a.	0	1.5	1	0.14	0	0.86	1	1-4	1	0.00	1	6	1	0.04	0	keep
q 36	Have you felt dizzy?	W01	0.48	n.a.	0	1.5	0	0.11	0	0.88	1	1-4	1	0.00	1	5	1	0.02	0	remove
q 37	Have you had a rash?	S06	0.62	0.62	1	1.3	0	0.07	0	0.91	0	1-4	1	0.00	1	4	0	0.03	0	keep
q 38	Have you had problems with hearing because of your teeth?	W01	n.a.	n.a.	1	1.5	0	0.15	0	0.84	1	1-4	1	0.00	1	5	1	0.05	0	remove
q 39	Has your skin color changed?	S06	0.62	0.61	1	1.4	0	0.11	0	0.88	1	1-4	1	0.00	1	5	1	0.04	0	keep
q 40	Have you been bothered by itchy skin?	S06	0.62	0.78	1	1.5	0	0.11	0	0.88	1	1-4	1	0.00	1	5	1	0.03	0	remove
q 41	Have you had trouble speaking clearly?	S06	0.64	0.76	1	2.2	1	0.35	0	0.64	1	1-4	1	0.00	1	6	1	0.12	1	keep
q 42	Have you had trouble talking in a noisy environment?	S06	0.64	0.60	1	2.1	1	0.33	0	0.66	1	1-4	1	0.00	1	6	1	0.07	0	keep
q 43	Has it been difficult to raise your arms or to move it sideways?	S06	0.64	n.a.	1	1.6	1	0.19	0	0.79	1	1-4	1	0.00	1	6	1	0.07	0	keep
q 44	Have you had pain in your shoulder?	S06	0.64	n.a.	1	1.7	1	0.19	0	0.81	1	1-4	1	0.00	1	6	1	0.04	0	keep
q 45	Have you had problems with transferred tissue flap	W01	0.45	n.a.	0	1.3	0	0.07	0	0.84	0	1-4	1	0.00	1	2	0	0.02	0	remove

Item Nr	wording	scale	hypothesized scale	α of hypothesized scale	α if item removed	decreased if item removed?	mean	propor-tion d'	crit 1	crit 2	crit 3	crit 4	crit 5	crit 6	crit 7	crit 8

	crit1	crit2	crit3	crit4	crit5	crit6	crit7	crit8									
Item Nr	wording	alpha	decreased alpha if item removed	mean	proportion of scores 3/4 > 50%	proportion of scores 1/2 > 50%	neither floor nor ceiling	% spending range	<5% spending range	<5% difficult	proportion >95% complete	size of attr. 1 to 7	size of attr. 5 to 7	proportion relevant	Decision		
q 57	Have you had pain in your jaw? *	0.85	0.82	1	1.6	1	0.20	0	0.20	1	0.00	1	0.00	1	0.07	0	keep
q 58	Have you had soreness in your mouth? *	0.85	0.77	1	1.9	1	0.24	0	0.24	1	0.00	1	0.00	1	0.11	1	keep
q 59	Have you had pain in your throat? *	0.85	0.86	0	1.9	1	0.26	0	0.26	1	0.00	1	0.00	1	0.12	1	keep
q 60	Have you had problems swallowing liquid? *	0.86	0.81	1	1.8	1	0.24	0	0.24	1	0.00	1	0.00	1	0.12	1	keep
q 61	Have you had problems swallowing pureed food? *	0.86	0.78	1	1.8	1	0.24	0	0.24	1	0.00	1	0.02	1	0.14	1	keep
q 62	Have you had problems swallowing solid food? *	0.86	0.82	1	2.3	1	0.41	0	0.41	1	0.00	1	0.00	1	0.20	1	keep
q 63	Have you choked when swallowing? *	0.86	0.86	0	1.7	1	0.16	0	0.16	1	0.00	1	0.02	1	0.11	1	keep
q 64	Have you had problems with your teeth? *	0.78	0.69	1	1.8	1	0.24	0	0.24	1	0.00	1	0.00	1	0.07	0	keep
q 65	Have you had problems opening your mouth widely? *	n.a.	n.a.	1	1.9	1	0.29	0	0.29	1	0.00	1	0.00	1	0.08	0	keep
q 66	Have you had a dry mouth? *	0.78	n.a.	1	2.4	1	0.46	0	0.46	1	0.00	1	0.00	1	0.16	1	keep
q 67	Have you had a sticky saliva? *	0.78	n.a.	1	2.3	1	0.40	0	0.40	1	0.00	1	0.00	1	0.15	1	keep
q 68	Have you had problems with your sense of smell? *	0.69	n.a.	0	1.7	1	0.24	0	0.24	1	0.00	1	0.00	1	0.05	0	keep
q 69	Have you had problems with your sense of taste? *	0.69	n.a.	0	2.2	1	0.39	0	0.39	1	0.00	1	0.00	1	0.12	1	keep
q 70	Have you had problems with coughing? *	n.a.	n.a.	1	1.9	1	0.25	0	0.24	1	0.00	1	0.00	1	0.05	0	keep
q 71	Have you been hoarse? *	0.84	0.89	0	1.9	1	0.26	0	0.25	1	0.00	1	0.00	1	0.04	0	change
q 72	Have you felt ill? *	n.a.	n.a.	1	1.8	1	0.24	0	0.25	1	0.00	1	0.00	1	0.03	0	remove
q 73	Has your appearance bothered you? *	0.87	0.85	1	1.6	1	0.16	0	0.85	1	0.00	1	0.00	1	0.03	0	keep

TABLE 3. Continued

Item #	wording	hypothesized and scale	α of hypothesized and scale	α if item removed	mean if item removed?	mean of 1.27	proportion of scores ≥ 1.27	proportion of scores ≥ 1.27	crit 2	crit 3	crit 4	crit 5	crit 6	crit 7	crit 8
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Abbreviations: LV, lymphedema; WOI, problems with wound healing; SOR, skin problems; MBJ, neurological problems; HBAR, problems with hearing; SP, speech problems; SHD, shoulder problems; TE, problems with teeth; PC, physical contact; SC, social contact; BL, body image; AW, anxiety; PA, pain; SW, problems with swallowing; OM, opening mouth; DB, dry mouth and sticky saliva; SE, problems with senses; CO, coughing; FI, feeling ill; SD, accidental injury; PK, pain; HBL, nutritional supplements; FE, feeding tube; WL, weight loss.

Note: When a criterion was fulfilled, the item is listed with "1" in contrast to "0" if it was not fulfilled.

*Item was part of the previous module version QLO-H9935.

with less formal education did not report more difficulty in completing the questionnaire than others.

The QLQ-H&N43 is now ready for wider use. After completing phase III, EORTC QLQ modules can be used free of charge for academic research upon request at the EORTC Quality of Life Department and by sending an e-mail to the principal investigator.

We would like to confirm that the QLQ-H&N35 can still be used in ongoing or future trials if the investigators prefer to keep this head and neck module version. In studies investigating multimodal treatment or targeted therapies, however, the QLQ-H&N43 might be more suitable to detect differences between patient groups; it is therefore possible to use this version for future protocols. Both versions, the QLQ-H&N35 and the QLQ-H&N43, have overlapping items and scales; hence if clinicians wish to use the updated module in the future, existing data from the previous head and neck module can be used.

Investigators should be aware that, after completion of the final phase IV validation study, the QLQ-H&N43 may be further shortened based on psychometric characteristics.

Acknowledgments

The authors acknowledge the collaborators who helped in data collection or translations: Karim Zaoui (University of Heidelberg), Annetie van Nieuwenhuizen (VU University Medical Center Amsterdam), Mehmet Sen (Leeds Teaching Hospitals NHS Trust), Efstratia Galou, Dimitra Galiti, and Evangelos Galitis (University of Athens), and Dagmara Kulis (EORTC Head Quarters, Brussels).

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International validation of the revised European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43: Phase IV.

ABSTRACT:

Background: We validated the new European Organisation for Research and Treatment of Cancer Quality of Life Head and Neck Module (EORTC QLQ-HN43).

Methods: We enrolled 812 patients with head and neck cancer from 18 countries. Group 1 completed the questionnaire before therapy, and 3 and 6 months later. In group 2 (survivors), we determined test–retest reliability using intraclass correlation coefficients (ICC). Internal consistency was assessed using Cronbach's Alpha, the scale structure with confirmatory factor analysis, and discriminant validity with known-group comparisons.

Results: Cronbach's alpha was >0.70 in 10 of the 12 multi-item scales. All standardized factor loadings exceeded 0.40. The ICC was >0.70 in all but two scales. Differences in scale scores between known-groups were >10 points in 17 of the 19 scales. Sensitivity to change was found to be sufficient in 18 scales.

Conclusions: Evidence supports the reliability and validity of the EORTC QLQHN43 as a measure of quality of life.

Received: 23 May 2018 | Revised: 25 October 2018 | Accepted: 10 December 2018

DOI: 10.1002/hnl.25609

WILEY

ORIGINAL ARTICLE

International validation of the revised European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43: Phase IV

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Abbreviations: AL, appetite loss; CF, cognitive functioning; CN, constipation; DI, diarrhea; EF, emotional functioning; FAT, fatigue; FD, financial difficulties; NV, nausea and vomiting; P, pain; PF, physical functioning; QL, global quality of life; RF, role functioning; SB, shortness of breath; SF, social functioning; SL, sleep problems.

This project was kindly supported by a grant from the EORTC Quality of Life Group. The following people kindly helped with data collection: Rivka Rappaport, Emre Vural, Márcio A. Moreno, Augusta Silveira and Teresa Sequeira, from Universidade Fernando Pessoa, Porto, kindly supported us with the translation process of the questionnaire to Portuguese from Portugal. Dagmar Kulis and her team from the EORTC Headquarters, Brussels, Belgium, were of great help in coordinating and supervising all the translations for this module.

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Funding information

European Organisation for Research and Treatment of Cancer, Grant/Award Number: HN_Phase IV

Abstract

Background: We validated the new European Organisation for Research and Treatment of Cancer Quality of Life Head and Neck Module (EORTC QLQ-HN43).

Methods: We enrolled 812 patients with head and neck cancer from 18 countries. Group 1 completed the questionnaire before therapy, and 3 and 6 months later. In group 2 (survivors), we determined test-retest reliability using intraclass correlation coefficients (ICC). Internal consistency was assessed using Cronbach's Alpha, the scale structure with confirmatory factor analysis, and discriminant validity with known-group comparisons.

Results: Cronbach's alpha was >0.70 in 10 of the 12 multi-item scales. All standardized factor loadings exceeded 0.40. The ICC was >0.70 in all but two scales. Differences in scale scores between known-groups were >10 points in 17 of the 19 scales. Sensitivity to change was found to be sufficient in 18 scales.

Conclusions: Evidence supports the reliability and validity of the EORTC QLQ-HN43 as a measure of quality of life.

KEYWORDS

chemoradiation, head and neck cancer, multimodal therapies, quality of life, validation

1 | INTRODUCTION

Head and neck malignancies and their treatments affect a variety of body functions, most notably breathing, swallowing, and speaking. As all of these functions are highly relevant for our survival and/or social life, head and neck cancer can cause significant physical, emotional, and social problems, reducing health-related quality of life (QoL) considerably. Consequently, in the early 1990s, the European Organisation for Research and Treatment of Cancer (EORTC) QoL Group developed a module for this specific group of patients to measure their QoL reliably, the EORTC QLQ-H&N35.^{1–3} The module is in use worldwide as one of the standard instruments for measuring QoL in patients with head and neck cancer.^{4,5}

However, treatment protocols of head and neck cancer have evolved over the past decades and include concomitant cisplatin- or anti-EGFR (epidermal growth factor receptor) antibody-based chemoradiation approaches or induction chemotherapy.^{6–9} Experimental intensification treatments currently being tested for locally advanced disease are often based on the integration of various targeted agents or immune checkpoint inhibitors with standard chemoradiation.^{10,11} Other trials investigate the safety and efficacy of therapeutic vaccines for human papilloma virus positive tumors, functional imaging-based tailored radiotherapy, dose-de-escalation, and dose intensification (dose-painting). Because of these changes, the EORTC Head and Neck Cancer Group and the EORTC Quality of

Life Group decided together to revise and update the QLQ-H&N35.

This update began with the identification of missing issues and their relevance to patients and health care providers (phases I and II).¹² In phase I, relevant new QoL issues were generated. For this, we first performed a systematic review of all studies that reported data using the QLQ-H&N35.¹³ From 136 original articles, information was drawn on psychometric properties and potential problems that were reported while using the QLQ-H&N35 including issues that were mentioned as missing in this module. A second systematic review was performed searching trials with patients with head and neck cancer. We documented the QoL issues investigated and checked whether they were covered in the QLQ-H&N35. Based on the two reviews and information on new drugs provided by pharmaceutical companies we created a list of additional issues. This new list was presented to 137 patients and 96 health care providers, together with the original QLQ-H&N35 and the EORTC core questionnaire (QLQ-C30). Patients and health care providers rated the issues for relevance and priority. In phase II, the selected issues were converted into a set of items. For all new issues, items from the EORTC item library were used whenever possible, resulting in a provisional new module version, the QLQ-H&N60.^{12,13}

In phase III, this provisional list of items was pilot-tested. As this was an update of an existing, well-established EORTC instrument, we included more patients than usual which provided extensive evidence to form our decisions. A total of 330 patients from 17 countries in Europe, Northern and Southern America, and Asia, representing different head and neck cancer sites and treatments, were interviewed. They were asked to complete the QLQ-H&N60 and the QLQ-C30. Debriefing interviews were conducted to identify any irrelevant, confusing or upsetting items. In total, 41 out of the 60 items were retained according to the pre-defined EORTC criteria for module development. For another two items the wording was refined, and 17 items were removed, resulting in the QLQ-HN43.¹⁴ Preliminary evidence from a study with Serbian patients suggested that a majority of the QLQ-H&N43 scales have acceptable internal consistency and promising construct validity.¹⁵

Finally, we carried out phase IV, testing the psychometric properties of the revised module in a large international prospective study, presented in this paper.

2 | PATIENTS AND METHODS

2.1 | Target population and inclusion criteria

The module is intended for patients with head and neck cancer with the following tumor sites (ICD-10 code): larynx (C32), lip (C00), oral cavity (C01-06), salivary glands (C07-08), oro-hypopharynx (C09-10, C12-14), nasopharynx (C11), nasal cavity (C30), nasal sinuses (C31), sarcoma in

the head and neck region (C49), and lymph node metastases from unknown primary in the head and neck area (C77, C80.0). Hence, patients with these entities were included in this study. There were no restrictions regarding stage, recurrence status, or treatments planned or performed.

The module is not meant for patients with a tumor of the eyes, orbit, thyroid, skin (even if in the head and neck area), or lymphomas in the head and neck region. Patients with these tumor sites were excluded.

Additional inclusion criteria were ability to understand and complete the questionnaires (language proficiency, cognitive functioning as judged by study coordinator upon inclusion), age 18 years or above, and written informed consent. Patients who had been included in phase I-III of the module development could not participate in phase IV.

2.2 | Patient groups

Two groups of patients were recruited; those just about to start their HNC treatment (group 1) and survivors whose diagnoses dated back a minimum of 24 months and who were currently disease free (group 2).

As the patients had their cancer in various disease sites and received different treatment, they were stratified into mutually exclusive categories based on diagnosis: laryngeal and/or hypopharyngeal, oropharyngeal, oral cavity, and other locations.

Another categorization was performed according to the treatment: monotherapy (surgery or radiotherapy alone), chemoradiotherapy without surgery +/- targeted therapy, chemoradiotherapy or radiotherapy with surgery +/- targeted therapy, other treatment combinations or palliative treatment. Based on these two stratifications, we created a sampling matrix with a predefined sample size per cell to ensure, on the

TABLE 1 Participation in the study

Time	Status	Group 1	Group 2	Total
t1	Participated	653	135	788
	Declined	2	0	2
	Deceased	1	0	1
	Not eligible	2	0	2
	Joined the study at t2	25	0	25
t2	Participated	499	88	587
	Could not be contacted again	49	0	49
	Declined	43	0	43
	Deceased	20	0	20
	Not eligible	2	0	2
t3	Participated	423	n.a.	423
	Could not be contacted again	49	n.a.	49
	Declined	52	n.a.	52
	Deceased	44	n.a.	44
	Not eligible	2	n.a.	2

Note: group 1 = enrolled prior to starting active treatment; group 2 = survivors diagnosed at least 2 years earlier and currently disease-free. n.a., not applicable.

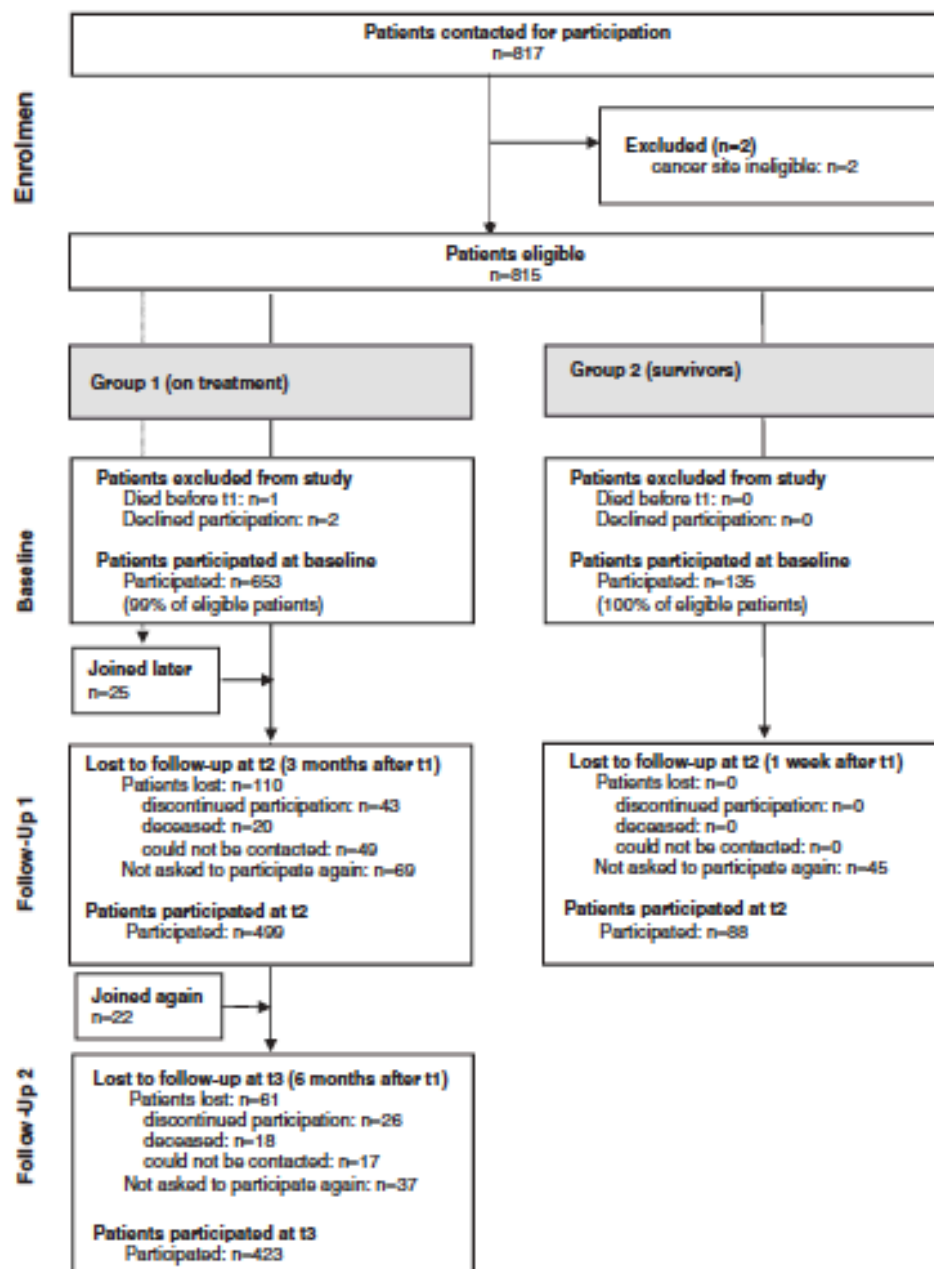


FIGURE 1 Patient flow through the study

one hand, that the most frequent tumor sites and treatment strategies were represented in the study and, on the other hand, that each cell has enough observations for reliably comparing the groups.

2.3 | Enrollment

Consecutively, eligible patients were introduced to the study and given a document which included written information and invitation to participate in accordance with ethical and governance requirements of each participating center. Patients

could ask any questions they had about the study and were allowed enough time to consider consenting to the study.

To ensure a broad, cross-cultural validation, enrollment was stopped in a country when 100 patients were included from all its institutions.

