One-year evolution of the quality of life in patients with locally advanced human papilloma virus positive treated with neoadjuvant chemotherapy followed by transoral robotic surgery and neck dissection

Alina Diaconescu, M.D.

Department of Otolaryngology, Head and Neck Surgery

McGill University, Montreal

September 2020

A thesis submitted to McGill University in partial fulfilment of the requirements

for the degree of

Master of Science

To Eva, Cezar and Radu

Table of Contents

Abstract

Background: Oropharyngeal cancer is the most common type of head and neck cancers, with a 5-year survival of 64.7%. Over the last 40 years, such risk factors and etiology have changed, with a reduced incidence due to usage of tobacco and alcohol, but with an increased incidence due to Human Papilloma Virus (HPV) infection in 70% of cases. Chronic treatment-related toxicity and functional loss of the standard of care concurrent chemoradiation (CRT) have had a significant impact on the quality of life (QOL) of survivors of oropharyngeal squamous cell carcinoma (OPSCC). Currently, there are different de-escalation treatments and trials that aim to reduce the treatment-related toxicity while maintaining the survival for locally advanced OPSCC. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ30) is the quality of life questionnaire most used worldwide to assess the quality of life of cancer patients.

Objectives: The objectives of this thesis are: (a) to review literature on 1-year evolution of quality of life of patients treated for OPSCC with standard of care CRT, and (b) to assess the quality of life in human papillomavirus positive (HPV+) OPSCC patients with locoregionally advanced disease treated with the experimental treatment neoadjuvant chemotherapy (NeC) followed by transoral robotic surgery (TORS) as definitive treatment.

Methods: The first study was a narrative literature review of treated OPSCC patients assessed with EORTC QLQ-30 and EORTC Head and Neck -35 (a) at pre-treatment, and (b) at 12-months post treatment. The second study was a prospective cohort study that took place at McGill University Health Centre in Montreal, Canada. Patients were diagnosed with stage III and IV

(according to AAJC 7th edition) HPV+ OPSCC and treated with NeC (docetaxel and cisplatin) followed by TORS and selective neck dissection, between January 2017 and July 2018.

Results: a) The first study showed that standard-of-care treatment surgery and adjuvant radiotherapy or more commonly utilized CRT produced chronic side effects, such as xerostomia, poor oral and dental health, dysphagia, feeding tube dependency, and other fibrotic changes likely caused by radiotherapy. or a combination of surgery and radiotherapy. b) The second study (19 eligible HPV+ patients of 23 recruited; 90% male; median age: 58; 7 patients with localized base-of-tongue cancer; 12 with localized palatine-tonsil cancer) showed that EORTC-H&N35 scores at 12-month post-treatment were not significantly different than pre-treatment values in the scales known to be most affected by standard of care CRT treatment toxicity, such as swallowing ($p = 0.38$), social eating problems ($p = 0.70$), or dry mouth and sticky saliva ($p = 0.87$). No patient in this cohort required a gastrostomy tube (PEG) at any time-point assessed.

Conclusions: Results of the first literature-review study showed that chronic standard of care CRT treatment-related toxicity and functional loss, such as xerostomia, poor oral and dental health, dysphagia, as well as feeding tube dependency had a significant negative impact on the 1-year QOL of survivors of oropharyngeal squamous cell carcinoma (OPSCC). Results of the second prospective study showed that QOL 12 months post-NeC-TORS treatment returned to the pre-treatment baseline, or improved, on all scales, including the symptom scales that are most negatively affected by the current standard of care treatment CRT. Patients had a rapid return to an oral diet. Findings suggest that NeC followed by TORS provides maintenance of QOL and improvement in many areas compared to pre-treatment levels.

Résumé

Contexte : Le cancer oropharyngien est le type le plus courant de cancer de la tête et du cou, avec une survie de 5 ans de 64,7 %. Au cours des 40 dernières années, ces facteurs de risque et l'étiologie ont changé, avec une incidence réduite en raison de la consommation de tabac et d'alcool, mais avec une incidence accrue en raison de l'infection par le virus du papillome humain (VPH) dans 70 % des cas. La toxicité chronique liée au traitement et la perte fonctionnelle de la chimiothérapie (TRC) concomitante standard de soins ont eu une incidence importante sur la qualité de vie (QOL) des survivants du carcinome pavimenteux oropharyngien (CSCSPO). À l'heure actuelle, il existe différents traitements et essais de désescalade qui visent à réduire la toxicité liée au traitement tout en maintenant la survie de l'OPSCC localement avancé. L'Organisation européenne pour la recherche et le traitement du cancer (EORTC QLQ30) est le questionnaire le plus utilisé dans le monde pour évaluer la qualité de vie des patients atteints de cancer.

Objectifs : Les objectifs de cette thèse sont les suivants : (a) passer en revue la documentation sur l'évolution d'un an de la qualité de vie des patients traités par CCSPO avec TRC standard de soins et (b) évaluer la qualité de vie chez les personnes atteintes du virus du papillome humain positif (VPH+) Les patients atteints d'une maladie locorégionale avancée traités par le traitement expérimental de chimiothérapie néoadjuvante (NeC) suivie d'une chirurgie robotique transorale (TORS) comme traitement définitif.