2.4 | Data collection

Patients in group 1 were approached three times over a period of 6 months. The data collection took place up to 14 days before start of treatment (t1), 3 months after t1 (t2),

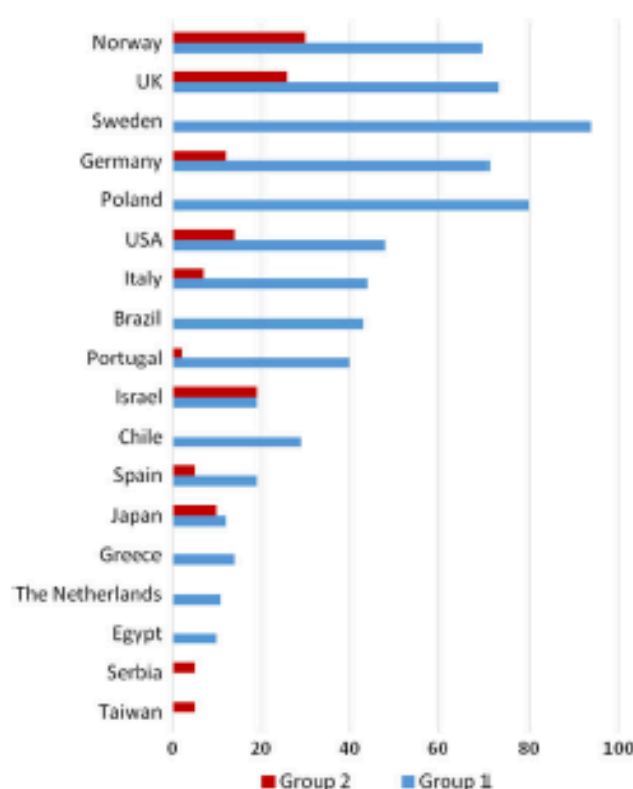


FIGURE 2 Number of participants per country ($n = 812$). Group 1 = patients on treatment, group 2 = survivors off treatment [Color figure can be viewed at wileyonlinelibrary.com]

and 6 months after t1 (t3). A window of 2 weeks before or after the exact date of t2 and t3 was allowed for data collection. The actual date of t1, t2, and t3 was documented on case report forms.

Patients in group 2 completed the questionnaires once (t1), at a minimum of 2 years post diagnosis. A part of this group completed the questionnaires a second time 1 week later (t2) to measure test-retest reliability.

The patients in both groups received two questionnaires at each measurement point, the QLQ-C30 and the QLQ-HN43. At t1, they also completed a debriefing interview regarding the time it took to complete the questionnaires, any assistance needed, and if they had additional comments.

Data collection was usually performed in person. It was however permitted to send out questionnaires by mail or to perform telephone interviews (except at t1). The method of questionnaire administration was reported on the case report form. Changes in treatment and disease status were documented throughout the study at each measurement point. TNM 7th edition was followed to stage patients.

A detailed study protocol was approved by the ethical committee of Rhineland-Palatinate, Germany, and by all national/local ethical committees according to national regulations within each country and at each center.

2.5 | Data analysis

Data analysis was performed in accordance with the EORTC Module Development Guidelines¹⁶ and with the recommendations of the International Society of QoL.¹⁷

We calculated the relative frequency of help needed to complete the questionnaire as well as the time it took to complete it.

The QLQ-HN43 consists of 43 items with a response format (4-point Likert scale) and time frame (1 week) equal to the QLQ-C30. A hypothesized scale structure was retrieved from phase III.¹⁴ According to the EORTC scoring manual,¹⁸ raw scale scores were constructed by summation and transformation from 0 to 100. Unless at least half of the items of a certain scale were available, no score was computed for that scale.

To test the module's reliability, we calculated the internal consistency using Cronbach's alpha for each multi-item scale using the full sample (ie, group 1 assessed at t2 and group 2). Values above 0.70 were considered acceptable for purposes of group comparison.^{17,19} Test-retest reliability was assessed by correlating scores of t1 and t2 in group 2 with intraclass correlation coefficients (ICC).¹⁶

We conducted confirmatory factor analysis (CFA) to examine the hypothesized scale structure of the QLQ-HN43, using the full sample (ie, group 1, again at t2, and group 2).

TABLE 2 Characteristics of the participants ($n = 812$)

Variable	Characteristic	No. of patients	Group 1 ($n = 677$)		Group 2 ($n = 135$)	
			No.	%	No.	%
Sex						
	Male	575	485	71.6	90	66.7
	Female	232	187	27.6	45	33.3
	Unknown	5	5	0.7	0	0.0
Age at begin of study, years						
	<50	92	77	11.4	15	11.1
	50-59	216	186	27.5	30	22.2
	60-69	277	227	33.5	50	37.0
	70-79	182	150	22.2	32	23.7
	≥80	42	34	5.0	8	5.9
	Unknown	3	3	0.4	0	0.0
Tumor site						
	Larynx	128	111	16.4	17	12.6
	Hypopharynx	64	58	8.6	6	4.4
	Oropharynx	268	223	32.9	45	33.3
	Oral cavity	257	210	31.0	47	34.8
	Salivary glands	36	30	4.4	6	4.4
	Nasal cavity and sinuses	27	22	3.3	5	3.7
	Unknown primary	29	20	3.0	9	6.7
	Unknown	3	3	0.4	0	0.0
UICC stage, 7th ed						
	I	86	75	11.1	11	8.2
	II	128	108	16.0	20	14.8
	III	138	115	17.0	23	17.0
	IV	376	335	49.5	41	30.4
	Not specified or unknown	84	44	6.5	40	29.6
Treatment						
	Surgery alone	145	132	19.5	13	9.6
	Radiotherapy alone	116	106	15.7	10	7.4
	Chemotherapy alone	14	14	2.1	0	0.0
	Radiochemotherapy without surgery	207	175	25.9	32	23.7
	Surgery with radiochemotherapy	144	108	16.0	36	26.7
	Surgery with chemotherapy	8	8	1.2	0	0.0
	Surgery with radiotherapy	142	99	14.6	43	31.9
	Other	34	33	4.9	1	0.7
	Unknown	2	2	0.3	0	0.0

We calculated standardized factor loadings for each item with regard to the corresponding scale and considered loadings above 0.40 to be sufficient.²⁰ Model-data-fit was assessed with the comparative fit index (CFI) and the Tucker–Lewis index (TLI), with both indices considered to indicate good fit if they exceeded a value of 0.95²¹ as well as with the root mean squared error of approximation (RMSEA) which should be below 0.06.²¹

Convergent and divergent validity was assessed in the full sample by correlating the scales of the QLQ-C30 and QLQ-HN43 using Spearman Rank tests. Coefficients ≥0.30 between scales measuring similar areas were considered to indicate convergent validity (eg, the *pain* scale of the C30 and the *pain in the head and neck* scale of the QLQ-HN43).

Coefficients <0.30 between scales measuring dissimilar areas were considered to indicate divergent validity (eg, the *diarrhea* scale of the C30 and the *shoulder functioning* scale of the QLQ-HN43).

Discriminant (or known-groups) validity was tested by comparing the means of the QLQ-HN43 scales between relevant clinical subgroups (patients receiving different treatments within group 1; survivors in group 2 vs group 1 patients in acute treatment at t2). We considered a difference of ≥10 points to be clinically relevant.²² We also compared scores between groups for selected scales using *t* tests.¹⁶

Sensitivity to change was determined by calculating mean changes between t1, t2, and t3 with 95% confidence intervals in group 1.¹⁶

TABLE 3 Reliability and scale structure of the EORTC QLQ-HN43 (at t2)

Abbreviation	Scale	N items	Cronbach's alpha	Test-retest*	Standardized factor loadings
AX	Anxiety	2	0.83	0.78	0.79-0.91
BI	Body image	3	0.83	0.88	0.73-0.87
CO	Coughing	1	—	0.75	—
DR	Dry mouth and sticky saliva	2	0.75	0.87	0.73-0.82
NE	Neurological problems	1	—	0.88	—
OM	Opening mouth	1	—	0.87	—
PA	Pain in the mouth	4	0.82	0.88	0.58-0.90
SC	Social contact	1	—	0.62	—
SE	Problems with senses	2	0.64	0.87	0.54-0.87
SH	Shoulder problems	2	0.86	0.95	0.83-0.91
SK	Skin problems	3	0.74	0.73	0.66-0.78
SN	Swelling in the neck	1	—	0.52	—
SO	Social eating	4	0.85	0.93	0.67-0.87
SP	Speech	5	0.89	0.86	0.46-0.89
SW	Swallowing	4	0.85	0.86	0.56-0.88
SX	Sexuality	2	0.89	0.91	0.83-0.97
TE	Problems with teeth	3	0.68	0.89	0.46-0.83
WL	Weight loss	1	—	0.87	—
WO	Problems with wound healing	1	—	0.73	—

* Intraclass correlation coefficient, measured in group 2 (survivors off treatment).

The results of all these statistics were discussed at Group meetings of the EORTC Quality of Life Group and the group of experts made decisions about the final scale structure (no changes to the hypothesized scale structure were needed). We then calculated the range, mean, SD, skewness, floor and ceiling effects, and percentage of missing values per scale with data from 2.¹⁶

Data cleaning and analysis were conducted using STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, Texas: StataCorp LP).

3 | RESULTS

3.1 | Enrollment and participation

During the study period, 817 patients were approached, 815 agreed to participate (2 declined), and 812 participated (2 were ineligible, 1 died before the interview could be performed). There were 677 participants in group 1 and 135 in group 2. In group 1, 653 participated at t1, 499 at t2, and 423 at t3. Until t3, 395 patients participated 3 times, 108 twice, and 174 once. In group 2, 135 patients participated at t1 and 88 at t2 (see Table 1 and Figure 1 for details).

3.2 | Sample characteristics

The 812 study participants came from 28 institutions in 18 countries (Figure 2), speaking 17 different languages: Arabic ($n = 10$), Chinese Cantonese ($n = 5$), Dutch ($n = 11$), English ($n = 161$), German ($n = 83$), Greek ($n = 14$), Hebrew ($n = 38$), Italian ($n = 51$), Japanese ($n = 22$),

Norwegian ($n = 100$), Polish ($n = 80$), Portuguese for Brazil ($n = 43$), Portuguese for Portugal ($n = 42$), Serbian ($n = 5$), Spanish for Chile ($n = 29$), Spanish for Spain ($n = 24$), and Swedish ($n = 94$).

About one third of the patients had cancer of the oral cavity (32%) or the oropharynx (33%), and a quarter cancer of the larynx or hypopharynx (24%). The histology was squamous cell carcinoma (86%), sarcoma (1%), other (7%), or unknown (6%).

In 8 %, the disease was recurrent, and in 5 %, it was a secondary malignancy (details see Table 2). Treatment was chemoradiation in 26%, surgery plus (chemo)radiotherapy in 34%, and monotherapy in 34% of the patients. Of the patients who had received any type of chemotherapy, the protocol was induction in 9%, concomitant in 85%, and monotherapy in 6%. Of those who had received any type of radiotherapy, it was 3D conformal in 26%, IMRT in 73%, and brachytherapy in 1%. Targeted therapy was received by 8% (53 patients in group 1 and 13 in group 2; by patients from 11 countries). It had been combined most frequently with chemotherapy alone, with radiotherapy alone, with surgery plus chemotherapy, and with surgery plus radiotherapy.

3.3 | Time and help needed

The time needed to complete the QLQ-C30 and QLQ-HN43 combined was <10 minutes in 35%, 11-15 minutes in 45%, 16-20 minutes in 14%, 21-30 minutes in 4 %, and more than 30 minutes in 2 % of the participants. The older the patients were, the more they needed time to complete the forms

TABLE 4 Correlations between the scales of the EORTC QLQ-C30 and the EORTC QLQ-HN43

	AX	BI	DR	PA	SX	SE	SH	SK	SO	SP	SW	TE	CO	SN	NF	OM	SC	WL	WO
PR	-0.40	-0.46	-0.38	-0.34	-0.26	-0.32	-0.15*	-0.30	-0.46	-0.50	-0.40	-0.33	-0.32	-0.28	-0.10	-0.22	-0.51	-0.30*	-0.22
RP	-0.37	-0.42	-0.41	-0.38	-0.32	-0.33	-0.06	-0.32	-0.52	-0.37	-0.39	-0.24	-0.28	-0.30	-0.04	-0.25	-0.49	-0.28	-0.26
RP*	-0.62*	-0.51*	-0.34	-0.43	-0.28	-0.28	-0.11	-0.38	-0.50	-0.46	-0.40	-0.35	-0.33	-0.32	-0.13	-0.29	-0.48	-0.36	-0.33
CF	-0.27	-0.38	-0.28	-0.32	-0.20	-0.30	-0.06	-0.28	-0.36	-0.39	-0.27	-0.26	-0.31	-0.22	-0.12	-0.25	-0.43	-0.20	-0.25
SP	-0.48	-0.52	-0.40	-0.41	-0.33*	-0.35	-0.05	-0.36	-0.57*	-0.43*	-0.45	-0.33	-0.30	-0.37	-0.10	-0.35	-0.53*	-0.34	-0.31
QL	-0.30	-0.46	-0.44	-0.44	-0.26	-0.32	-0.09	-0.38	-0.54	-0.44	-0.45	-0.31	-0.37	-0.29	-0.11	-0.30	-0.51	-0.41	-0.30
PA7	0.43	0.47	0.43	0.41	0.26	0.37	0.11	0.31	0.55	0.43	0.41	0.33	0.34	0.29	0.08	0.30	0.54	0.31	0.26
NV	0.28	0.30	0.25	0.32	0.22	0.20	0.06	0.23	0.35	0.31	0.35	0.11	0.30	0.22	0.13	0.16	0.33	0.27	0.13
P	0.43	0.41	0.38	0.40*	0.28	0.31	0.16	0.35	0.52	0.42	0.48*	0.37	0.31	0.32	0.13	0.27	0.43	0.28	0.32*
SB	0.29	0.24	0.28	0.25	0.11	0.25	0.08	0.24	0.24	0.31	0.20	0.19	0.23*	0.18	0.19	0.09	0.33	0.14	0.20
SL	0.33	0.32	0.25	0.31	0.20	0.24	0.09	0.22	0.20	0.35	0.24	0.24	0.26	0.20	0.06	0.24	0.33	0.17	0.17
AL	0.32	0.37	0.47	0.40	0.31	0.47	-0.01	0.30	0.28	0.36	0.47	0.24	0.31	0.25	0.04	0.30	0.41	0.31	0.28
CS	0.12*	0.19*	0.29*	0.21*	0.13*	0.17*	0.07*	0.18*	0.21*	0.29*	0.22*	0.19*	0.18*	0.17*	0.14*	0.19*	0.19*	0.19*	0.19*
DE	0.15*	0.17*	0.15*	0.16*	0.12*	0.22*	0.02*	0.16*	0.19*	0.18*	0.18*	0.07*	0.14*	0.11*	0.12*	0.05*	0.16*	0.16*	0.17*
PD	0.32	0.34	0.07	0.14	0.17	0.05	0.10	0.20	0.19	0.27	0.14	0.23	0.19	0.17	0.17	0.13	0.19	0.21	0.15

Notes: Displayed are the correlation coefficients (Spearman rank correlation). Coefficients >0.30 are printed in bold.

* Scale pairs where a high correlation was expected because of similar concepts.

† Scale pairs where a low correlation was expected because of dissimilar concepts.

($r = 0.23$, $P < .001$). Patients with education below 10 years did not need more time than patients with higher education ($P = .26$).

In 67%, the patients completed the forms on their own, in 33% the researcher read the questions aloud and recorded the patient's responses. Practical help (eg, reading the questions aloud when the patient could not find his glasses) was required by 22%, supportive help (eg, just sitting next to the patient while he completes the form) by 8%, and help with understanding some of the items in the questionnaire by 3% (see Supporting Information eFigure S1 for results by language).

3.4 | Reliability and scale structure

Cronbach's Alpha of the scales was >0.70 in 10 of the 12 multi-item scales. It ranged from 0.89 to 0.64 (Table 3). The scales with Alpha <0.70 were *problems with senses* and *problems with teeth*.

In the confirmatory factor analysis, all standardized factor loadings exceeded the threshold of 0.40 (0.46–0.97), confirming the hypothesized scale structure of the QLQ-HN43 (Table 3 and Supporting Information eTable S1). The comparative fit index (CFI) = 0.88, the Tucker-Lewis fit index (TLI) = 0.85, and the RMSEA = 0.07 indicated moderate fit of the model and the data.

ICC between t1 and t2 in group 2 were > 0.70 except for *social contact* (ICC 0.62) and *swelling in the neck* (ICC 0.52).

3.5 | Convergent and divergent validity

Of the 285 possible correlations between the QLQ-C30 and QLQ-HN43 scales, 132 (46%) were ≥ 0.30 . Size and direction of the correlations were in accordance with the conceptual assumptions (see Table 4), indicating convergent and divergent validity. None of the correlations were >0.70, which implies that the core questionnaire and the head and neck module cannot replace each other and should be used in conjunction.

3.6 | Discriminant validity

The mean scores of the QLQ-HN43 per treatment group are displayed in Figure 3, for group 1 patients assessed at t2. When comparing patients under monotherapy vs those who received (chemo)radiotherapy plus surgery, we found that the difference was ≥ 10 points (ie, clinically meaningful) for 9 of the 19 scales. When comparing patients under monotherapy vs those who received chemoradiation, the difference was ≥ 10 points for 10 of the scales. When combining this information, the score difference in any comparison was ≥ 10 points in 17 scales. Two scales, *swelling in the neck* and *wound healing*, did not differ by ≥ 10 points between treatment groups (for details see Supporting Information eTable S2).

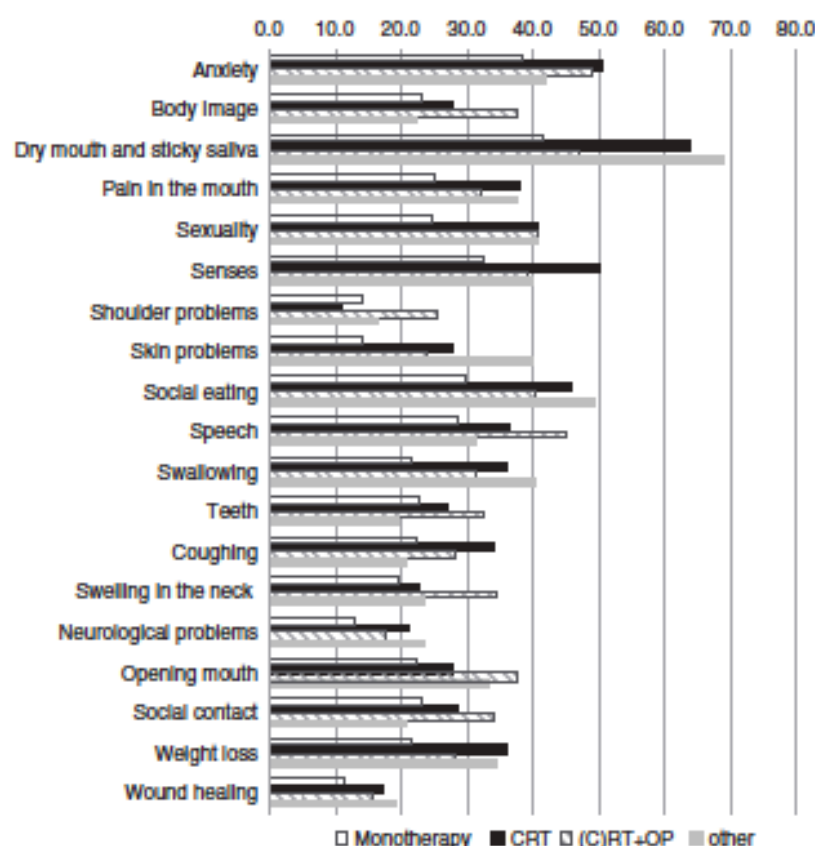


FIGURE 3 Mean scores per scale of the EORTC QLQ-HN43 in patients with monotherapy, chemoradiotherapy (CRT), (chemo)radiotherapy with surgery (CRT + OP), or other treatment

The difference in *skin problems* was 21 points in those who had received targeted therapy (mean: 41 points) vs those who had not (mean: 19.7 points), in group 1 ($P < .001$). This difference was 11 points in *dry mouth* and 6 points in *problems with senses*.

The difference between survivors (group 2) and patients in acute treatment (group 1 assessed at t2) was ≥ 10 points in 12 out of the 19 scales of the QLQ-HN43 (Figure 4). The largest differences were found in the following scales: *social contact* (22 points), *anxiety* (20 points), *weight loss* (19 points), and *speech* (16 points).

3.7 | Sensitivity to change

Eighteen out of the 19 scales in the QLQ-HN43 indicated changes between t1 and t2 because the 95% confidence interval did not include the zero (Table 5). These changes were always in the expected direction, that is, symptoms worsened. Only in the *anxiety* scale symptoms decreased.

Between t2 and t3, all scales indicated improvement of QoL. In 14 out of the 19 scales, the confidence interval for change did not include zero (Table 5).

3.8 | Decision about final module

Based on the results of all these findings, the group of experts decided to keep the module as it is. No changes regarding wording, the addition or removal of items were considered to be necessary. It was noted and discussed that *swelling in the neck* was insensitive to change and also test-retest was limited but the clinicians in the group said it was important to keep this scale because of its clinical relevance, pending further research. It is also important to emphasize that this item should be interpreted with caution, it only means that the patient experienced a swelling on the neck for whatever reason, it can be related to lymphedema or a tumor in the neck.

3.9 | Distribution of values per scale

Finally, the characteristics of the module were computed for group 1 patients assessed at t2 (Table 6). At all scales, the participants had used the entire range of possible scores, from 0 to 100. The highest mean scores were found at *dry mouth and sticky saliva* (49.6), *anxiety* (42.2), and *problems with senses* (37.5). These were also the scales with lowest skewness. In all but 1 scale (*sexuality*), the proportion of missing values was below 5%.

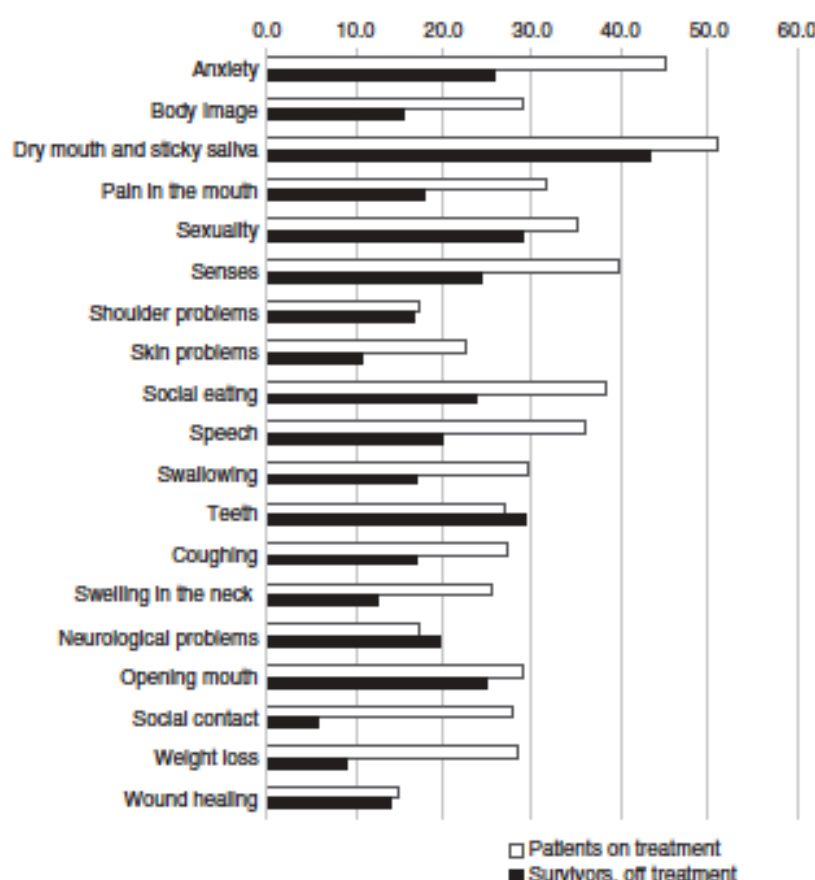


FIGURE 4 Mean scores per scale of the EORTC QLQ-HN43 in patients on treatment (□) vs survivors off treatment (■)

4 | DISCUSSION

In order to develop more effective and less toxic treatment strategies for patients with head and neck cancer, current approaches go beyond the classic treatments of surgery, radiotherapy, and chemotherapy. Now they include multimodal treatments, immunotherapy, and targeted therapy.^{8,10,11,23}

To be able to capture side effects and QoL effects of these new treatment strategies, the EORTC decided to update and revise the QLQ-H&N35.^{12–14} We now present the results of the final field validation of the QLQ-HN43.

This module measures QoL in patients with head and neck malignancies. Patients representing different tumor sites, tumor stages, treatment options, and treatment phases were included in this update to ensure that the module is applicable in a broad variety of clinical studies.

Compared to the previous version QLQ-H&N35, it contains additional questions regarding skin problems, a typical symptom after targeted therapy,²⁴ neurological side-effects, which are known problems of taxane,²⁵ and shoulder problems, whereas some issues that can be assessed more reliably by other means were removed (eg, weight or pain medication). However, the QLQ-HN43 contains many scales of the QLQ-H&N35, thus data from studies using the two different

versions of the EORTC head and neck module are comparable to some extent. Some minor linguistic changes were done to improve the translatability of the module. For example, the word “bother” has various meanings and it is difficult to translate that into other languages unambiguously. It should be replaced by words that carry the same meaning in various languages, for example, by “problems.” This was done in the current version of the module. The revised version is particularly useful in studies where the new items are of relevance.

Another new feature is that we tested the module’s sensitivity to change which was not done in the original version.³ We found that the instrument is highly responsive both regarding deterioration and improvement of QoL. The only scale score that decreased between baseline and 3-month follow-up was anxiety but this is also in accordance with clinical expectations and with other studies. Anxiety levels are often most elevated at the beginning of treatment because the uncertainty is highest here.^{26–28}

Strengths of this study include the large, clinically, and culturally diverse sample, which encompassed participants from 18 countries. Current findings build on the results of three previous phases of instrument development,^{12–14} and thus represent a rigorous and systematic approach to refining

TABLE 5 Sensitivity to change of the EORTC QLQ-HN43

Scale	Change between t1 and t2	Change between t2 and t3
	Mean difference (95% confidence interval)	Mean difference (95% confidence interval)
Anxiety	-5.5 (-8.9; -2.1)	-5.7 (-8.4; -2.9)
Body image	12.8 (10.3; 15.2)	-3.8 (-6; -1.7)
Coughing	8.1 (4.9; 11.2)	-3.9 (-6.9; -0.9)
Dry mouth and sticky saliva	31.0 (27.6; 34.3)	-3.0 (-5.6; -0.3)
Swelling in the neck	1.9 (-1.8; 5.6)	-0.3 (-3.9; 3.4)
Neurological problems	7.8 (5.2; 10.4)	-1.0 (-3.9; 1.9)
Opening mouth	13.2 (10.2; 16.2)	-4.4 (-7.2; -1.6)
Pain in the mouth	8.5 (5.8; 11.1)	-8.1 (-10.4; -5.9)
Sensuality	12.2 (8.7; 15.8)	-0.5 (-3.6; 2.5)
Social contact	15.4 (12.2; 18.5)	-7.1 (-10.5; -3.8)
Senses	27.3 (24.3; 30.3)	-8.1 (-10.6; -5.6)
Shoulder problems	8.9 (6.4; 11.5)	-0.5 (-2.6; 1.6)
Skin problems	16.2 (13.8; 18.6)	-8.4 (-10.7; -6.2)
Social eating	19.5 (16.5; 22.5)	-8.4 (-11; -5.8)
Speech	13.7 (10.9; 16.5)	-5.7 (-8.2; -3.3)
Swallowing	13.0 (10.1; 15.8)	-7.6 (-10; -5.2)
Problems with teeth	6.0 (3.6; 8.5)	-1.7 (-3.8; 0.4)
Weight loss	14.5 (11.3; 17.7)	-4.0 (-6.9; -1.1)
Problems with wound healing	6.7 (3.9; 9.6)	-2.8 (-5.6; -0.1)

Displayed are the differences in score points, measured in group 1 (patients on treatment).

the module. The new module version exhibits very good psychometric properties. Its scales' reliability, validity, and sensitivity to change are high. The factor structure of the QLQ-HN43 is promising which is notable in that prior versions of the head and neck module had not been evaluated for factorial validity. There were few missing values, indicating good acceptance from the patients' perspective. It should be noted that 33% of the patients preferred to have the questionnaire read out aloud to them instead of completing it on their own. We found considerable cultural differences regarding this pattern. Whether the mode of application (self-completed vs interview) has an impact on the instrument's psychometric properties was investigated by comparing some of the results between the groups with different applications. We found no relevant differences (data not shown). However, a more in-depth analysis might be warranted in future studies.

Other limitations should also be recognized. Two of the 12 multi-item scales of the QLQ-HN43 (ie, *senses*, *teeth*) had somewhat lower internal consistency (which does not seem surprising given that they comprised only 2 to 3 items), and 2 of the 19 scales (*swelling in neck*, *social contact*) had relatively limited test-retest reliability. The confirmatory factory analysis confirmed the hypothesized structure of the instrument, but the fit indices were modest (below the targeted thresholds). Enrollment was well in accordance with the sampling matrix except regarding "other sites"—we had

estimated 150 patients here but achieved only 92. Although this is a heterogeneous group anyway and the subsample size is still considerably high, we agreed that this limitation was acceptable, but we refrained from comparing treatment groups within this site group. Another consequence is that the module has limited evidence for patients with tumors in the salivary glands, nasal cavity, and so forth, pending further research on psychometric properties of the module in these groups of patients.²⁹ We also included no patients with immunotherapy because this was not yet approved for patients with head and neck cancer when we started this study. The participation rate of patients in our study was very high. There are several explanations possible: first, patients were not requested to commit themselves to a randomized allocation to treatments (such as in a trial) but only to complete rather short questionnaires. It is easier to enroll patients into observational studies compared to interventional trials because they do not have to decide about their treatment options. In other observational studies having patients with head and neck cancer, where patients are approached in person and not via a letter, participation rates usually vary from 85% to 100%.^{30–34} A second explanation is that the collaborators approached those patients more often where they expected them to participate. If this would have been the case, it would have potentially introduced a bias because the more motivated and compliant persons would then be represented in our study. It is in our view not very likely that this would have had an effect on the scale structure but it surely is related to the percentage of missing items.

Information regarding convergent validity (ie, comparisons to other established measures of the same constructs) was obtained only for the QLQ-C30. In particular, further research might be helpful to evaluate the convergent validity of the newly added scales (eg, correlations of the *anxiety* scores or *body image* scores with existing measures of these problems). Additional efforts to evaluate the known-groups validity of the new scales would be useful as well (eg, differences in shoulder problems scores for subgroups who received extensive vs limited lymph node dissections). Data regarding minimally important clinical differences will be the subject of a separate manuscript.

The QLQ-HN43 has been validated in 17 language versions: Arabic, Chinese Cantonese, Dutch, English, German, Greek, Hebrew, Italian, Japanese, Norwegian, Polish, Portuguese for Brazil, Portuguese for Portugal, Serbian, Spanish for Chile, Spanish for Spain, and Swedish. There are also French and Danish versions available. All translations followed a standardized forward-backward procedure¹⁶ and were checked by native speakers with a clinical background. In addition, all translations were pilot-tested before applying them in this phase IV study.

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TABLE 6 Characteristics of the EORTC QLQ-H&N35 scales (at t2, both groups combined)

Scale	Range	Mean	SD	Skewness	Percentage of missing values	Ceiling (percentage of patients with > 95 points)	Floor (percentage of patients with < 5 points)
Anxiety*	100	42.2	32.4	0.4	2%	13%	18%
Body image*	100	26.9	28.1	0.9	1%	4%	34%
Dry mouth and sticky saliva	100	40.6	32.3	0.1	0%	15%	14%
Pain in the mouth	100	29.5	26.1	0.8	0%	2%	19%
Sexuality	100	34.1	37.1	0.7	6%	16%	43%
Senses	100	37.5	30.6	0.4	0%	7%	24%
Shoulder problems*	100	17.0	26.1	1.6	2%	3%	60%
Skin problems*	100	20.5	23.3	1.3	2%	1%	35%
Social eating	100	36.1	30.6	0.6	3%	6%	20%
Speech	100	33.5	29.2	0.6	2%	3%	18%
Swallowing	100	27.6	27.8	0.9	0%	3%	25%
Problems with teeth	100	27.2	26.7	1.0	1%	4%	27%
Coughing	100	25.7	30.7	1.0	1%	7%	30%
Swelling in the neck*	100	23.4	31.8	1.2	2%	8%	57%
Neurological problems*	100	17.6	27.4	1.5	2%	4%	64%
Opening mouth	100	28.5	32.3	0.9	1%	9%	46%
Social contact	100	34.5	34.2	1.1	3%	11%	59%
Weight loss	100	25.3	33.5	1.0	2%	9%	56%
Problems with wound healing*	100	14.6	27.1	1.9	2%	5%	72%

* Scale is new compared to the EORTC QLQ-H&N35.

either of these questionnaires the following website should be checked: www.eortc.be/ql.

CONFLICT OF INTEREST

All authors except SS, NK, and PB confirm they have no conflicts of interest.

DISCLOSURE OF INTERESTS

SS received a grant from Pfizer, honoraria from Lilly, and lecture fees from Pfizer, Bristol-Myers Squibb, and Boehringer Ingelheim; all were outside of this study. NK received research grants from Bristol-Myers Squibb, ONO, AstraZeneca and Pfizer and honoraria from Bristol-Myers Squibb, ONO, Bayer and Eisai; all were outside of this study. PB states advisory role for Merck Serono and Bristol-Myers Squibb, unrelated to this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Singer S, Amdal CD, Hammerlid E, et al. International validation of the revised European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43: Phase IV. *Head & Neck*. 2019;1-13. <https://doi.org/10.1002/hed.25609>

Head and Neck Cancer Early Identification of Malnutrition High Risk Patients and Quality of Life Optimization.

ABSTRACT:

Malnutrition in Head and neck cancer (HNC) patients can be present at the moment of diagnosis. The nutritional status is determinant for the treatment success and quality of life of the patients. The nutritional status gradually declines during treatment and the majority of patients undergoing treatment will need nutritional therapy. On the other hand, HNC, like other cancers, can induce a paraneoplastic syndrome that leads to cachexia. This cachexia status is most of the times the cause of death or the cause of treatment failure. So, early identification of malnutrition high risk patients is crucial to start an adequate nutrition support intervention in HNC patients. This study aims to identify HNC patients who present malnutrition or higher risk of malnutrition; to signalize variables that support early identification of high-risk patients of becoming malnourished and to establish a dynamic relationship between malnutrition risk in these patients and Quality of Life (QoL) impacts. For six months consecutive outpatients with HNC admitted at the Head & Neck Unity of Oncology Portuguese Institute - Porto were asked to participate in the research (n = 114). The European Organisation for Research and Treatment of Cancer (EORTC) cancer-specific HRQoL questionnaire-QLQ-C30 and Malnutrition Universal Screening Tool, MUST were used. At the moment of first presentation, 32 patients (28.1%) presented high-risk of malnutrition. HNC patients with oral cavity and oropharynx tumour locations, older, with low literacy or with BMI under 18.5 at the moment of diagnosis, represent a high-risk group. When HNC is considered, a dynamic and bi-directional connection between malnutrition and QoL is observed. A significant ($p < 0.001$) difference in the scores of Global health status/QoL according to the malnutrition risk group was found: 62.96, 53.33, 42.71 for low, medium and high malnutrition risk respectively. Also, Emotional and social functional scales and all symptom scales - including pain, presented significant differences between high and medium risk of malnutrition patients. Fatigue, pain, insomnia, appetite loss and financial difficulties were domains directly related to high risk of malnutrition patients. Pain scores were significantly higher (43.23) in the high-risk patients when compared to medium risk patients (11.67). Nutrition support should be considered at any stage of the pathway -

especially in high risk group - in order to optimize tumour treatment results, reduction of adverse effects of therapy and improving both QoL and survival.



Head and Neck Cancer Early Identification of Malnutrition High Risk Patients and Quality of Life Optimization

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How to cite this paper: Silva, J.C., Silveira, A., Sacau, A., Monteiro, E. and Sequeira, T. (2019) Head and Neck Cancer Early Identification of Malnutrition High Risk Patients and Quality of Life Optimization. *International Journal of Otolaryngology and Head & Neck Surgery*, 8, 204-216.
<https://doi.org/10.4236/ijohns.2019.86023>

Received: August 19, 2019

Accepted: November 2, 2019

Published: November 5, 2019

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Abstract

Malnutrition in Head and neck cancer (HNC) patients can be present at the moment of diagnosis. The nutritional status is determinant for the treatment success and quality of life of the patients. The nutritional status gradually declines during treatment and the majority of patients undergoing treatment will need nutritional therapy. On the other hand, HNC, like other cancers, can induce a paraneoplastic syndrome that leads to cachexia. This cachexia status is most of the times the cause of death or the cause of treatment failure. So, early identification of malnutrition high risk patients is crucial to start an adequate nutrition support intervention in HNC patients. This study aims to identify HNC patients who present malnutrition or higher risk of malnutrition; to signalize variables that support early identification of high-risk patients of becoming malnourished and to establish a dynamic relationship between malnutrition risk in these patients and Quality of Life (QoL) impacts. For six months consecutive outpatients with HNC admitted at the Head & Neck Unit of Oncology Portuguese Institute—Porto were asked to participate in the research (n = 114). The European Organisation for Research and Treatment of Cancer (EORTC) cancer-specific HRQoL questionnaire-QLQ-C30 and Malnutrition Universal Screening Tool, MUST were used. At the moment of first presentation, 32 patients (28.1%) presented high-risk of malnutrition. HNC patients with oral cavity and oropharynx tumour locations, older, with low literacy or with BMI under 18.5 at the moment of diagnosis, represent a high-risk group. When HNC is considered, a dynamic and bi-directional connection between malnutrition and QoL is observed. A significant ($p < 0.001$) difference in the scores of Global health status/QoL according to the malnutrition risk group was found: 62.96, 53.33, 42.71 for low, medium and

high malnutrition risk respectively. Also, *Emotional* and *social functional* scales and all *symptom* scales—including *pain*, presented significant differences between high and medium risk of malnutrition patients. *Fatigue*, *pain*, *insomnia*, *appetite loss* and *financial difficulties* were domains directly related to high risk of malnutrition patients. Pain scores were significantly higher (43.23) in the high-risk patients when compared to medium risk patients (11.67). Nutrition support should be considered at any stage of the pathway—especially in high risk group—in order to optimize tumour treatment results, reduction of adverse effects of therapy and improving both QoL and survival.

Keywords

Oncology, Head and Neck Cancer, Body Mass Index Malnutrition, Nutritional Support, Quality of Life, Malnutrition Universal Screening Tool

1. Introduction

Head and neck cancer (HNC) accounts for more than 550,000 cases and 380,000 deaths annually [1]. In the United States 63,000 new cases occur every year while in Europe a higher incidence is seen—250,000 new cases per year. HNC squamous cell carcinoma represents 3% and 6% of all cancer cases respectively [2] [3] [4].

HNC comprehends several locations: the oral cavity, pharynx, larynx, paranasal sinuses and salivary glands and is necessarily related to malnutrition during the disease process and the treatment [5].

Studies reveal that tumour locations, cancer stage, treatment plan, dietary habits, initial weight and body mass index (BMI), lifestyle factors, alcohol and tobacco consumption, oral health performance, social conditions, financial circumstances and cachexia syndrome can guide HNC patients to malnutrition [6] [7] [8].

Significant weight loss and resultant malnutrition caused by a decrease in food intake are expected in HNC patients undergoing radiotherapy. Additionally, poor oral health and chemotherapy act as co-factors in HNC undernourishment. Still, head and neck surgery may cause swallowing dysfunction, xerostomia and severe dysphagia leading to underfeeding. At diagnosis, 20% - 67% HNC patients are malnourished or at high risk of becoming malnourished. The malnutrition prevalence rate of HNC patients overtakes 80% [9] [10] [11].

This aspect is often associated with weight and muscle loss, decrease functioning, depression and negative impacts in Quality of Life (QoL). HNC patients often present delayed wound-healing, oedema and reduced response to chemotherapy and radiotherapy being the effective curative treatments often unsatisfactory. Malnutrition is still linked to increased risk of infection and post-operative complications. Patients malnourished present higher mortality rates and urgent hospital readmissions with economic implications [5] [6] [8] [12].

The overall risk of malnutrition is defined by the sum of all points allocated to each parameter and is classified as follows: 0 = low-risk; 1 = medium-risk; 2 = high-risk [13].

Analysis Strategies and Statistics

Completed questionnaires were scored according to EORTC instructions. Health-related QoL data were analysed by the Statistical Package for Social Sciences (SPSS), version 17 for Windows. Descriptive data are presented with means, standard deviations, medians, ranges, and proportions as appropriate. The chi-squared test was used for testing relationships between the studied variables and to determine whether if there was a significant difference between the expected frequencies and the observed frequencies in the studied variables.

1.3. Results

1) HNC Patients' Characteristics

Sociodemographic and clinical characteristics of the studied sample is presented in Table 1 (n = 114). Patients were mainly male (93.9%) and the majority was

Table 1. Head and neck cancer patients characteristics (n = 114).

Characteristics	n (%)
Gender	
Male	107 (93.9)
Female	7 (6.1)
Age (years)	
18 - 30	1 (0.9)
31 - 45	19 (16.7)
46 - 65	72 (63.2)
>65	22 (19.3)
MUST risk	
Low	72 (63.2)
Medium	10 (8.8)
High	32 (28.1)
Tumor location	
Oral cavity & oropharynx	38 (33.3)
Hypopharynx & larynx	61 (53.5)
Other	15 (13.2)
BMI	
>18.5	102 (89.5)
<18.5	12 (10.5)
Education	
≤6 years	86 (75.4)
>6 years	28 (24.6)

46 – 65 years old (63.2%), revealed low-risk of malnutrition (63.2%), a BMI greater than 18.5 (89.5%) and a low educational level (only 24.6% completed more than 6 schooling years). Hypopharynx and larynx were found to be the major tumour locations (53.5%).

2) Early identification of high risk of malnutrition in HNC patients according to age, tumour location, BMI and education

As depicted in Table 2, we found clear relationship between patient's age and the risk levels of malnutrition: high-risk patients were significantly younger than the low-risk malnutrition group ($p = 0.007$) and less heterogeneous (51.94 ± 6.56 and 58.94 ± 12.66 , respectively) presenting a lower age range (from 39 to 64 years old).

An association between tumour location and the risk of malnutrition was identified (Chi-squared = 20.287 degrees of freedom = 4, $p = 0.000$). Indeed, the high-risk malnutrition group presented greater tumour incidence in oral cavity & oropharynx (15 cases observed compared to 10.7 expected) and revealed an incidence in hypopharynx and larynx locations as expected (16 cases observed similar to 17.1 expected).

It was found an association between BMI and the risk for malnutrition (Chi-squared = 26.884; degrees of freedom = 2; $p = 0.000$). Indeed, all patients but one, presenting a BMI lower than 18.5, belonged to the high-risk group for malnutrition.

A relation between education and the risk for malnutrition was detected (Chi-squared = 6.763; degrees of freedom = 3; $p = 0.034$) as depicted in Table 2. In fact, higher education (more than 6 schooling years) was associated with a low-risk of malnutrition—this group presented fewer patients than expected with high-risk of malnutrition (ratio 0.63) and more patients than expected in

Table 2. Early identification of MUST risk in HNC patients ($n = 114$) according to age, tumour location, BMI and education (Chi-squared test was used, * $p < 0.005$; ** $p < 0.001$; Low, $n = 72$; Medium, $n = 10$; High, $n = 32$).

MUST risk	Low	Medium	High
Age mean $\pm$ SD (n)	58.94 $\pm$ 12.66 (72)	52.20 $\pm$ 11.34 (10)	51.94 $\pm$ 6.56 (32)*
Tumor location % (n)			
Oral cavity & oropharynx	13.16 (15)	7.02 (8)	13.16 (15) **
Hypopharynx & larynx	37.72 (43)	1.75 (2)	14.04 (16)
Other	12.28 (14)	0.00 (0)	0.88 (1)
BMI % (n)			
>18.5	62.28 (71)	8.77 (10)	18.42 (21)
<18.5	0.88 (1)	0.00 (0)	9.65 (11)**
Education % (n)			
Up to 6 years ($n = 86$)	42.98 (49)	8.77 (10)*	23.68 (27)*
More than 6 years ($n = 28$)	20.18 (23)*	0.00 (0)	4.39 (5)

the low-risk group of malnutrition (ratio 1.30). On the contrary, the less educated group proved to be more vulnerable to malnutrition risk, having more patients than expected both in the high-risk group (ratio 1.12) and in the medium-risk group of malnutrition (1.33).

3) Malnutrition risk in HNC patients and QoL impacts

It was found that the risk of malnutrition has consistent impact on QoL (Table 3).

Patients at high-risk of malnutrition revealed a constant and significantly lower mean score in Global health status and in QoL. A median of 42.71 was found for high-risk patients group significantly lower than the median found low or medium risk groups, with 62.96 and 53.33 respectively.

When we look for all functional scales—and therefore worse QoL and functioning—the results are comparable, showing lower scores in the high-risk group of patients.

Similar trend was found when considering all symptoms scales where the higher scores—reflecting greater symptomatology—were always found in this group (high-risk).

When considering the functional scales, no differences were found between medium and low risk patients. But for *Role*, *Emotional* and *Social Functioning scales*, significant differences ($p < 0.001$) occurred between high and medium patient's risk (median scores of 66.15, 65.63 and 77.08 for high-risk patients and 96.67, 90.00 and 96.67 for medium-risk patients when considering *Role*, *Emotional* and *Social Functioning scales* respectively).

Table 3. Impact of malnutrition (MUST risk) on HNC patient's QoL assessed by EORTC QLQ C-30 (Chi-squared test was used; Low, $n = 72$; Medium, $n = 10$; High, $n = 32$).

	Low	Medium	High	p
Global health status/QoL	62.96 ± 23.73	53.33 ± 23.31	42.71 ± 24.39	0.001
Physical functioning	82.72 ± 16.39	86.67 ± 7.70	75.00 ± 17.60	0.014
Role functioning	89.12 ± 20.01	96.67 ± 10.54	66.15 ± 36.30	0.001
Emotional functioning	79.17 ± 17.47	89.17 ± 13.06	65.63 ± 26.33	0.001
Cognitive functioning	91.67 ± 13.12	90.00 ± 8.61	79.69 ± 24.22	0.004
Social functioning	92.13 ± 13.98	96.67 ± 7.03	77.08 ± 27.35	0.001
Fatigue	14.35 ± 15.66	14.44 ± 20.32	34.72 ± 25.04	0.001
Nausea and vomiting	2.32 ± 7.56	1.67 ± 5.27	7.81 ± 16.93	0.052
Pain	15.75 ± 23.18	11.67 ± 13.72	43.23 ± 29.59	0.001
Dyspnea	1.36 ± 0.64	1.10 ± 0.32	1.66 ± 0.90	0.049
Insomnia	1.76 ± 0.91	1.70 ± 1.06	2.56 ± 1.01	0.001
Appetite loss	1.39 ± 0.66	1.50 ± 0.71	2.09 ± 1.06	0.001
Constipation	1.19 ± 0.55	1.00 ± 0.00	1.72 ± 1.05	0.001
Diarrhea	1.14 ± 0.39	1.00 ± 0.00	1.06 ± 0.25	0.332
Financial difficulties	1.29 ± 0.39	1.60 ± 1.08	2.13 ± 0.88	0.001

In symptom scales, scores were always higher in the high risk of malnutrition group, revealing to be significantly different from the low risk of malnutrition group except for *Diarrhoea* and *Nausea and vomiting*.

The major associations were found in *Fatigue*, *Pain*, *Insomnia*, *Appetite loss* and *Financial difficulties* symptoms ($p = 0.001$). Moreover, *Fatigue*, *Pain*, *Insomnia* and *Constipation* symptom's differences also occurred between high and medium risk patients. A particularly significant difference verified was in *Fatigue* and *Pain* scales, with median scores for high-risk patients of 34.72 and 43.23 and median scores for low-risk patients of 14.35 and 15.75, respectively. The same differences were encountered for medium-risk patients (medium scores of 14.44 for *Fatigue scale* and 11.67 for *Pain scale*).

Just like in the functional scales, when considering the symptom scales, no differences were found between medium and low risk patients.

2. Discussion

HNC patient's demographic patterns have been changing over the past 30 years—they are more likely to be younger adults in their 40s and 50s who never smoked or had reduced tobacco exposure. It is suggested that 70% - 90% of new cancers are oropharyngeal, an evidence of the human papillomavirus (HPV) [14]. The studied sample does not follow such trend since patients are older (63.2% having 46 - 65 years old) and the major tumour location was not oropharyngeal but hypopharynx and larynx.

These findings may reflect a limitation of our study because patients were included while they have been presented to first time consultation in our department for a consecutively period of 6 months. So, this study population may not reflect the real incidence of HNC in Portugal when we are looking for some demographic data or incidence according to HNC primary sites.

Pharynx, larynx, and oral cavity tumour location is a predictor of greater weight loss. Side effects are related to HNC, mainly in oral cavity and oropharynx tumour locations: dysphagia and odynophagia, oral mucositis, dry mouth, taste loss, trismus, muscles fibrosis, ulcerations, teeth loss, chewing and swallowing difficulties [8] [15] [16] [17].

More than half of the problems influenced by HNC have some connection with nutritional problems. Eating-related problems (oral pain, fit of the dental prostheses, prolonged eating time, reduced eating pleasure, and not being able to eat with family and friends) usually appear early and often even before diagnosis (20% - 67% are malnourished or at high risk of becoming malnourished at diagnosis). So, malnutrition high risk in HNC patients can happen at presentation and the nutritional status gradually declines during treatment and most patients undergoing treatment will need nutritional therapy [8] [15] [16] [17].

We found the majority of HNC patients had low risk of malnutrition (63.2%), a clear contrast to values often described in the literature referring up to 80% malnourished because of their lifestyle and the risk factors associated with this

disease [18]. Such difference may be explained by the fact that assessment occurred when patients were admitted at the Head & Neck Unity, before any treatment [19] [20].

Nutritional assessment supports and institutional awareness, may favour early nutritional intervention on nutritional status [21] [22]. Awareness of this fact is of major importance when establishing a treatment and follow-up schemes in HNC patients.

HNC are a naturally diverse group of tumours linked by anatomical proximity [4]. HNC patients are commonly associated with low patient health literacy as a result of poor education and socioeconomic status [23] [24]. Indeed, the low patient's literacy level found (only 24.6% completed more than 6 schooling years) reinforces this idea and adds new challenges. Once more the patient recruiting process used in our study can be a limitation when looking to this data because of the possible bias in the population selected.

Certainly, with an aging population and advances in diagnosis and treatment, the number of patients living with the effects of HNC and its treatment continue to rise. Thus, literacy and educational support for both patients and caregivers, particularly in areas of survivorship, are important to optimize well-being [25] [26].

BMI should be always considered when analysing HNC patients in order to follow weight loss described during treatments [27]. An association between BMI and survival has been described [28]. The BMI observed, greater than 18.5 for the vast majority of the studied patients (89.5%) seems thus to constitute a positive prognostic factor. On the other hand, as said before, the recruiting process used in our study may not represent with accuracy the true HNC patients in Portugal. But in this case we don't see this as a limitation of our study because the purpose of the study was to see the relationship of the malnutrition risk in HNC patients and its impact on QoL.

In the present study, patients at high risk of malnutrition revealed a constant and significantly poor QoL in multiple domains. Nutritional status is a strong predictor for HNC patients' QoL before, during and after treatment. Weight loss and malnutrition conduces to nutritional interventions: oral, enteral and parenteral and immune-enhanced nutrition. Tube feeding, usually an invasive procedure, is associated with extended hospitalization, QoL negative impacts and risk of mortality. On the other hand, oral nutritious supplements may introduce several problems: decrease salivary flow and quality, reduce oral clearances, increase bacteria colonization, risk of oral diseases or oral dehydration. QoL domains, such as: swallowing, taste and smell, sticky saliva, mouth pain, speech problems, discouragement or feeling ill, are commonly affected by nutritional interventions. Percutaneous endoscopic gastrostomy, used when long-term tube feeding is necessary, is associated with improved QoL. Quality of nutritious supplements make all difference: the ideal oral supplement should be ready-to-eat, most resemble to regular food (solid like), chewable, moisten, and easy to swallow [15]

[29] [30] [31]. Our study shows that patients with high-risk for malnutrition have low scores for Global QoL. So routine QoL evaluation, complementing the usual follow-up schemes, is a good surveillance tool and an eventually a good nutritional indicator.

Emotional and social functioning scales and all *symptom scales* presented significant differences between high and medium risk of malnutrition patients. Functional impairments and psychological distress are common in HNC (20% - 60% of patients have depressive symptomatology two to three months post-diagnosis). In the present study, *fatigue, pain, insomnia* and *appetite loss* were domains particularly associated to high risk of malnutrition group. There is a dynamic and reciprocal association between QoL domains (depressive and anxiety symptoms, pain, nausea, fatigue, appetite) and weight loss. Pain is considered a robust predictor of poorer QoL in HNC [7] [32] [33].

In this study we can state that pain is the most limitation related to malnutrition. Our data shows that patients in the high-risk group for malnutrition have poorer scores on *Pain scale* and the impact only occurs in this group (low and medium risk group of patients have similar scores in *Pain scale*). Future development of this finding could relate QoL evaluation, pain control and analgesics consumption, with nutritional status.

Lifestyle mediation (nutritional and psychosocial support, physical activity orientation) at the moment of diagnosis has been recognized as an important intervention, helping patients to manage side effects and improve their QoL [5].

HNC patients should be subject to a plan contemplating early identification of malnutrition high risk and nutrition interventions. Comprehensive nutritional assessment, documentation, weight loss follow-up and QoL evaluation should be include since admission. It would contribute to identify different needs during the disease trajectory in order to ensure appropriate interventions. Effective nutritional interventions should ultimately aim to improve QoL [16] [17] [19] [22] [34].

3. Conclusions

HNC patients are a recognized high-risk group for malnutrition and the diagnostic criteria used to define patients as malnourished lacks uniformity. Perform pre-treatment nutrition and QoL assessments allows early identification of high-risk patients representing a fundamental step to identify nutrition status at baseline, in order to improve it during and after treatments.

HNC patients with oral cavity and oropharynx tumour locations, older, with low literacy or with BMI under 18.5 at the moment of diagnosis, represent a high-risk group.

When HNC is considered, a dynamic and bi-directional connection between malnutrition and QoL is observed. *Emotional and social functional scales* and all *symptom scales*—including *pain*, presented significant differences between high and medium risk of malnutrition patients. *Fatigue, pain, insomnia, appetite loss*

and *financial difficulties* were domains directly related to high risk of malnutrition patients.

Nutrition support should be considered at any stage of the pathway—especially in high risk group—in order to optimize tumour treatment results, reduction of adverse effects of therapy and improving both QoL and survival.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Health Related Quality of Life and Biochemical markers for Cachexia evaluation in Head and Neck Cancer patients

ABSTRACT:

Cachexia is a multifactorial syndrome related to unintentional weight loss and to loss of muscle and fat mass. In head and neck cancer (HNC) its incidence is important and not only related to a deficient intake of food due to the impact of the disease in the vital functions. A complex disturbance in the normal metabolism of the patient promotes a persistent inflammatory state and a shifting in the metabolism balance toward a catabolic predominance affecting primarily the skeletal muscle. This leads to severe impairment of the functional, emotional and social status and quality of life of the patients that will compromise response to treatment and the disease prognosis.

Understanding this deleterious syndrome and mainly identifying it in early stages of the disease is of a major importance in achieving better outcomes to head and neck cancer patients. This study pretends to identify clinical aspects related to cachexia in HNC in a clinical perspective for application on the routine clinical practice.

In our study, 30 HNC patients were enrolled and evaluated in terms of nutritional values (actual and loss of weight in the past 6 months, body mass index (BMI), nutritional risk index (NRI), malnutrition universal screening tool), serum biochemical markers (albumin, total proteins, cholesterol, triglycerides, urea, C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α) and myostatin) and health related quality of life (HRQoL) evaluation (using European Organisation for the Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ): EORTC QLQ-C30 and EORTC QLQ-HN43). A minimum follow-up of 48 months was considered for all patients.

Our results showed that NRI is a good and sensitive index to identify cachexia. This index uses two parameters, one constitutional (loss of weight) and one biochemical (level of serum albumin). According to this criteria, 16 patients were assigned to the No-cachexia group and 14 patients to the Cachexia group. Significant differences in the constitutional and nutritional values between the two groups were found: the median weight loss was 4,44 kg in the No-cachexia group and 11,29 kg in the Cachexia group, while the BMI was 21,88 and 18,33, respectively. In terms of

biochemical markers, significant low values of albumin and cholesterol in the Cachexia group were encountered when compared to the No-cachexia group. Regarding to the inflammatory and cachexia biomarkers studied, the results show that patients in the Cachexia group had significantly higher levels of CRP and of the proinflammatory cytokines IL-6 and TNF- α and presented significantly raised levels of the myostatin. In terms of HRQoL evaluation, the scores of the EORTC QLQ-C30 revealed that all the scales and the Summary Score showed lower scores in the Cachexia group, indicating worst quality of life evaluation. The items scores were globally higher in the Cachexia group indicating more important problems related to those items in the Cachexia group. The difference encountered between the groups was significant ($p < 0.001$) in all considered scales but two: Dyspnoea and Constipation. Considering the EORTC QLQ-HN43 all the scales and in all single items but one (Wound Healing) the scores were higher in the Cachexia group, indicating a worst degree of problems affecting these group of patients. The difference found between the groups was significant ($p < 0.001$) in all scales and items but six: Dry Mouth and Sticky Saliva, Skin problems, Problems with Teeth, Trismus, Social Contact and Wound Healing.

There were no significant differences in the clinical presentation of the disease between the two groups. The median survival was of 13.5 months in the Cachexia group, significantly lower when compared to the No-cachexia group ($p < 0.0001$), confirming the major impact of cachexia in survival and clinical outcomes in HNC patients.

These results of our study show that HRQoL evaluation and serum biochemical markers are sensitive and important tools in identifying and screening cachexia in HNC patients. The methodology followed in this study correlating HRQoL with biochemical markers support the development of clinical protocols in HNC that include cachexia evaluation. Hopefully this new approach can help to improve prognosis of the disease.

Health Related Quality of Life and Biochemical Markers for Cachexia Evaluation in Head and Neck Cancer Patients

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How to cite this paper: Castro Silva, J., Tavares, P., Ferreira, R., Santos, L.L. and Monteiro, E. (2021) Health Related Quality of Life and Biochemical Markers for Cachexia Evaluation in Head and Neck Cancer Patients. *International Journal of Otolaryngology and Head & Neck Surgery*, 10, 320-335.

<https://doi.org/10.4236/ijohns.2021.104029>

Received: June 30, 2021

Accepted: July 18, 2021

Published: July 21, 2021

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Abstract

Cachexia is a multifactorial syndrome related to unintentional weight loss and to loss of muscle and fat mass. In head and neck cancer (HNC) its incidence is important and not only related to a deficient intake of food due to the impact of the disease in the vital functions. A complex disturbance in the normal metabolism of the patient promotes a persistent inflammatory state and a shifting in the metabolism balance toward a catabolic predominance affecting primarily the skeletal muscle. This leads to severe impairment of the functional, emotional and social status and quality of life of the patients that will compromise response to treatment and the disease prognosis. Understanding this deleterious syndrome and mainly identifying it in early stages of the disease is of a major importance in achieving better outcomes to head and neck cancer patients. This study pretends to identify clinical aspects related to cachexia in HNC in a clinical perspective for application on the routine clinical practice. In our study, 30 HNC patients were enrolled and evaluated in terms of nutritional values (actual and loss of weight in the past 6 months, body mass index (BMI), nutritional risk index (NRI), malnutrition universal screening tool), serum biochemical markers (albumin, total proteins, cholesterol, triglycerides, urea, C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α) and myostatin) and health related quality of life (HRQoL) evaluation (using European Organisation for the Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ): EORTC QLQ-C30 and EORTC QLQ-HN43). A minimum follow-up of 48 months was considered for all patients. Our results showed that NRI is a good and sensitive index to identify cachexia. This index uses two parameters, one constitutional (loss of weight) and one biochemical (level of serum albumin). According to this criterion, 16 patients were assigned to the No-cachexia

group and 14 patients to the Cachexia group. Significant differences in the constitutional and nutritional values between the two groups were found: the median weight loss was 4.44 kg in the No-cachexia group and 11.29 kg in the Cachexia group, while the BMI was 21.88 and 18.33, respectively. In terms of biochemical markers, significant low values of albumin and cholesterol in the Cachexia group were encountered when compared to the No-cachexia group. Regarding the inflammatory and cachexia biomarkers studied, the results show that patients in the Cachexia group had significantly higher levels of CRP and of the proinflammatory cytokines IL-6 and TNF- α and presented significantly raised levels of the myostatin. In terms of HRQoL evaluation, the scores of the EORTC QLQ-C30 revealed that all the scales and the Summary Score showed lower scores in the Cachexia group, indicating worst quality of life evaluation. The items scores were globally higher in the Cachexia group indicating more important problems related to those items in the Cachexia group. The difference encountered between the groups was significant ($p < 0.001$) in all considered scales but two: Dyspnoea and Constipation. Considering the EORTC QLQ-HN43 all the scales and in all single items but one (Wound Healing) the scores were higher in the Cachexia group, indicating a worst degree of problems affecting these group of patients. The difference found between the groups was significant ($p < 0.001$) in all scales and items but six: Dry Mouth and Sticky Saliva, Skin problems, Problems with Teeth, Trismus, Social Contact and Wound Healing. There were no significant differences in the clinical presentation of the disease between the two groups. The median survival was of 13.5 months in the Cachexia group, significantly lower when compared to the No-cachexia group ($p < 0.0001$), confirming the major impact of cachexia in survival and clinical outcomes in HNC patients. These results of our study show that HRQoL evaluation and serum biochemical markers are sensitive and important tools in identifying and screening cachexia in HNC patients. The methodology followed in this study correlating HRQoL with biochemical markers supports the development of clinical protocols in HNC that include cachexia evaluation. Hopefully this new approach can help to improve prognosis of the disease.

Keywords

Cachexia, Head Neck Cancer, Quality of Life, Biochemical Markers, Malnutrition

1. Introduction

Head and neck cancer (HNC) treatment has evolved through the times, particularly in the last decades with the introduction of the so-called organ preservation treatments either with the use of new drugs or the development of more conservative surgeries using laser or robotics. Nevertheless, besides all this progress, overall survival didn't change much, particularly for larynx cancer and recurrent or metastatic disease [1] [2] [3].

On the other hand, the impact of HNC on the global status of the patients is

important, contributing to a progressive worsening of the physical, emotional and social conditions with a major impact on their quality of life. Understanding these factors can help us to improve global status of these patients and eventually get a better prognosis for their disease. One of these conditions that impacts the prognosis and quality of life of HNC patients is cachexia [4] [5].

Cachexia is a multifactorial syndrome related with loss of skeletal muscle and fat mass. It's not only, but mostly related with cancer. In HNC its incidence is important and more than 50% of patients with advanced HNC have important weight loss and cachexia [6].

HNC patients with cachexia present with important unintentional weight loss, asthenia, anorexia, anaemia, fatigue, sarcopenia which led to significant decrease in global functional status.

The establishment of this syndrome considerably affects prognosis of the disease and has a negative impact on the response to treatment, increasing toxicities and complications. This implies a poor overall survival in these patients: cachexia is the cause of death in 20% of all-cancer patients [6].

The metabolic changes associated with HNC patients are due not only to the limitations imposed by the disease or treatments that limit the adequate intake of nutrients, but the disease itself induces changes at the cellular and molecular level that originate these very metabolic changes leading to a state of cachexia. This multi-factorial paraneoplastic syndrome leads to progressive weight loss and to a permanent inflammatory response.

Weight loss is often observed when the first signs of disease appear and when it reaches 30% it is generally fatal [6].

The inflammatory response is related to an accentuated catabolism that is mediated by factors released by the tumor and the host. These mediators seem to induce an imbalance between protein synthesis and degradation, leading to protein depletion and, consequently, loss of muscle mass, the degree of which is inversely correlated with the patients' lifespan. In the inflammatory response several biomarkers are implicated: C-reactive protein (CRP), albumin, proteins, interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), myostatin and others [7] [8] [9].

Thus, cachexia seems to result from a natural evolution of the oncological disease, regardless of the quantity or quality of food intake.

The cachexia syndrome related to HNC patients is an important factor in these patients and conditioning the prognosis of the disease. HNC patients with cachexia will have worst functional status with impact on their quality of life [5] [6] [7]. Also, these patients will have worst responses to treatment, with lower rates of adhesion to treatment and higher rates of toxicities and complications.

Early identification of cachexia in HNC patients will promote an early intervention in these patients to start a clinical strategy to improve patient status and prevent refractory cachexia that can lead to a better response and adhesion to treatment and reduce rates of toxicities and complications, improving outcomes

and quality of life.

Quality of life evaluation, body weight and cachexia biomarkers screening can be important tools to the early identifications of patients in risk of cachexia regarding to HNC.

In the literature all these parameters are already studied and their importance in the clinical setting is well proved. Nevertheless, we didn't find any study that has evaluated all these parameters and its inter-relations in the clinical practice in HNC and we found in recent reviews references to promote these studies in cachexia research [10] [11] [12] [13]. To understand the relations between all these factors and understand their close relation to cachexia in a clinical application perspective was the main purpose of this prospective study.

2. Material and Methods

Patients with head and neck squamous cell carcinoma between 2016 and 2017 were evaluated in its first presentation at Department of Otorhinolaryngology of Instituto Português de Oncologia do Porto Francisco Gentil (IPOPFG).

The eligibility criteria included patients: 1) no obese (body mass index—BMI < 30) and no diabetic; 2) no prior history of cancer nor submitted to prior cancer treatment.

Body weight, lost of weight in the last 6 months, BMI and Malnutrition Universal Screening Tool (MUST) score were recorded. Serum levels of biochemical markers were determined after blood sample: albumin, total proteins, cholesterol, triglycerides, urea, C-reactive protein, interleukin-6, tumour necrosis factor- α and myostatin.

The blood samples were collected and treated in the same manner of other routine blood tests done in our Institution.

Health Related Quality of life (HRQoL) evaluation was done using European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ): EORTC QLQ-C30 and EORTC QLQ-HN43. These questionnaires are translated and validated for Portuguese and were answered by the patients with the assistance of clinical staff when needed. The Department of Otorhinolaryngology of IPOPFG has implemented since more than a decade routine evaluation of HRQoL for all patients treated.

This methodology was chosen to ensure that all the evaluation and collecting data was taken as it would be on the usual daily clinical routine of the Department and could be reproducible in different clinical Institutions.

This study was approved by the Ethical Committee and all patients signed a consent form.

Thirty males were enrolled with a minimum follow-up of 48 months, and they were assigned into two groups—Cachexia and No-cachexia—according to the Nutritional Index Score.

Values are presented as mean $\pm$ standard deviation for each group. The statistical significance of the differences between groups was determined using the

unpaired student t-test.

The level of significance was set at 5% (p-value < 0.05). These statistical analyses were performed with the GraphPad Prism® software.

3. Results

Thirty patients with HNC were included in this study. All patients were male, with an average age of 55 years (range 43 to 77 years).

After a preliminary analysis of the experimental data from biochemical markers and body weight loss and BMI, patients were redistributed based on the nutrition risk index (NRI) [14] [15].

Nutritional risk was assessed through the application of the NRI tool developed by the Veteran Affairs Total Parenteral Cooperative Study Group [16]. This is a tool with high sensitivity and specificity [17] [18]. The NRI is determined using the values of serum albumin, and of the actual and usual percentage weight, based on the following equation:

$$NRI = 1.519 \times \text{Alb serum (g/dl)} + 0.417 \times ((\text{actual weight/usual weight}) \times 100))$$

The following criteria were used for the analysis of results: above 100 indicate satisfactory nutritional status; between 97.5 and 100, mild risk of malnutrition; from 83.5 to 97.5, moderate risk; and below 83.5, severe risk.

Patients with NRI equivalent to a satisfactory nutritional status or mild risk were considered without cachexia and thus included in the No-cachexia group. Patients with moderate or severe risk were considered with cachexia and included in the Cachexia group.

According to this criteria, 16 patients were assigned to the No-cachexia group and 14 patients to the Cachexia group.

Albumin serum levels were significantly lower (Table 3) as were significantly higher the percentage of body weight loss (Table 1) in the Cachexia group. This difference was already expected since these values were used for the determination of NRI (criteria to define the two groups). Regarding BMI, this was lower in patients in the Cachexia group (p < 0.01). Patients from No-cachexia group presented an average BMI of 22, which is an indicator of healthy weight [19].

Patients were screened also using the MUST score and we observe that in the No-cachexia group most of the subjects presented with a MUST score of 0. On the other hand, in the Cachexia group 25% of patients were identified at high risk of malnutrition, presented a MUST score of 4 (Table 1).

No significant age differences were noticed between groups (54.9 ± 7.3 on Cachexia group and 58.3 ± 9.3 on No-cachexia group). There were also no significant differences between the clinical presentation of the tumours between the two groups. In Cachexia group all patients presented with TNM stage IV tumours and most of them in the pharynx: 5 patients in the oropharynx, 1 in the nasopharynx, 7 in the hypopharynx and 1 in the oral cavity; in No-cachexia group most of the patients presented locoregionally advanced tumours (12 patients with TNM stage IV and 3 patients with TNM stage III) and only 1 pre-

sented with a TNM stage I tumour and also most of these tumours were located in pharynx: 3 in the oropharynx, 1 in the nasopharynx, 4 in the hypopharynx, 5 in the larynx and 3 in the oral cavity (Table 2).

A minimum follow-up of 48 months was considered to all patients and overall survival was recorded. A median survival of 13.5 months in the Cachexia group was significantly lower when compared to the No-cachexia group ($p < 0.0001$) and survival comparison between the groups is shown by the Kaplan-Meier

Table 1. Characterization of patients relative to NRI, age, body weight loss, BMI and MUST score.

	Groups	
	Cachexia	No-cachexia
NRI	86.90 $\pm$ 7.31****	104.60 $\pm$ 3.12
Age (years)	54.9 $\pm$ 7.3	58.3 $\pm$ 9.3
Body weight loss (Kg)	11.29 $\pm$ 6.08**	4.44 $\pm$ 3.87
BMI (Kg/m ²)	18.33 $\pm$ 2.96**	21.88 $\pm$ 3.53
MUST (n)		
0	1	9
1	3	1
2	5	4
3	1	2
4	4	0
TOTAL	14	16

Values are expressed as mean $\pm$ standard deviation. ** $p < 0.01$; **** $p < 0.0001$.

Table 2. Characterization of patients relative to location and TNM stage of the disease.

Location (n)	Groups	
	Cachexia	No-cachexia
Oral cavity	1	3
Nasopharynx	1	1
Oropharynx	5	3
Hypopharynx	7	4
Larynx	0	5
TOTAL	14	16
TNM Stage (n)		
I	0	1
II	0	0
III	0	3
IV	14	12
TOTAL	14	16

graphic (Figure 1).

Concerning biochemical parameters assessed in serum samples, albumin levels were significantly lower in the Cachexia group ($p < 0.0001$), already expected since these values were used in NRI calculation and, consequently, in patients' assessment to each group. A significant decrease in cholesterol levels ($p < 0.001$) was observed in the Cachexia group (Table 3).

For the remaining biochemical parameters assessed (glucose, urea, total proteins and triglycerides), no differences were observed between groups (Table 3).

Regarding to the inflammatory and cachexia biomarkers studied, the results show that patients in the Cachexia group had significantly higher levels of CRP and of the proinflammatory cytokines IL-6 and TNF- α and presented significantly elevated levels of the myostatin, which may be suggestive of muscle mass loss in this group of patients (Table 3).

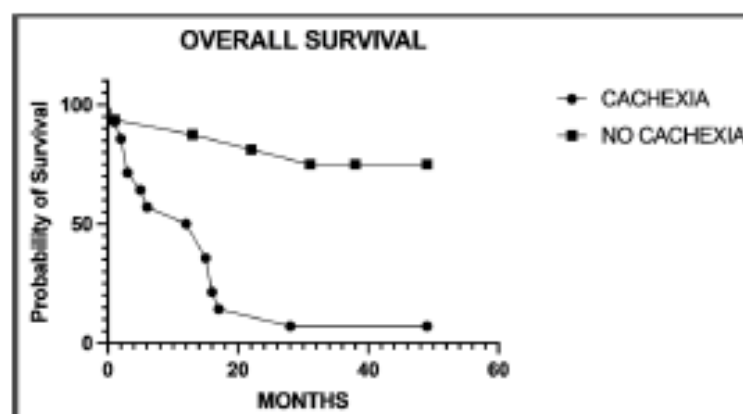


Figure 1. Overall survival (Kaplan-Meier).

Table 3. Characterization of patients relative to serum biochemical parameters.

	Groups	
	Cachexia	No-cachexia
Albumin (g/L)	34.21 $\pm$ 1.49****	43.25 $\pm$ 0.66
Glucose (mmol/L)	5.521 $\pm$ 0.217	5.531 $\pm$ 0.203
Total Proteins (g/L)	72.14 $\pm$ 2.163	72.81 $\pm$ 1.108
Urea (mmol/L)	3.336 $\pm$ 0.291	4.939 $\pm$ 0.248
Cholesterol (mmol/L)	3.653 $\pm$ 0.205***	4.931 $\pm$ 0.248
Triglycerides (mmol/L)	1.114 $\pm$ 0.092	1.334 $\pm$ 0.178
CRP (mg/L)	49.79 $\pm$ 10.73**	15.86 $\pm$ 4.739
IL-6 (OD)	856.5 $\pm$ 65.41*	691.5 $\pm$ 60.94
TNF- α (OD)	681.9 $\pm$ 72.43**	482.7 $\pm$ 80.66
Myostatin (OD)	700.7 $\pm$ 57.02**	504.7 $\pm$ 34.11

Values are expressed as mean $\pm$ standard deviation. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. OD – arbitrary units of optical density. (from immunoblot analysis)

All patients underwent quality of life evaluation answering at first time observation to the EORTC Quality of life Questionnaire C-30 (EORTC QLQ-C30) [20] and the updated EORTC Head and Neck Quality of life Questionnaire module HN43 (EORTC QLQ-HN43) [21] [22].

EORTC QLQ-C30 has 30 questions that are combined in 13 scales: Global Quality of Life, Physical Functioning, Role Functioning, Social Functioning, Emotional Functioning, Cognitive Functioning, Fatigue, Pain, Nausea and Vomiting, Dyspnoea, Sleeping Disturbances, Appetite loss, Constipation, Diarrhoea and Financial Impact. Also, there is a global score, the EORTC-QLQ-C30 Summary Score [23], that was calculated. All the scales and the Summary Score showed lower scores in the Cachexia group, indicating worst quality of life evaluation. The items scores were globally higher in the Cachexia group indicating more important problems related to those items in the Cachexia group. The difference encountered between the groups was significant ($p < 0.001$) in all considered scales but two: Dyspnoea and Constipation (Table 4).

EORTC QLQ-HN43 module has 43 questions and is combined into 12 scales (Fear of Progression, Body Image, Dry Mouth and Sticky Saliva, Pain in the Mouth, Sexuality, Problems with Senses, Problems with Shoulder, Skin Problems, Social Eating, Speech, Swallowing and Problems with Teeth) and 7 single items (Coughing, Swelling in the Neck, Neurological Problems, Trismus, Social Contact, Weight Loss and Wound Healing). In all the scales and in all single

Table 4. EORTC QLQ C-30 scores.

Scales and items	Cachexia	No-cachexia	p
Global health status/QoL	42.27 ± 35.12	64.07 ± 23.51	<0.001
Physical functioning	70.41 ± 20.10	87.09 ± 13.21	<0.001
Role functioning	75.00 ± 25.11	87.50 ± 18.76	<0.001
Emotional functioning	72.03 ± 19.51	84.38 ± 15.77	<0.001
Cognitive functioning	82.15 ± 25.71	89.59 ± 15.96	0.010
Social functioning	73.81 ± 31.16	93.75 ± 14.75	<0.001
Fatigue	40.48 ± 30.07	17.37 ± 16.22	<0.001
Nausea and vomiting	2.33 ± 18.20	3.13 ± 12.50	0.010
Pain	36.91 ± 20.86	23.96 ± 24.32	<0.001
Dyspnoea	11.91 ± 28.06	12.50 ± 16.67	0.797
Sleeping Disturbances	47.62 ± 38.60	31.25 ± 30.96	<0.001
Appetite loss	35.72 ± 42.29	18.75 ± 29.74	<0.001
Constipation	9.52 ± 24.21	6.25 ± 13.44	0.199
Diarrhoea	7.14 ± 26.73	0.00 ± 0.00	0.010
Financial difficulties	45.24 ± 46.42	20.84 ± 26.88	<0.001
Summary Score	74.45 ± 13.60	85.38 ± 11.09	<0.001

Values are expressed as mean ± standard deviation.

items but one (Wound Healing) the scores were higher in the Cachexia group, indicating a worst degree of problems affecting these group of patients. The difference found between the groups was significant ($p < 0.001$) in all scales and items but six: Dry Mouth and Sticky Saliva, Skin problems, Problems with Teeth, Trismus, Social Contact and Wound Healing (Table 5).

4. Discussion

Patients with HNC have high rates of morbidity and mortality that are closely associated with critical weight loss, a common feature in these patients [24].

When compared to other cancers, HNC patients have greater weight loss incidence, in part due to the difficulty in swallowing presented by these patients [25].

Also, in these patients, smoking and drinking habits, the most common etiological factors associated to the development of HNC, are important and have been associated to malnutrition [25]. Some studies indeed showed that the risk of malnutrition increases with the amount of alcohol consumed [26].

On the other hand, several studies associate HNC patients with cachexia and showed that this syndrome was not reverted by parental nutrition [27].

Table 5. BORTC QLQ HN-43 scores.

Scales and Items	Cachexia	No-cachexia	p
Fear of progression	44.05 ± 21.29	34.38 ± 23.15	<0.001
Body image	42.86 ± 32.57	21.53 ± 18.80	<0.001
Dry mouth & sticky saliva	25.00 ± 20.41	22.92 ± 20.97	0.298
Pain in the mouth	42.86 ± 27.90	20.31 ± 19.71	<0.001
Sexuality	36.91 ± 31.37	19.79 ± 25.98	<0.001
Problems with senses	17.86 ± 27.32	7.2975 ± 10.49	<0.001
Problems with shoulder	19.05 ± 31.25	8.33 ± 10.54	<0.001
Skin problems	4.76 ± 10.42	4.16 ± 7.99	0.513
Social eating	24.41 ± 24.56	11.98 ± 22.56	<0.001
Speech	30.95 ± 28.24	19.17 ± 14.17	<0.001
Swallowing	33.33 ± 26.75	21.88 ± 24.13	<0.001
Problems with teeth	22.22 ± 28.24	18.75 ± 15.03	0.136
Coughing	35.71 ± 35.72	25.00 ± 22.77	<0.001
Swelling in the neck	42.86 ± 40.15	22.92 ± 26.44	0.362
Neurological problems	19.05 ± 25.20	6.25 ± 13.44	0.551
Trismus	21.43 ± 30.96	18.75 ± 29.74	<0.001
Social contact	9.52 ± 24.21	8.33 ± 14.91	<0.001
Weight loss	50.00 ± 31.35	18.75 ± 24.25	0.001
Wound healing	2.38 ± 8.91	6.25 ± 13.44	<0.001

Values are expressed as mean ± standard deviation.

The evidence shows that clinical management of cachexia is difficult and complex and poorly recognized or assessed [14] [28]. The cause of this can be in part justified by a misdiagnosis of cachexia in head and neck cancer patients. So, in our study a special focus was put in the definition of the criteria to differentiate patients with cachexia and without cachexia.

Although loss of weight or percentage of lost weight in the past 6 months, and even MUST scores, showed differences between patients it was the Nutritional Risk Index that showed high sensitivity to compare the patients in terms of with or without a wasting phenotype when analysed with the biochemical markers. The NRI was the index chosen because it is highly sensitive when compared to other nutritional assessments. Studies showed that when investigating the ability to detect conditions such as sarcopenia, pre-cachexia, and cancer cachexia, NRI presented the better accuracy (about 74.7%) in identifying patients with at least one of these conditions, when compared to other screening tools (e.g. MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool) [14].

In this way, our study confirms NRI as a good indicator and screening tool to evaluate cachexia in the context of HNC patients. This tool uses values related to the nutritional and constitutional aspects of the patients: the percentage of weight lost, and a biochemical marker of depletion, serum albumin. We can say that NRI addresses a good compromise between these two factors so important in the definition of cachexia.

Once established the experimental groups by the nutritional criteria above defined, we've enrolled two groups of patients that are homogeneous in terms of demographic and clinical patterns. We have only enrolled males to avoid differences due to a different hormonal environment in women. There were no differences between ages. In terms of clinical presentation and staging of the disease there were no asymmetries between the two groups. As expected, all of the patients in the Cachexia group presented with a locoregional advanced disease—TNM stage IV, but we manage to have a similar group of patients in the No-cachexia group, with only one patient with early stage disease—TNM stage I. In terms of location of the tumour there were also few asymmetries between the groups: eventually a higher proportion of pharynx cancers in the Cachexia group and a higher proportion of larynx cancers in the No-cachexia group. This can be explained in terms of a bigger impact of the pharynx tumours in the intake and swallow of food when compared to larynx tumours, even when considered locally advanced tumours.

With the two groups well defined, we've done a minimum follow-up of 48 months and encountered a significant difference in overall survival between the groups. In the Cachexia group only one patient in the fourteen considered is still alive and conclude the treatment proposed, all the others died from the disease with a median survival of 13.5 months and most of them didn't complete the treatment proposed or didn't have the conditions for elective treatment. In the

No-cachexia group most of the patients completed the proposed treatment and overall survival was similar to the overall survival for HNC patients. Our study confirms that cachexia and nutritional impairment has a negative impact in prognosis and survival for HNC patients.

Cachexia is a multifactorial syndrome that is responsible for the presence of an inflammatory state and a catabolic environment in the patients. These features are expressed in the high levels of some biomarkers in serum samples from these patients. The presence of this Inflammation state is a major characteristic of this syndrome and distinguishes it from other syndromes like sarcopenia [29] [30]. On the other hand inflammation is always present in head and neck cancer patients, even if not at very high levels [31]. So, another point in our study was to demonstrate the relation between inflammation and body weight loss and cachexia in head and neck cancer patients.

In our study we found a significant difference in the serum levels of CRP, IL-6 and TNF- α between our two groups of patients. We can assume that HNC patients with cachexia have a significant level of inflammation when compared to patients without cachexia.

CRP, although not specific, is a sensitive marker of inflammation and it is synthesized in the liver induced by proinflammatory cytokines, mainly IL-6. The persistence of this inflammatory state leads to a continuous production of this acute phase protein, promoting the reprioritization of amino acid metabolism in peripheral tissues, especially muscles, towards the liver. Therefore, muscle catabolism occurs. Our study showed an increase of circulating CRP levels in the group of Cachexia patients and was paralleled by the increase of IL-6, which is known to promote the liver synthesis of CRP [32] [33].

Besides that, TNF- α high serum levels were previously associated with HNC [34]. We also found in our study a significantly high level of TNF- α in the Cachexia group confirming once more the relationship of inflammation with the wasting phenotype.

On the other hand, studies demonstrated IL-6 and TNF- α are related to cellular pathways that mediate muscle mass loss and protein synthesis inhibition [35] [36]. Myostatin is secreted and expressed mainly by skeletal muscle cells and has a main role in the regulation of muscle mass, blocking myoblast proliferation and suppression of satellite cell activation [37]. So, there is a negative correlation between elevated myostatin serum levels and skeletal muscle mass and studies have demonstrated that myostatin is involved in various diseases involving muscle mass loss [38] [39] [40]. Our data shows that patients in Cachexia group have significant higher levels of myostatin when compared to patients in the No-cachexia group. So myostatin is an important marker related to skeletal muscle mass loss and can signalling cachexia.

Health related quality of life evaluation has an important role in the management of HNC patients. This evaluation addresses issues that consider the patient as an individual and its relations in terms of himself, his family and society

where he lives. This evaluation is well established and accurate and changes verified, in the settle of HNC, among others, are related to changes in terms of the disease [20] [41] [42] [43]. EORTC has developed validated questionnaires and recently have made an actualization of the specific questionnaire module for head and neck cancer, the EORTC QLQ-HN43 [21] [22]. In our study we have applied to all patients at presentation both questionnaires proposed by EORTC to evaluate head and neck cancer patients: the EORTC QLQ-C30 with the newest EORTC QLQ-HN43. Our data showed that most of the scales and items were related to significantly worst quality of life parameters in the patients of the Cachexia group. The Global QoL and the Summary Score for EORTC QLQ-C30 can be global measures of HRQL [23] [44] [45] for these patients and show significant differences when considering cachexia patients. Scores for Dyspnoea and constipation scales didn't show significant differences and we can say that these items aren't important in the settle of cachexia when considering HNC patients.

The newly specific head and neck cancer module, the EORTC QLQ-HN43, also gave significant differences in the scores of most of the scales and items, demonstrating worst scores in the Cachexia patients group. The presence of a non-significant difference in the scores between the two groups in the scales and items Dry Mouth and Sticky Saliva, Problems with Teeth, Trismus, can be considered that these problems affect all HNC patients and eventually can show that cachexia in HNC patients is not, at least in part, related exclusively to the limitation of eating and swallowing.

These results from our study support the usefulness of HRQoL in the evaluation and follow-up of HNC patients and can be important in the identification of cachexia in these patients.

In resume our study developed a methodology with significantly results in terms of nutritional parameters, biochemical markers and HRQoL scores in the evaluation of cachexia in the clinical context of HNC that can be used in on a routine clinical practice, contributing to fill a gap seen in the research in this field that can help improving prognosis and HRQoL in HNC patients.

5. Conclusions

Cachexia is a deleterious condition and has a negative impact on prognosis of HNC patients. Overall survival of patients with cachexia is very low with a median overall survival of 13.5 months in our study.

Cachexia patients present with significant weight loss and significantly high levels of serum biomarkers of inflammation and muscle wasting like CRP, IL-6, TNF- α or myostatin, and significantly lower levels of nutritional serum markers like albumin or cholesterol.

NRI is an important screening tool to identify cachexia in head and neck cancer patients.

HRQoL evaluation, using validated questionnaires like the EORTC QLQ-C30 and EORTC QLQ-HN43, is an important tool in the management of HNC can-

cer patients and can identify early deterioration of the global or specific conditions of HNC patients.

The implementation of clinical protocols using these tools, NRI, serum biomarkers (albumin, CRP, IL-6, TNF- α , myostatin) and HRQoL evaluation, can promote an early identification of cachexia in HNC patients leading to a strategic clinical approach to control this negative condition and improve patients' prognosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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GLOBAL DISCUSSION

1 - Quality of life assessment in patients with head and neck cancer

Head and neck cancer affects mostly the mucosa of the superior aerodigestive tract, including ear, nose, pharynx and larynx. These organs and structures are responsible or have a fundamental role in many functions important for human life.

Not only vital functions, like breathing or eating, but also functions like smelling, tasting, voice and speech and also non-verbal communication can be seriously impaired by head and neck cancer. The impact of the disease itself and treatments consequently has a major impact in the life of patients.

In this context, the management of head and neck cancer is a challenging task. As in other cancers, survival is still the main goal for these patients. Nevertheless, in patient's and not on the disease perspective, quality of survival is probably the major issue to consider in the management of head and neck cancer.

So, HRQoL evaluation is a relevant parameter in head and neck cancer patients' treatment decision.

HRQoL is a multidimensional constructed concept that has been difficult to define for many years, until some consensus has been achieved with several definitions proposed like:

- state of well-being with two components: the ability to perform everyday activities that reflect physical, psychological, and social well-being; and patient satisfaction with levels of functioning and control of the disease;

or

- functional effect of an illness and its consequent therapy upon the patient as perceived by the patient;

or

- individual's overall satisfaction with life and general sense of personal well-being;

or

- patient perception of their position in life in the context of the culture and value;
- or
- systems in which they live and in relation to their goals, expectations, standards, and concerns.

When applied to cancer patients, HRQoL includes subjective perceptions of the positive and negative aspects of patients' symptoms in all aspects (physical, emotional, social, and cognitive functions) and disease symptoms and side effects of treatment. Attending to these aspects, HRQoL evaluation is a difficult task when considering application in the clinical practice, mostly due to its subjectivity and fastidious forms of evaluation.

In this context, EORTC has developed a great work with the development and validation of different instruments for the evaluation of HRQoL in cancer. Regarding head and neck cancer a specific questionnaire (QLQ-HN35) that when applied in conjunction with the EORTC quality of life core questionnaire (QLQ-C30) has demonstrated to be an accurate instrument to measure HRQoL in these patients.

To improve accuracy an actualization of the specific module was done, with the purpose to bring the questionnaire closer to the recent reality of new treatment options in head and neck cancer.

We have participated in this project, and we achieved to obtain an actualized and accurate questionnaire, translated and validated in portuguese language, to evaluate HRQoL in head and neck cancer – the QLQ-HN43 [Appendix I].

Questionnaires are structured in a specific number of questions that are grouped in specific scales and items. EORTC QLQ-C30 has 30 questions that are combined in 7 scales (Global Quality of Life, Physical Functioning, Role Functioning, Social Functioning, Emotional Functioning, Cognitive Functioning) and 6 items (Fatigue, Pain, Nausea and Vomiting, Dyspnoea, Sleeping Disturbances, Appetite loss, Constipation, Diarrhoea and Financial Impact). Scales' scores are calculated in the way that the value will indicate a direct proportion of that specific functions (a higher score will indicate a better function). In the items, scores are calculated in the way that the value will indicate the degree of impact of that specific problem (a higher score will indicate a worst problem).

EORTC QLQ-HN43 module has 43 questions combined into 12 scales (Fear of Progression, Body Image, Dry Mouth and Sticky Saliva, Pain in the Mouth, Sexuality, Problems with Senses, Problems with Shoulder, Skin Problems, Social Eating, Speech, Swallowing and Problems with Teeth) and 7 single items (Coughing, Swelling in the Neck,

Neurological Problems, Trismus, Social Contact, Weight Loss and Wound Healing) with the same form of calculation of the QLQ-C30.

When scores are analysed, there are global scales like the global quality of life scale of the QLQ-C30 that can give a global indication of quality of life (we can consider a “quantification” of the quality of life of a patient). On the other hand, other scales and items give information on specific aspects of patients, allowing to understand which aspects are more affected by the disease or by the treatments.

This information is of utmost importance when we consider the follow-up of patients, once changes in scores of the scales or items can indicate deterioration or improve of a specific aspect and may alert clinicians for specific attention to some aspects, eventually signalling a recurrence or a good response to treatment respectively.

These aspects are not always easy to implement on a routine clinical basis. In the Department of ORL of IPOPFPG a computerised platform was developed that analysed the data obtained from the questionnaires and a real-time graphic output was produced giving instant information for clinical use.

The information on the graphic output is represented mainly by two forms:

- the actual scores of the different scales (figure 1) with a colour differentiation of scores according to the expected values: blue if the value is above the expected and red if it is below the expected. A green line traces the global quality of life score.

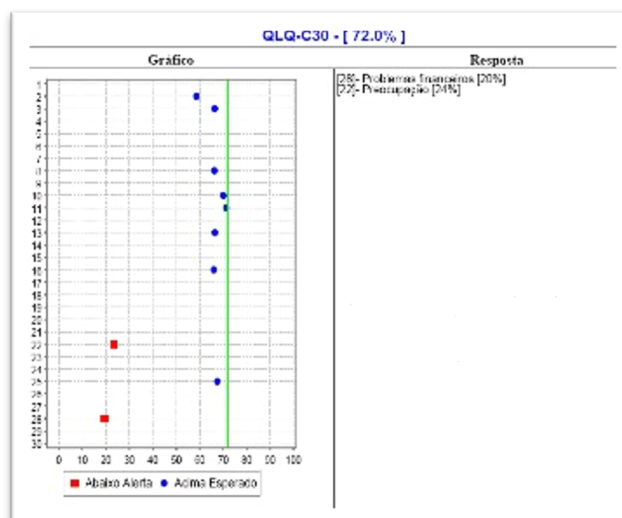


Figure 1 – Graphic output QLQ-C30 of QoLCPIPOFPG

- a layout that shows the scores in terms of progression over time, between previous evaluations (figure 2).

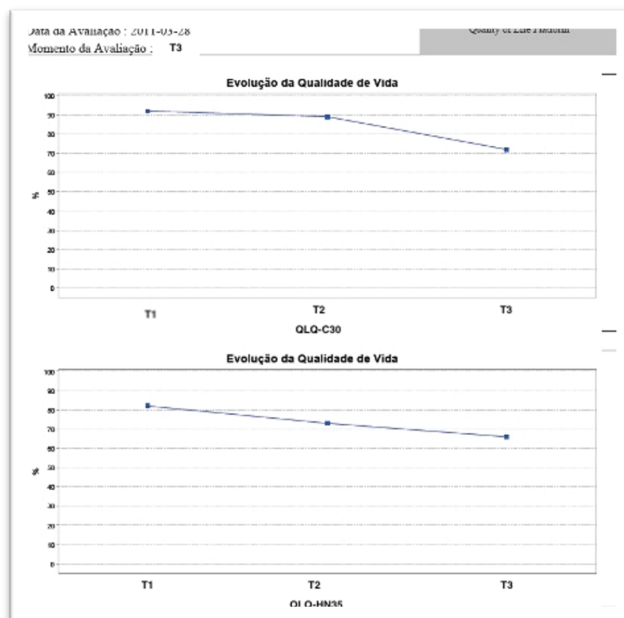


Figure 2 – Graphic output QoLFUp of QoLCPIPOPG

This application can contribute to a better implementation of HRQoL evaluation in a routine clinical practice. It reduces time in collecting symptoms and is an appealing application with real-time information with good adhesion by clinicians. [Appendix II]

Correlation of voice rehabilitation with tracheoesophageal voice and quality of life was never described in the literature, although evidence refer that voice rehabilitation improves quality of life. The results of a study carried by our group showed significant better scores in global quality of life scales in patients using tracheoesophageal voice and better scores in the items speech, social contact and sexuality, revealing the impact of voice in socialization and other aspects associated with well-being of patients.

These analyses demonstrated that HRQoL evaluation is important for the clinical assessment of head and neck cancer patients and the EORTC QLQ C-30 and HN43 are good and accurate instruments to measure HRQoL in these patients.

2 - Quality of life and assessment of nutritional imbalance in patients with head and neck cancer

Head and neck cancer patients usually have impaired nutrition status, that impacts negatively the outcome of their treatments, worsening their quality of life. Our retrospective study relating HRQoL with malnutrition risk evaluation (using the QLQ-C30) confirmed this evidence. Global quality of life scale scores were significantly lower in the group of patients with high-risk of malnutrition when compared to patients in other groups of risk. In the same manner, the items fatigue, pain, sleeping disturbances and appetite loss, presented with significantly higher scores in the high-risk group of patients, point to a major impact of malnutrition in these specific aspects of the patients.

This research has demonstrated that HRQoL is a good measure to identify head and neck cancer patients in risk of malnutrition, and its use in a clinical practice can improve the early identification of malnutrition, concurring for a prompt application of clinical strategies of malnutrition correction. In the same context, HRQoL evaluation can be a good tool for the screening of the nutrition status of head and neck cancer patients.

3 - Clinical evaluation of cachexia in patients with head and neck cancer considering weight, nutritional, biochemical and quality of life parameters

Cachexia definition and diagnostic criteria have evolved from the simple unintentional weight loss to a more elaborated and complex concept that includes body weight, nutritional aspects, biochemical, quality of life, body composition and even response to treatments. This complexity results from an increased research in this field, but nowadays remains a controversial matter. Literature fully demonstrates the importance of all these factors, but evidence is lacking in the correlation of these parameters and their clinical application.

This prospective study intended to evaluate the association of two parameters that seems to us, as explained in the Rational and Aims chapter, to have relevance in a clinical scenario for cachexia evaluation in head and neck cancer: quality of life and biochemical markers of cachexia. Quality of life was assessed using the EORTC QLQ C-30 and HN43, already tested in the previous phases of the project. The biochemical markers analysed were albumin, total proteins, cholesterol, triglycerides, urea, CRP, IL-6, TNF- α and myostatin. Except for IL-6, TNF- α and myostatin (immunoblot analysis) that were analysed

in the Department of Chemistry of the University of Aveiro, all other biochemical markers were analysed in the IPOPFG laboratory. This was the main reason why we have selected these markers, because was for us simple to analyse these biochemical markers in the routine clinical activity.

Patients were divided in two groups according to the criterium of cachexia. Initially they were selected for each group according to the percentage of weight lost in the last 6 months and to the BMI. However, after a preliminary analysis with these biochemical markers, namely albumin and CRP, we've realized that many patients without weight loss presented already levels of biochemical markers pointing to a cachexia status. This can be an evidence that often cachexia is already present without weight loss.

With these findings we realized that the optimal criterium for the definition of cachexia should be a measurement that include weight loss and biochemical information.

In our study, we used the NRI according to the Veteran Affair Total Parenteral Cooperative Study Group, as a criterion to assign patients in the two groups: with cachexia and without cachexia. NRI showed to be a useful and accurate tool to identify the presence of cachexia in head and neck cancer patients. Correlating a nutritional/constitutional parameter (percentage of weight loss) and a biochemical marker (serum levels of albumin) we can get a good information about the cachexia status of patients. We can say that this approach is a good tool for application in the clinical practice, allowing a good identification of the status of the patients and eventually reducing misdiagnosis of cachexia in head and neck cancer patients.

Once defined the enrolling criteria, patients were selected in order to obtain two homogenous groups in terms of demographics and clinical presentation of the disease (location and TNM staging). This methodology has permitted to compare the clinical behaviour and the differences in biochemical markers and quality of life between patients with cachexia and without cachexia.

Cachexia is already known as a deleterious condition that impacts negatively the prognosis and survival in cancer. In head and neck cancer, the impact of cachexia in the outcomes of patients is of major importance, due either to the disease itself either to treatments response and toxicities. This fact is evident in the literature but rarely is presented on a prospective way with cohorts of patients equally distributed, namely in head and neck cancer. Our investigation confirms a significant decrease in survival of head and neck cancer patients with cachexia, when compared to patients without cachexia and is independent of the clinical staging. In the cachexia group only one patient in the fourteen considered is still alive. All others patients died from the disease with a median survival of 13,5 months and most of them didn't completed the treatment proposed or didn't have conditions for elective treatment.

When outcome results in head and neck cancer patients were analysed in the past decades, it's evident that overall survival didn't follow the advances achieved in terms of diagnostic and treatment options.

Cachexia is one of the factors that when corrected is associated with a clear improvement in survival, namely if associated to the advances observed in head and neck cancer field.

In clinical practice cachexia is usually unrevealed or misdiagnosis. Usually, clinical approaches are toward the disease, its diagnosis and treatment, and patients' conditions and global status are not taken in consideration.

That's why a good screening and identification of the risk of cachexia is determinant for an adequate characterization of the problem. A special focus on this aspect was made in our research. Head and neck cancer patients often present unwanted weight loss, with impact on their BMI and in the scores of nutritional risk scales, like MUST. Nevertheless, sometimes the presence of cachexia was not seen associated with weight loss. On the other hand, cachexia promotes a state of permanent inflammation and metabolic changes that leads to alteration in many biochemical markers. The conjugation of these two information's, constitutional and biochemical parameters, seems a good compromise to achieve a good tool to screen cachexia in head and neck cancer patients.

Cachexia is a multifactorial syndrome that is responsible for the presence of an inflammatory and catabolic status in patients, with an increase of several serum levels of some biochemical markers. Our study has confirmed that biochemical markers like CRP, IL-6, TNF- α and myostatin were significantly augmented in head and neck cancer patients with cachexia. This evidence observed in a clinical scenario confirms the relevance of the presence of an inflammatory and catabolic status in these patients, most of the times already present in the first clinical evaluation of patients.

Routine evaluation of these biochemical markers in all head and neck cancer patients can help to characterize cachexia status, leading to an early identification of inflammatory and metabolic disturbances in patients. This is important for the prompt application of clinical measures tending to correct and control cachexia status, improving by this way better treatments responses. In the same context, these biochemical markers might be a good screening tool to evaluate patient's response to clinical measures adopted to control the cachexia status. In this way, biochemical markers used in the clinical routine can be indirect indicators of the patient's performing status. This was a limitation of our study, since the short survival of patients with cachexia, didn't permit to have a minimum follow-up time to analyse the variations of these biochemical markers over time. Future studies will be important to elucidate this.

As demonstrated in the previous section, HRQoL evaluation is important for the identification of malnutrition risk in head and neck cancer patients.

In the context of the cachexia, HRQL evaluation is also important. In head and neck cancer the presence of cachexia status has a negative impact in quality of life of these patients.

In our prospective study we have applied to all patients at presentation both questionnaires: EORTC QLQ-C30 and the newly developed EORTC QLQ-HN43. The results demonstrate that most of the scales and items were related to significant worst quality of life parameters in patients of the cachexia group. An additional index was calculated: the Summary Score for EORTC QLQ-C30. This is a global score that consider all the 13 scales of the EORTC QLQ-C30 except two: the global QoL scale and the item financial impact. This summary score is a more accurate measure of global QoL when compared to the different scales and items of the EORTC QLQ-C30, particularly the global QoL scale. The summary score calculated for the patients with cachexia was significantly lower than the values found in the group of patients without cachexia.

With respect to the other scales and items, scores for dyspnoea and constipation items didn't show significant differences between groups, concluding that these items aren't important in the evaluation of cachexia when considering head and neck cancer patients.

The results of the EORTC QLQ-HN43 also demonstrate significant differences in the scores of most of the scales and items, demonstrating worst scores in the cachexia patient's group. The presence of a non-significant difference in scores between the two groups, in the scales and items dry mouth and sticky saliva, teeth problems, trismus, show that these problems usually affecting all head and neck cancer patients, can demonstrate that cachexia in head and neck cancer patients is not, at least in part, exclusively related to the limitation of eating and swallowing.

These results support the utility of HRQoL for the evaluation and follow-up of head and neck cancer patients and can be important in the identification of cachexia in these patients. EORTC QLQ 's are good instruments for the clinical practice and its scales and items helps to identify global impact of cachexia in HRQoL in head and neck cancer patients as well as specifics problems in the diversity of patients and disease.

CONCLUSIONS

Cachexia is a deleterious condition with a negative impact on prognosis and survival of head and neck cancer patients.

A good screening of this topic is mandatory to obtain an adequate orientation of patients. The present research has demonstrated that nutritional risk index is an important screening tool to identify cachexia in head and neck cancer patients. The implementation of this index in the clinical practice will improve the detection of patients in risk of cachexia promoting early clinical measures to control this problem.

Patients with cachexia present with significant weight loss and significant high levels of serum inflammatory and muscle wasting biochemical markers like CRP, IL-6, TNF- α or myostatin. Clinical evaluation of these markers is important to identify inflammatory status associated to cachexia in head and neck cancer patients, promoting a more targeted therapeutic action to control the cachexia status. In terms of the follow up of these patients and monitorization of therapeutic results, after cachexia prevention, future investigations are needed, since our research couldn't follow patients with cachexia enough time due to the poor overall survival.

HRQoL evaluation, using validated questionnaires like EORTC QLQ-C30 and EORTC QLQ-HN43, is an important tool in the management of head and neck cancer and can identify early deterioration of the global quality of life or specific conditions of head and neck cancer patients. HRQoL evaluation in head and neck cancer patients with cachexia is relevant not only for the global evaluation of patients but also to identify specific problems that other way could be unrevealed or misdiagnosed. Another conclusion about the usefulness of HRQoL in the cachexia management is in the follow-up of the patients.

Evidence of this research is that both biochemical markers and HRQoL are important in the assessment and clinical management of cachexia in head and neck cancer patients. The development of clinical protocols including HRQoL evaluation and determination of biochemical markers for the evaluation and follow-up of head and neck cancer patients is one aspect of relevant importance supported by this research.

The implementation of these protocols will favour early identification of cachexia in head and neck cancer patients, promoting clinical interventions to improve the global status of patients. On the same way, the use of these protocols in the follow-up will help clinical teams to identifying problems with prompt correction helping patients and improving their quality of life.

FUTURE PERSPECTIVES

- **Perspectives in quality of life evaluation**

1 - As in all other cancers, head and neck cancer treatment is a huge challenge due to the need of optimizing survival with quality of life.

This research showed cachexia is of major impact in this both parameters and a good screening of this condition is crucial for the outcome of the patients.

The implementation of clinical protocols on a routine clinical basis is a key point to achieve that screening.

The use of HRQoL evaluation in the clinical practice is a difficult task mainly because clinicians don't adhere to it. The use of computerised platforms for HRQoL evaluation have demonstrated to be a valuable instrument to bring this important measure into the daily practice and can overcome the resistance of the clinicians. As presented before in the discussion chapter, the Department of Otorhinolaryngology of IPO-PFG has developed a computerised platform to evaluate HRQoL in head and neck cancer patients. This platform was object of an oral communication I presented in 2015 in the 3rd Congress of CEORL-HNS in Prague: "Real time quality of life evaluation in routine clinical practice of head and neck cancer patients – the development of a new computerised platform at IPO-Porto" [Appendix II]

The development of a computerised platform that includes the evaluation of all the data considered in the settle of cachexia (constitutional, nutritional, biochemical and quality of life) is an important future development of the results from this research.

2 - The clinical application of the questionnaires for health related quality of life has always been the most important factor for the success of this methodology. The reasons for a difficult clinical implementation are essentially the subjectivity inherent to quality of life and the time consuming of the instruments used and the not immediate or evident results of that measurement. Different strategies have been adopted attempting to reduce these limitations.

One of this strategy is found the most meaningful questions in the questionnaire for the subject in evaluation and in this way reduce the vast questionnaire to a limited number of questions maintaining the same accuracy of the whole questionnaire.

A step to this goal is to determine some intrinsic values of the questionnaire, notably two important concepts: the minimal important difference and the minimal important

change. MID is the minimal difference in quality of life between patient groups that is clinically relevant, and the MIC is the minimal change in quality of life over time that is clinically relevant.

To improve the value of the new developed EORTC QLQ-HN43 the next step is the determination of this values. Indeed, a study to determine the MID and the CIM for the EORTC QLQ-HN43 using the swallowing scale has been done by the EORTC Quality of Life Group, with my participation, published in the Quality of Life Research publication. [Appendix III]

Further research and studies should follow to improve the accuracy and clinical application of this questionnaire.

• Perspectives in cachexia evaluation

1 - The role of the biochemical parameters in the following-up of the patients was considered a limitation of this research due to the poor survival observed in patients with cachexia. A further development of this research is to evaluate the evolution of these patients throughout time in order to find the importance of these markers in this context.

A larger study including more patients in all clinical stages with multiple time points of analysis and treatment options, will continue our study and might improve the evidence already showed.

This next step could allow a better orientated clinical intervention in the metabolic impairment observed in the cachexia, using new drugs to control inflammation or sarcopenia, nutritional supplements or a program of exercise to favour muscle anabolism. These clinical interventions are important in controlling the development of cachexia and avoid a refractory state of cachexia usually fatal. This perspective of new studies can lead to the development of programmes for conditioning and fitting the patients for the treatments proposed. The success of this so-called pre-habilitation programmes could be monitored using the tools and protocols proposed in this present study.

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EORTC QLQ - H&N43

Por vezes os doentes dizem que têm os seguintes sintomas ou problemas. Por favor, indique em que medida sentiu estes sintomas ou problemas durante a última semana. Por favor, responda fazendo um círculo no número que melhor se aplica a si.

Durante a última semana:	Nada	Um pouco	Bastante	Muito
31. Teve dores na boca?	1	2	3	4
32. Teve dores na mandíbula?	1	2	3	4
33. Sentiu a boca dorida?	1	2	3	4
34. Teve dores de garganta?	1	2	3	4
35. Teve problemas em engolir líquidos?	1	2	3	4
36. Teve problemas em engolir alimentos moles?	1	2	3	4
37. Teve problemas em engolir alimentos sólidos?	1	2	3	4
38. Engasgou-se ao engolir?	1	2	3	4
39. Teve problemas com os dentes?	1	2	3	4
40. Teve problemas por causa da perda de alguns dentes?	1	2	3	4
41. Teve problemas em abrir bem a boca?	1	2	3	4
42. Teve boca seca?	1	2	3	4
43. Teve saliva pegajosa?	1	2	3	4
44. Teve problemas com o olfacto (cheiro)?	1	2	3	4
45. Teve problemas com o paladar (gosto)?	1	2	3	4
46. Teve problemas em tossir?	1	2	3	4
47. Teve problemas de rouquidão?	1	2	3	4
48. Teve problemas com o seu aspecto físico?	1	2	3	4
49. Sentiu-se menos atraente fisicamente por causa da sua doença ou tratamento?	1	2	3	4

Por favor, passe à página seguinte

PORTUGUESE (PORTUGAL)

Durante a última semana:	Nada	Um pouco	Bastante	Muito
50. Sentiu-se insatisfeito com o seu corpo?	1	2	3	4
51. Teve problemas em comer?	1	2	3	4
52. Teve problemas em comer à frente da sua família?	1	2	3	4
53. Teve problemas em comer à frente de outras pessoas?	1	2	3	4
54. Teve problemas em apreciar as suas refeições?	1	2	3	4
55. Teve problemas em falar com outras pessoas?	1	2	3	4
56. Teve problemas em falar ao telefone?	1	2	3	4
57. Teve problemas em falar em sítios barulhentos?	1	2	3	4
58. Teve problemas em falar claramente?	1	2	3	4
59. Teve problemas em ir a lugares públicos?	1	2	3	4
60. Sentiu menos interesse pelo sexo?	1	2	3	4
61. Teve menos prazer sexual?	1	2	3	4
62. Teve problemas em levantar o braço ou movê-lo para os lados?	1	2	3	4
63. Teve dores no ombro?	1	2	3	4
64. Teve um inchaço no seu pescoço?	1	2	3	4
65. Teve problemas de pele (ex. comichão, pele seca)?	1	2	3	4
66. Teve uma erupção cutânea?	1	2	3	4
67. A cor da sua pele mudou?	1	2	3	4
68. Tem-se sentido preocupado por o seu peso ser demasiado baixo?	1	2	3	4
69. Tem-se sentido preocupado com os resultados de exames ou testes?	1	2	3	4
70. Tem-se sentido preocupado com a sua saúde futura?	1	2	3	4
71. Teve problemas com a cicatrização de feridas?	1	2	3	4
72. Teve formigamento ou dormência nas mãos ou pés?	1	2	3	4
73. Teve problemas em mastigar?	1	2	3	4

APPENDIX II

Real time quality of life evaluation in routine clinical practice of head and neck cancer patients – the development of a new computerised platform at IPOPorto.

Communication presented in the 3rd Congress of CEORL-HNS in Prague in June of 2015

- This is original work not included in the main research of the thesis but that was referred in the Discussion and Conclusions of the present dissertation.

ABSTRACT

Quality of life evaluation is assuming an important role in clinical orientation and investigation in head and neck oncology. Health related quality of life is in use in some institutions as a health outcome measure, mainly related to research. Health related quality of life measure can be utilized to identify patient risk groups and provide prognostic information with benefits relatively to traditional clinical factors and could be consider as a new prognostic marker for survival.

A clinical model that can use all the information on real time basis is still in definition. Computerised platforms are being developed for this purpose.

Portuguese Institute of Oncology - Porto (IPO-Porto) and its partnership Fernando Pessoa University have implemented a routine quality of life evaluation in the ENT Department based on a computerised platform. This platform allows a friendly patient interface and immediately processes all data and presents to the clinician the result in a table or a graphic layout, giving a real time “measure” of quality of life.

During the last three years ENT Department of IPO-Porto proceed to routine quality of life evaluation of all head and neck cancer patients based on this computerised platform that use EORTC-QLQ C30 and EORTC- H&N35 questionnaires.

A preliminary report of the use of this methodology is made, showing the impact in clinical decisions, in identifying potential needs or patient risk groups and providing prognostic information. Additionally, further development and improvement of this platform will also be presented.

Methodological approach for determining the Minimal Important Difference and Minimal Important Change scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module (EORTC QLQ-HN43) exemplified by the Swallowing scale

Published:

Singer, S., Hammerlid, E., Tomaszewska, I.M., Amdal, C.D., Bjordal, K., Herlofson, B.B., Santos, M., Silva, J.C., Mehanna, H. *et al.* Methodological approach for determining the Minimal Important Difference and Minimal Important Change scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module (EORTC QLQ-HN43) exemplified by the Swallowing scale. *Qual Life Res* (2021).

<https://doi.org/10.1007/s11136-021-02939-6>.

- This original work is not included in the main research of the thesis but that was referred in the Future Perspectives of the present dissertation.

ABSTRACT

Purpose: The aim of this study was to explore what methods should be used to determine the minimal important difference (MID) and minimal important change (MIC) in scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43.

Methods: In an international multi-centre study, patients with head and neck cancer completed the EORTC QLQ-HN43 before the onset of treatment (t1), three months after baseline (t2), and six months after baseline (t3). The methods explored for determining the MID were: (1) group comparisons based on performance status; (2) 0.5 and 0.3 standard deviation and standard error of the mean. The methods examined for the MIC were patients' subjective change ratings and receiver-operating characteristics (ROC) curves, predictive modelling, standard deviation, and standard error of the mean. The EORTC QLQ-HN43 Swallowing scale was used to investigate these methods.

Results: From 28 hospitals in 18 countries, 503 patients participated. Correlations with the performance status were $|r| < 0.4$ in 17 out of 19 scales; hence, performance status was

regarded as an unsuitable anchor. The ROC approach yielded an implausible MIC and was also discarded. The remaining approaches worked well and delivered MID values ranging from 10 to 14; the MIC for deterioration ranged from 8 to 16 and the MIC for improvement from – 3 to – 14.

Conclusions: For determining MIDs of the remaining scales of the EORTC QLQ-HN43, we will omit comparisons of groups based on the Karnofsky Performance Score. Other external anchors are needed instead. Distribution-based methods worked well and will be applied as a starting strategy for analyses. For the calculation of MICs, subjective change ratings, predictive modelling, and standard-deviation based approaches are suitable methods whereas ROC analyses seem to be inappropriate.



Methodological approach for determining the Minimal Important Difference and Minimal Important Change scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module (EORTC QLQ-HN43) exemplified by the Swallowing scale

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Accepted: 5 July 2021
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Abstract

Purpose The aim of this study was to explore what methods should be used to determine the minimal important difference (MID) and minimal important change (MIC) in scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43.

Methods In an international multi-centre study, patients with head and neck cancer completed the EORTC QLQ-HN43 before the onset of treatment (I1), three months after baseline (I2), and six months after baseline (I3). The methods explored for determining the MID were: (1) group comparisons based on performance status; (2) 0.5 and 0.3 standard deviation and standard error of the mean. The methods examined for the MIC were: patients' subjective change ratings and receiver-operating characteristics (ROC) curves, predictive modelling, standard deviation, and standard error of the mean. The EORTC QLQ-HN43 Swallowing scale was used to investigate these methods.

Results From 28 hospitals in 18 countries, 503 patients participated. Correlations with the performance status were $|r| < 0.4$ in 17 out of 19 scales; hence, performance status was regarded as an unsuitable anchor. The ROC approach yielded an implausible MIC and was also discarded. The remaining approaches worked well and delivered MID values ranging from 10 to 14; the MIC for deterioration ranged from 8 to 16 and the MIC for improvement from -3 to -14.

Conclusions For determining MID's of the remaining scales of the EORTC QLQ-HN43, we will omit comparisons of groups based on the Karnofsky Performance Score. Other external anchors are needed instead. Distribution-based methods worked well and will be applied as a starting strategy for analyses. For the calculation of MIC's, subjective change ratings, predictive modelling, and standard-deviation based approaches are suitable methods whereas ROC analyses seem to be inappropriate.

Keywords Minimal important difference · Minimal important change · MCID · Clinical significance · Subjective significance · EORTC QLQ-HN43

Background

Quality of Life (QoL) domains are usually reported in terms of scores. In order to assess the effects of a new drug or intervention, researchers must determine the minimal

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difference in these scores deemed clinically important. Only by knowing that, can they calculate the sample size for a trial and interpret which results are clinically meaningful.

Likewise, clinicians, patients, and policy-makers need to know what changes in QoL scores over time or differences in scores between groups are clinically relevant. If, say, we have a scale with a potential range of 0–100, and a patient had a score of 87 before surgery and 80 afterwards, would the difference be clinically relevant?

The difficulty lies in (a) how best to define these concepts and (b) how to measure them empirically. Numerous terms are used to describe the issue at hand—minimal important difference, minimal detectable change, clinical significance, etc. [1]. We will use the terms minimal important difference (MID) and minimal important change (MIC), the MID being the minimal difference in QoL *between patient groups* that is clinically relevant and the MIC being the minimal change in QoL *over time* that is clinically relevant [2].

A familiar definition for MID is the least difference that would lead to a change in treatment [1, 3, 4], while the MIC is defined as the minimal difference over time considered relevant by the patient [5]. Both can be measured using so called anchor-based approaches (which map QoL scores onto an external indicator) or distribution-based approaches (which rely on statistical criteria). Several papers summarise and discuss these approaches and the various methods for deriving estimates [1, 6–9]. There is no “gold-standard” method for estimating MID or MIC. Distribution-based methods alone have often been found insufficient [10] because they do not directly capture the patient’s or clinician’s perspective regarding the meaning of scores, and this should be resolved by combining them with anchor-based approaches. A further recommendation is to report a range of numbers instead of a single one, since different methods may yield different estimates [1].

A difference of 10 points is often assumed to be the appropriate MID and MIC for the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire), based on the work of Osoba [5]. Cocks et al. recommended using scale-specific MICs [11]. Recently, the EORTC Quality of Life Group performed analyses of previous EORTC trials to define various MICs for the EORTC QLQ-C30 scales [12]. The MIC definitions were obtained by other authors carrying out observational studies [13, 14] or using existing data from past clinical trials [15]. For the EORTC disease-specific modules (as opposed to the core instrument) initial studies investigating MIDs or MICs have been published [16, 17]. It is our aim to calculate MID and MIC estimates for the recently updated head and neck module, the EORTC QLQ-HN43 [18–20]. As there is no gold standard method for calculating MID and MIC, we first developed a methodological

approach, exploring various methods, the results of which are presented in this paper.

The research questions of the current study were: 1. What methods should we use to determine the clinically relevant minimal score differences of the EORTC QLQ-HN43 scales between patient groups (the MID)? 2. What methods should we use to determine the clinically relevant minimal changes in score over time for the EORTC QLQ-HN43 scales (the MIC)?

In the current paper, we focus on the Swallowing scale, in view of the importance of swallowing difficulties for patients with head and neck cancer and its wide use in clinical studies [21]. We anticipated that these efforts would provide a useful model for approaching the determination of MIDs/MICs for the other scales in the EORTC QLQ-HN43 module.

Methods

Study design

In an international, multi-centre prospective validation study of the updated EORTC head and neck cancer module [18], patients with head and neck cancer under active treatment (Group 1) completed a questionnaire at the following time points: before the onset of treatment (t1), three months after baseline (t2), and six months after baseline (t3). Based on previous studies [22–27] and on clinical experience, we assumed Quality of Life would deteriorate for most patients between t1 and t2 and would somewhat improve between t2 and t3. In the validation study, there was also a group of head and neck cancer post-treatment survivors (Group 2) included to determine test-retest reliability. For the determination of MID and MIC presented in this paper, we used the data of Group 1 only.

Inclusion criteria, exclusion criteria, and data collection

Patients with the following ICD-10 codes were included: larynx (C32), lip (C00), oral cavity (C01–C06), salivary glands (C07–C08), oro-hypopharynx (C09–C10, C12–C14), nasopharynx (C11), nasal cavity (C30), nasal sinuses (C31), sarcoma in the head and neck region (C49), and lymph node metastases from unknown primary in the head and neck area (C77, C80.0). We did not include patients with tumours of the eyes, orbit, thyroid, skin (even if in the head and neck area), or lymphomas in the head and neck region. Additional inclusion criteria were sufficient language proficiency and sufficient cognitive functioning (assessments made by study coordinator), aged 18 years or over, and written informed consent.

Upon admission to the hospital or clinic, eligible patients received an invitation to participate in the study, and oral and written information in accordance with ethical and governance requirements of each participating centre. All sites obtained ethical approval in accordance with regional and national requirements. Patients were given time to consider the study and ask any questions before consenting and participating.

Instruments

The EORTC QLQ-C30 [28] and the EORTC QLQ-HN43 [18, 19] questionnaires were administered at all three time points.

At t2 and t3, a subset of participants also completed the Subjective Significance Questionnaire (SSQ) [5]. In the SSQ, patients were asked to rate the extent that their QoL had changed (improved or worsened) in the domains swallowing, speech, dry mouth, and global quality of life compared to the previous time point. The first three domains were chosen as they were previously rated as having the highest priority by patients with head and neck cancer [20] and global quality of life was included because of its general applicability. The response options for each of these items ranged from very much worse to very much better on a 7-point Likert scale. Consistent with the literature, the options "a little worse" and "a little better" defined the MIC from the patient's perspective, since these categories represent minimal change [29]. The current analyses included the Swallowing item, since this was most relevant for the EORTC QLQ-HN43 Swallowing scores.

Information on the patient's gender, age, education, tumour site, tumour stage, Karnofsky Performance Score (KPS), and treatment received was documented on a Case Report Form by study staff.

Analysis

The statistical analysis plan was developed based on information from published papers and experiences from research clinicians involved in the study. After discussions in the group, we decided to employ a variety of methods to determine the MID and MIC in order to examine their applicability for the EORTC QLQ-HN43 scales using the Swallowing scale as an example. The results of this should serve as a decision basis for what methods to use when analysing the MID and MIC for all the other EORTC QLQ-HN43 scales. The Swallowing scale was used because it was applied most often in previous trials and clinical studies according to a systematic review [21].

Descriptive analyses

The sample for the MID and MIC analyses comprised patients under active treatment who participated at least twice. The frequencies and percentages of the following variables were calculated: gender, age, education, tumour site, UICC tumour stage, Karnofsky Performance Score (KPS), and treatment received (as documented at t2).

For the EORTC QLQ-HN43 Swallowing scale, the mean change (Δ) and its standard deviation, minimum, and maximum were calculated for changes between t1 and t2 and between t2 and t3.

Methods for determining the Minimal Important Difference (MID)

1. Anchor-based approach The assumption was that patients differ clinically when they have a KPS of 60 (requires some assistance but able to care for most of own needs) vs. 70 (cares for self, unable to carry on normal activity or do active work) and when they have a KPS of 70 vs. 80 (normal activity with effort), since these are often the thresholds for participation in clinical trials and treatment recommendations. However, it was unclear whether KPS correlates with the various domains of the EORTC QLQ-HN43 questionnaire, which is necessary if it is to work as a suitable anchor. The group decided, therefore, to calculate the Spearman correlation coefficients for KPS at t2 with the EORTC QLQ-HN43 scales at t2. If the correlation coefficient with KPS was ≥ 0.40 , the following calculations were planned: mean difference for the EORTC QLQ-HN43 scale score in patients with KPS 60 vs. 70 (at t2), mean difference for the EORTC QLQ-HN43 scale score in patients with KPS 70 vs. 80 (at t2). If the correlation coefficient was < 0.40 , we considered that it was not a suitable anchor for this scale in this population [30]. The calculation of the Spearman correlation coefficients for KPS with the EORTC QLQ-HN43 scales were repeated for t1 to investigate robustness of the results.

2. Distribution-based approach We calculated the 0.5 and the 0.3 standard deviation [7] and the standard error of measurement (SEM) of the Swallowing scale score at t2. The SEM was defined as follows: $SEM = SD \times \text{square root of } (1 - \text{Cronbach's Alpha})$, which gives the measurement error for an individual measurement (i.e. at patient-level). The values for Cronbach's alpha are published elsewhere [18]. For the Swallowing scale, the Cronbach's alpha was 0.85 at t2.

Methods for determining the Minimal important change (MIC)

1. Anchor-based approach We calculated the mean delta of the Swallowing scale scores for those patients who reported their swallowing had changed “a little” for changes between t1 and t2, as well as between t2 and t3. Calculations were made separately for patients with improved and deteriorated swallowing.

In addition, we used Receiver Operating Characteristics (ROC) curves, as suggested by Kvam et al. [13]. The procedure was as follows:

- We created groups of patients with improved, unchanged, and deteriorated swallowing, using responses for the Swallowing change item from the SSQ. Responses of “very much worse,” “moderately worse,” and “a little worse” were classified together as “deteriorated”, and responses of “very much better,” “moderately better,” and “a little better” were classified together as “improved”. Patients responding “about the same” were classified as “unchanged”.
- Based on step a, two dichotomous variables were created for the SSQ swallowing anchor: improved vs. not improved (with “unchanged” and “deteriorated” considered as “not improved”) and deteriorated vs. not deteriorated (with “unchanged” and “improved” considered as “not deteriorated”).
- The area under the curve (AUC) was calculated separately for deterioration between t1 and t2, because most patients were expected to experience a worsening of functioning during the treatment period when toxicities are pronounced, and improvement between t2 and t3, because most participants were expected to report gains in functioning during the immediate post-treatment period. The cut-off point with the highest Youden-Index (sensitivity + specificity - 1) was considered to be the MIC [31].

Lastly, we applied predictive modelling to obtain MIC estimates as suggested by Teruini [32]. Here, the MIC is defined as $(\ln(\text{odds-pre}) - \text{intercept}) / \text{regression coefficient}$.

2. Distribution-based approach We calculated the 0.3 and 0.5 standard deviation as well as the SEM of the delta for Swallowing scores between t1 and t2 to determine the MIC for deterioration and the 0.3 and 0.5 standard deviation as well as SEM of the delta in Swallowing scores between t2 and t3 to determine the MIC for improvement.

Results

Sample

From 28 treatment centres in 18 countries, 812 patients were enrolled into the validation study, of which 677 were in Group 1 (Fig. 1). Of these, 503 participated at more than one time point, and their data were used for the MID and MIC analyses; 108 participated twice and 395 thrice. The patient characteristics are displayed in Table 1. KPS at t1 ranged from 40 to 100 (mean = 89, skewness = -1.1), at t2 from 20 to 100 (mean = 82, skewness = -0.8), and at t3 from 10 to 100 (mean = 84, skewness = -1.4).

There was no evidence that age, gender, education, tumour site, and tumour stage differed between patients who participated just once to those who participated more than once (data not shown).

Mean change in the Swallowing scale score

On average, patients reported increased difficulties with swallowing during the treatment period, followed by partial recovery in the acute post-treatment phase. Between t1 and t2, swallowing problems increased by approximately 13 points on average (SD = 31, range: -100 to +100). Between t2 and t3, the mean delta was -8 (SD = 25, range: -92 to +100).

Minimal important difference (MID)

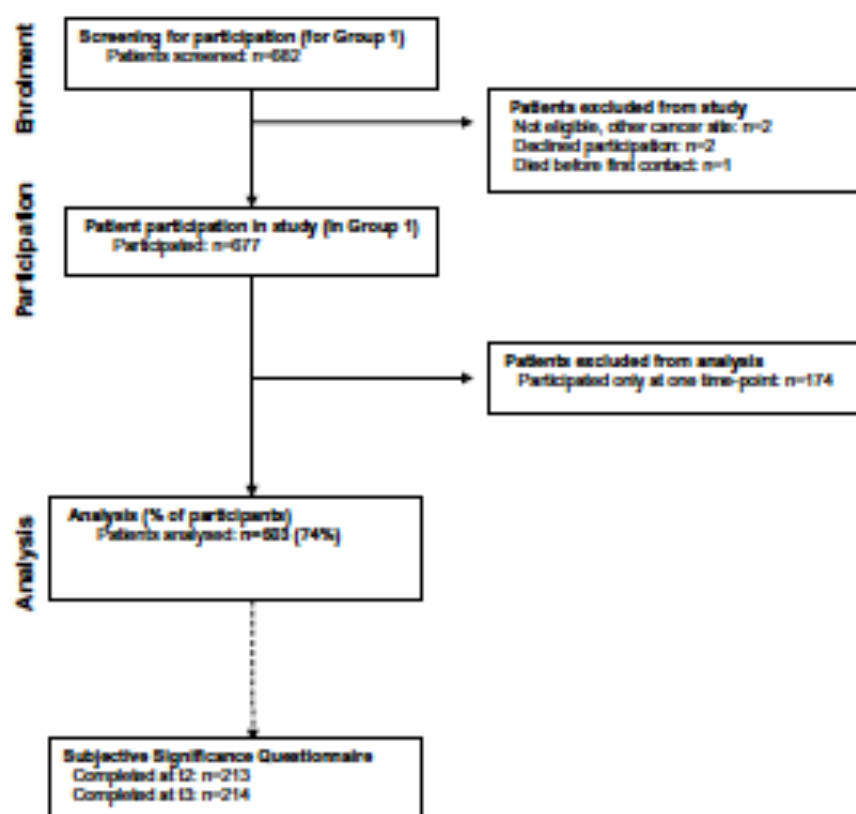
Anchor-based approach

The correlation of the KPS with the EORTC QLQ-HN43 Swallowing scale at t2 was -0.36, which fell below the required threshold of 0.40. More broadly, the correlations between the KPS and the EORTC QLQ-HN43 scales ranged from -0.12 (Neurological Problems) to -0.42 (Social Contact). Of all the 19 scales, only two (Social Contact and Social Eating) correlated $r \geq 0.40$ with the KPS. The correlation of the KPS with the EORTC QLQ-HN43 Swallowing scale at t1 gave similar results (see Supplemental Material, eTable 1 for details). Based on these results, it was concluded that the KPS is not a valid external anchor for group comparisons for this module and no further analyses with this approach were performed.

Distribution-based approach

The 0.5 and 0.3 standard deviation estimates of the Swallowing scale at t2 were 14.3 and 9.5, respectively. The standard error of measurement (SEM) of the Swallowing scale was 11.

Fig. 1 Patient flow through the study



Minimal important change (MIC)

Anchor-based approach

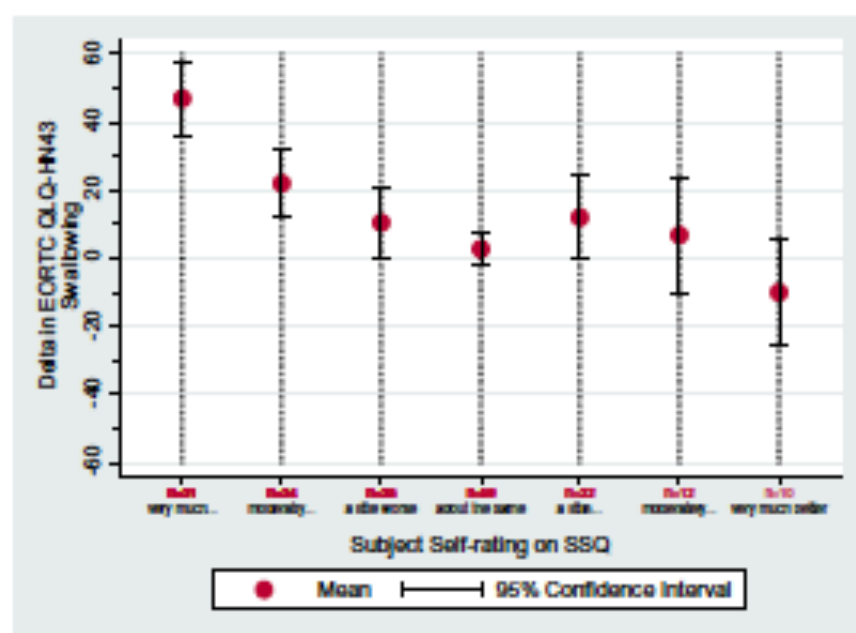
Using patient ratings of “a little change” in the SSQ. A total of 213 patients completed the SSQ at t2, and 214 at t3 (Table 2). At t2, 35 patients reported that their swallowing had worsened a little compared to t1. The respective mean delta in EORTC QLQ-HN43 Swallowing was 11 points (95% CI 0; 21). Thirty-two patients reported their swallowing had improved a little at t2 on the SSQ; the mean delta was 12 (95% CI 0; 24). The correlation coefficient between the SSQ Swallowing score and the delta in EORTC QLQ-HN43 Swallowing was $r = -0.42$ (correlation of SSQ with Swallowing score at t1 was $r = 0.001$ and with Swallowing score at t2 $r = -0.46$). Notably, the mean delta in EORTC QLQ-HN43 Swallowing scores for the improved group was a deterioration of 12 points (95% CI 0; 24), meaning that their scores in the Swallowing scale *worsened* on average by 12 points even though all these patients subjectively reported improved swallowing function. As this was a counterintuitive finding, we looked at the number of patients with positive and negative delta in more detail, to find out whether the result was due to an outlier. Of those 32 patients who said

their swallowing had improved a little on the SSQ, 11 had indeed a lower (better) score in the Swallowing scale at t2 compared to t1, but 16 had a higher score, indicating more swallowing difficulty at t2 compared to t1. The remaining patients had the same Swallowing score at t1 and t2. This implies that the results were not due to few outliers. (Fig. 2).

At t3, 16 patients reported a little worse swallowing on the SSQ; the corresponding mean delta in the EORTC QLQ-HN43 Swallowing scale was 18 points (95% CI 4; 32). At t3, 45 patients said their swallowing was a little better on the SSQ, and the mean delta on the EORTC QLQ-HN43 Swallowing scale was -14 points (95% CI -21; -7), reflecting the expected improvement. The correlation coefficient between the SSQ Swallowing score at t3 and the t2-t3-delta in EORTC QLQ-HN43 Swallowing was $r = -0.41$ (correlation of SSQ with Swallowing score at t2 was $r = 0.03$ and with Swallowing score at t3 $r = -0.39$).

Using ROC curves The ROC curve-derived MIC for deterioration was 8 (Table 3 and Supplemental Material for details), derived from patients who reported a deterioration in Swallowing between t1 and t2 in the SSQ. The corresponding AUC was 0.73 and the Youden index was 0.41. The AUC value suggests that this analysis was able to discriminate

Fig. 2 Subjective changes in swallowing between t1 and t2, measured with the Subjective Significance Questionnaire (SSQ), and the corresponding delta (mean and 95% confidence interval) in the Swallowing Scale of the EORTC QLQ-HN43



between anchor groupings better than chance alone during the treatment period.

The MIC for improvement was - 83, based on data from patients who reported improvement in Swallowing between t2 and t3, which is not a plausible number. The AUC was 0.29 and the Youden index 0; i.e., both indicate poor performance of the model during the post-treatment period (see eFigure 1 in Supplemental Material for details). The calculations were repeated for improvement between t1 and t2 but the outcome remained the same (data not shown).

In both calculations, there were ties, which may have biased the estimates.

Using predictive modelling The MIC derived from regression analysis was 14.6 for deterioration (odds_{pre} 0.89, regression coefficient = 0.03, 95% CI: 0.02 to 0.04, intercept = - 0.51) and - 3.1 for improvement (odds_{pre} 1.02, regression coefficient = - 0.03, 95% CI: - 0.05 to - 0.02, intercept = - 0.09).

Distribution-based approach

The standard deviation of the delta in Swallowing scale score between t1 and t2 was 32 points. The corresponding MICs for deterioration were 10 (0.3 SD), 16 (0.5 SD), and 12 (SEM) points.

The standard deviation of the delta in Swallowing between t2 and t3 was 25 points. The MICs for improvement were, therefore, 8 (0.3 SD), 12 (0.5 SD), and 10 (SEM) points.

Results of various approaches combined

The MID for the Swallowing scale ranged from 10 to 14, the MIC for deterioration from 8 to 16 and the MIC for improvement from - 3 to - 14 (Table 4).

Discussion

In this study, we examined which methods would be useful to determine the MID and MIC for the head and neck cancer module of the EORTC questionnaire. Both distribution- and anchor-based approaches were used and applied to the Swallowing scale because this is an important domain of QoL in head and neck cancer patients, and the corresponding scale in the EORTC instrument is most often used in clinical studies [21]. The aim was to explore which of the methods can be used later on for determining the MIC for all scales of the EORTC QLQ-HN43.

The various results were presented side by side (anchor-based vs. distribution-based; MID vs. MIC; results for deterioration vs. improvement). Although clinicians often prefer integration of results into single MID and MIC values, it is important first to understand the variety of findings and explore the applicability of the various approaches. It is also essential to keep in mind that the various estimates found in our study are based on conceptually different approaches (for example, the criterion for change can be defined by the patient or by external anchors). Researchers must determine which concept is most appropriate for their study.

Quality of Life Research

Table 1 Patient characteristics (n = 503)

	N (%)	Percent (%)
Cancer site		
Larynx	81	16
Hypopharynx	44	9
Oropharynx	173	34
Oral cavity	151	30
Parotid gland	22	4
Nasal cavity and sinuses	17	3
Unknown primary	13	3
Missing information	2	0
Cancer stage		
I	59	12
II	90	18
III	93	18
IV	249	50
Missing information	12	2
Karnofsky Performance Score (at baseline)		
40	2	0.4
50	1	0.2
60	11	2
70	40	8
80	87	17
90	174	35
100	180	36
Missing information	8	2
Treatment		
Surgery alone	95	1
Radiotherapy alone	86	17
Chemotherapy alone	11	2
Radiochemotherapy without surgery	136	27
Radiochemotherapy with surgery	74	15
Surgery and chemotherapy	6	1
Surgery and radiotherapy	68	14
Other	27	5
Gender		
Male	365	73
Female	134	27
Missing information	4	1
Age		
< 30 years	30	10
30–59 years	134	27
60–69 years	178	35
70–79 years	113	22
≥ 80 years	27	5
Missing information	1	0
Education		
< 10 years	157	31
10 years	83	17
> 10 years	223	44
Missing information	40	8

The findings show that the anchor-based approach was ineffective in defining minimal important differences between patient groups (the MID) as the only external anchor available was the Karnofsky Performance Score, and correlations with it were poor, according to our pre-defined thresholds. This result highlights the importance of verifying instead of assuming that potential anchors have meaningful associations with the target QoL measure. A recent review [9] reported that roughly a quarter of oncology investigations seeking to determine anchor-based MIDs for patient-reported outcome measures neglected to verify these correlations. In the current study, the modest correlation between performance status and the EORTC QLQ-HN43 Swallowing scale removed a convenient anchor; on the other hand, these results seem to bolster the discriminant validity of the EORTC QLQ-HN43 Swallowing scale and the other domains, since they were initially developed largely because clinician-rated performance measures were deemed inadequate for capturing the richness and nuances of patients' experiences. Future studies could explore whether other external anchors are more suitable; using the current example of the Swallowing scale, tools that objectively assess swallow function or use of feeding tube, such as the Functional Oral Intake Scale [33], penetration-aspiration score [34] or Dynamic Grade of Imaging Toxicity [35] might be useful; for the Social Eating scale a subjective score of functional behaviour (for example, frequency of patient eating out) such as the MD Anderson Dysphagia Inventory [36] or Mann Assessment of Swallow Ability [37] might be used. It is likely that external anchors are scale-specific, i.e., they cannot be used to determine the MID for all scales.

Distribution-based approaches were applicable. The criteria of one-third and one-half standard deviation and standard error of the mean yielded MIDs between 9.5 and 14.3. The advantage of the standard error of the mean is that it is relatively independent from the sample size, as it is largely an attribute of the measure rather than a characteristic of the sample [2]. However, on their own, distribution-based methods are often considered suboptimal relative to those which are anchor-based as they are not intuitively understood by clinicians or patients and do not directly reflect patients' perceptions of meaningful differences [2, 8]. So, what alternatives can be applied if we want to find group differences that are relevant to patients? Cocks et al. performed qualitative interviews with breast cancer patients and discovered that patients are able to interpret findings from published literature and give opinions about the significance of differences found between groups [38]. Similarly, Sully et al. used qualitative interviews to explore meaningful QoL score changes among multiple myeloma patients [16]. This suggests patients' opinions can work as an external anchor. Although this is an interesting approach, it requires additional data collection and careful interviewing; calculations

Table 2 Subjective changes in swallowing, measured with the SSQ, and the corresponding delta in the Swallowing Scale of the EORTC QLQ-HN43

Patients reporting their swallowing in...	t1-t2					t2-t3				
	Delta in Swallowing					Delta in Swallowing				
	N	Percent (%)	Mean	Min	Max	N	Percent (%)	Mean	Min	Max
Very much worse	31	15	47	-17	100	9	4	27	-33	100
Moderately worse	34	16	22	-100	92	10	5	9	-30	75
A little worse	35	16	11	-58	83	16	7	18	-33	75
About the same	59	28	3	-30	58	71	33	-2	-58	67
A little better	32	15	12	-30	83	45	21	-14	-58	42
Moderately better	12	6	7	-25	58	34	16	-12	-83	25
Very much better	10	5	-10	-33	42	29	14	-17	-30	8
All patients	213		13	-100	100	214		-8	-83	100

A positive change score (delta) implies that the problems with swallowing have increased (i.e., quality of life is worse); negative scores imply fewer problems (i.e., quality of life is better)

SSQ Subjective Significance Questionnaire, EORTC QLQ-HN43 head and neck cancer specific module, t time

Table 3 Minimal important change scores according to the ROC analyses

Patients say their swallowing is	N	Cutpoint	Sensitivity	Specificity	Youden-Index	Area under the curve (95% confidence interval)
Deteriorated (between t1 and t2)	100 (of 213)	8	71%	70%	0.41	0.73 (0.66; 0.80)
Improved (between t2 and t3)	108 (of 214)	-83	100%	0%	0.00	0.29 (0.22; 0.36)

ROC receiver-operating characteristics, t time

Positive scores indicate more problems with swallowing

Table 4 Minimal important difference (MID) and change (MBC) scores for the EORTC QLQ-HN43 Swallowing Scale, derived by various approaches

MID		MBC	
		Deterioration (t1 to t2)	Improvement (t2 to t3)
Anchor-based	Mean difference of x at t2 in patients with KPS 60 vs. KPS 70 at t2	Mean delta in patients who say that their swallowing is "a little worse"	Mean delta in patients who say that their swallowing is "a little better"
	Discarded because of poor correlation	11	-14
	Mean difference of x at t2 in patients with KPS 70 vs. KPS 80 at t2	ROC derived cut-point	ROC derived cut-point
	Discarded because of poor correlation	8	Discarded because of poor AUC
Distribution-based	0.5 SD of Swallowing at t2	Based on predictive regression modelling	Based on predictive regression modelling
	14	15	-3
	0.3 SD of Swallowing at t2	0.5 SD of delta in Swallowing	0.5 SD of delta in Swallowing
	10	16	-12
	SEM at t2	0.5 SD of delta in Swallowing	0.5 SD of delta in Swallowing
	11	10	-8
		SEM of delta in Swallowing	SEM of delta in Swallowing
		12	-10

SD standard deviation, SEM standard error of the mean, ROC receiver-operating characteristics, AUC area under the curve, t time, KPS Karnofsky Performance Score

cannot simply be performed using existing data which is why we could not use it.

The anchor-based approach using subjective patient ratings for determining minimal clinically relevant changes over time (the MIC) yielded—in part—useable results. Problems occurred when we applied ROC methodology, especially when investigating *improvement* of quality of life; patients sometimes rated their quality of life retrospectively as improved although their module scores had actually worsened during that interval (this phenomenon was observed in both time intervals). This was an interesting observation as both measures, the SSQ and the EORTC QLQ-HN43, were completed by patients themselves. Patients were asked in the EORTC module to assess their current ability to swallow (solid food, pureed food, liquids, etc.), whereas in the SSQ they were asked to make a retrospective judgment on their changes in swallowing compared to the previous measurement 3 months before. Obviously, the change score required more cognitive and emotional processing: patients were asked to make a judgement on the status of their current condition, recall the previous status of their condition, and make comparisons and a judgement of change between the two. It is likely that (dis)satisfaction with the changes may additionally influence the latter. Satisfaction itself may be viewed as comprising two components: the expectations we have and the evaluation of the situation. This can lead to the so-called satisfaction paradox: if patients expect little improvement, they may be more satisfied with small improvements than if they had expected things to be much better, and vice versa [39]. In this case, perhaps some patients experienced less deterioration in swallowing than they had anticipated or possibly an adaptive sensory response to physiological motoric decline. Other processes that most likely play a role here are response shift and recall bias [6, 40, 41].

This finding emphasises there is no ‘one size fits all’ approach for determining MIC even for patient global ratings of change. Therefore, the conclusion of our study group was to continue using a variety of concurrent approaches—distribution and anchor-based. As we move forward in future studies to determine MICs and MIDs of the other scales in the EORTC QLQ-HN43, we plan to omit ROC analyses and comparisons of groups based on the Karnofsky Performance Score and apply all the other methods. It is hoped that additional investigators will be able to evaluate additional clinical anchors. It should be noted though that the results of the methods are particular to this specific study. Although not viable for the current dataset, ROC analyses were suitable methods to estimate the MIC in other studies [13].

While developing the statistical analysis plan, we realised that many decisions needed to be taken prior to knowing the results and the difficulties this would entail. However, we also wanted to avoid ‘fishing for the best results’. Consequently, we agreed to be decisive in certain aspects beforehand, and more

explorative in others. For example, based on previous literature [22–27], we assumed that swallowing deteriorates between the time before treatment starts and three months later and we assumed improvement of swallowing between three and six months after baseline. We therefore decided to compare scores with ‘a little change’ in the patient ratings between these two time spans and investigated the MIC for deterioration between t1 and t2 and the MIC for improvement between t2 and t3. However, was this a good decision? There was indeed an average deterioration of EORTC QLQ-HN43 Swallowing scores between t1 and t2 and an improvement between t2 and t3 on a group-level, but there were also some patients where the reverse was true. This might be related to improved symptom relief including pain medication. Moreover, data were considerably heterogeneous which could have contributed to the pattern of results that we observed.

Another point for discussion is that the mean change score on the EORTC QLQ-HN43 Swallowing Scale was not zero for ‘no change’ on the anchor. In future studies, a calibration could be used in such situations, i.e., taking the difference between mean changes on the EORTC QLQ-HN43 Scale of interest between adjacent categories of the anchor measure.

Another potential limitation is that we had decided a priori to calculate the distribution-based values for data at t2, not at t1 or t3. We did so because the time-point matched with one that is frequently used in clinical trials. We did not calculate it for all time-points because we wanted to establish a method that could be applied to all scales of the module and restrict the number of possible MID and MIC values for one scale to a reasonable amount. Failure to do so could potentially confuse clinicians and consequently let them return to the simpler 10-point rule [5] or the 16% of the range-rule [8]. However, concentrating on only one time point bears risks. For example, if Cronbach’s alpha of the instrument differs following treatment (t2) in contrast to before (t1), then these SEM-based estimates differ as well. In our study, the differences in reliability were luckily very small (Cronbach’s alpha was 0.83 at t1, 0.85 at t2 and 0.85 at t3).

A further point discussed in our group was the difficulty encountered in trying to determine MIC and MID, and we consider thresholds [42, 43] as a potential alternative. However, we decided to continue determining MIDs and MICs because of their importance not only for researchers and clinicians but also for regulatory bodies.

Conclusions

In summary, the current study used a variety of anchor- and distribution-based approaches to examining MIDs and MICs for Swallowing scores in a newly refined QoL

instrument, the EORTC QLQ-HN43. The investigation drew on a large, international database encompassing repeated assessments completed by over 500 patients from 28 treatment centres around the world. To develop a feasible model, we focused on impaired swallowing, a domain of QoL that is of direct importance to head and neck cancer patients and clinicians. Findings illustrate some of the challenges of obtaining appropriate clinical anchors. Nonetheless, the estimates generated may help clinicians and investigators to interpret the meaning of EORTC QLQ-HN43 Swallowing scores and plan investigations. Results identified a number of strategies that appear to be useful in generating MIDs and MICs for this instrument, and we look forward to further examining their value with respect to additional scales on the module.

Supplementary Information The online version of this article (<https://doi.org/10.1007/s11136-021-02939-6>) contains supplementary material, which is available to authorized users.

Funding Open Access funding enabled and organized by Projekt DEAL. We thank the EORTC Quality of Life Group for funding this study (Grant #001/2014).

Data availability The data of this study are stored in the EORTC data repository and can be accessed by other researchers.

Code availability The software used for this study was STATA 12.1 (StataCorp LP, Texas, USA).

Declarations

Conflict of interest CA, IA, IB, KB, AB, PB, CB, JCS, WC, JR-D, AF, LF-G, AF, RG, HH, BBH, JJ, ON-G, DS, MS, AS, KT, IT, SK-T, and NY declare they have no conflicts of interest. NK reports honoraria from ONO PHARMACEUTICAL, Bristol Myers Squibb, Merck Biopharma, Astra-Zeneca, Merck Sharp & Dohme, Eisai, Bayer and Chugai Pharmaceutical, all outside the submitted work. LL reports grants and personal fees from Astra-Zeneca, BMS, Boehringer-Ingelheim, Debiopharm International SA, Eisai, Merck-Serono, MSD, Novartis, Roche; personal fees from Bayer, Sobti, Ipsen, GSK, Dexa Pharmaceuticals, Incyte Biosciences Italy, Amgen, Novartis; grants from Celgene International, Facileis, Hoffmann-La Roche, IRX Therapeutics, Medpace, Pfizer, all outside the submitted work. HM reports grants from Cancer Research UK, during the conduct of the study; personal fees and other from Warwickshire Head Neck Clinic Ltd, personal fees from Astra-Zeneca, MSD, Sanofi Pasteur, Merck, grants from GSK Biologicals, Sanofi Pasteur, GSK PLC, Astra-Zeneca, non-financial support from Sanofi Pasteur, MSD, Merck, outside the submitted work. He is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. MP reports personal fees from MeetingWords, outside the submitted work. CS reports grants from Roche, Intuitive; personal fees from Pfizer, Merck, MSD, Seattle Genetics, all outside the submitted work. SS reports personal fees from Lilly, Pfizer, Boehringer-Ingelheim, all outside the submitted work.

Ethical approval All sites obtained ethical approval in accordance with regional and national requirements. Approval Number from the principal investigator's institution: 837.281.14 (9520).

Consent to participate Patients were given time to consider the study and ask any questions before consenting and participating.

Informed consent All participants provided written informed consent.

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Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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