Méthodologie : La première étude était une revue de la littérature narrative sur les patients traités par le CCSPO évalués avec EORTC QLQ-30 et EORTC Head and Neck -35 (a) avant le

traitement, et (b) 12 mois après le traitement. La deuxième étude était une étude de cohorte prospective qui a eu lieu au Centre universitaire de santé McGill à Montréal, au Canada. Les patients ont reçu un diagnostic de stade III et IV (selon la 7e édition de l'AAJC) d'OPSCC HPV+ et ont été traités avec du NeC (docetaxel et cisplatine), suivi d'un TORS et d'une dissection sélective du cou, entre janvier 2017 et juillet 2018.

Résultats : a) La première étude a montré que la chirurgie de traitement standard et la radiothérapie adjuvante ou la TRC plus couramment utilisée produisaient des effets secondaires chroniques, tels que la xérostomie, une mauvaise santé buccodentaire et dentaire, la dysphagie, la dépendance au tube d'alimentation, et d'autres changements fibrotiques probablement causés par la radiothérapie. Ou une combinaison de chirurgie et de radiothérapie. b) La deuxième étude (19 patients admissibles atteints de VPH+ sur 23 recrutés; 90 % d'hommes; âge médian : 58; 7 patients atteints d'un cancer localisé de la base de la langue; 12 avec un cancer localisé de la bouche et des amygdales) ont montré que les scores EORTC-H&N 35 à 12 mois après le traitement n'étaient pas significativement différents des valeurs pré-traitement dans les échelles connues pour être les plus touchées par la toxicité du traitement CRT standard de soins, comme la déglutition ($p = 0,38$), problèmes alimentaires sociaux ($p = 0,70$) ou bouche sèche et salive collante ($p = 0,87$). Aucun patient de cette cohorte n'a eu besoin d'un tube de gastrostomie (PEG) à un moment quelconque évalué.

Conclusions : Les résultats de la première étude documentaire ont montré que la toxicité chronique liée au traitement par CRT et la perte fonctionnelle, comme la xérostomie, une mauvaise santé buccodentaire et dentaire, la dysphagie et la dépendance au tube d'alimentation, ont eu un impact négatif important sur la l'année QOL des survivants d'un carcinome

pavimenteux oropharyngien (CCSPO). Les résultats de la deuxième étude prospective ont montré que la QDV 12 mois après le traitement par le TORS-CNE est retournée à l'état de référence avant le traitement, ou s'est améliorée, à toutes les échelles, y compris les échelles de symptômes qui sont les plus touchées négativement par la TRC actuelle du traitement standard de soins. Les patients ont eu un retour rapide à un régime oral. Les résultats suggèrent que le NeC suivi par le TORS assure le maintien de la qualité de vie et l'amélioration dans de nombreux domaines par rapport aux niveaux de pré-traitement.

Acknowledgements

Firstly, I would like to thank my supervisors, Dr Maida Sewitch and Dr Nader Sadeghi. Dr Sewitch has invested time and knowledge along with guidance, helping me to develop skills that are the basis for a researcher. I would also like to thank my clinical supervisor, Dr Nader Sadeghi, who has developed the treatment protocol of NeC and TORS for OPSCC and recruited the patients into the study. He has helped me comprehend and enhance the clinical importance and relevance of the study and its immediate impact on clinical practice. I would like to thank Dr Bernard Segal, the graduate Programme Director who proved to be an excellent advisor, listened to understand and helped with his expertise and experience every time there was a need. I would like to acknowledge the help I received from Sebastian Ionascu with the French versions of different documents as well as with the abstract translation. Lastly, I would like to thank my husband, Radu, for his support throughout the program.

Contribution of Original Knowledge

This thesis compares the quality of life of human papillomavirus (HPV) positive oropharyngeal cancer patients before and after neoadjuvant chemotherapy followed by transoral robotic surgery (NeC+TORS). A brief literature review showed that patients with unspecified-HPV-status oropharyngeal cancer who were treated with standard of care treatment (surgery followed by adjuvant radiotherapy or CRT) had quality of life estimates that were lower 12-month after treatment than before treatment. In contrast, patients with locally advanced OPSCC HPV+ who were treated with NeC+TORS had quality of life estimates at 12-month after treatment that were not significantly different from pre-treatment hence maintaining the quality of life despite cancer treatment. This is a departure with improved outcomes compared to standard CRT. Further studies are required to determine the generality of this result.

Contribution of Authors

The research question was developed by Dr Alina Diaconescu, Dr Nader Sadeghi, and Dr Maida Sewitch. The research protocol was written by Dr Alina Diaconescu and guided methodologically by Dr Maida Sewitch with clinical feedback from Dr Nader Sadeghi. Ethical approval was received from McGill University Health Center Research Ethics Board (MP-37-2018-3568) with guidance also from Dr Marco Marcarella. Both the manuscript, as well as the thesis itself, were written by Dr Alina Diaconescu with editorial assistance from Drs Maida Sewitch and Nader Sadeghi.

The research protocol was designed by Dr Alina Diaconescu with guidance and approval from Drs Maida Sewitch, Nader Sadeghi and Bernard Segal. Nahid Golabi was the research assistant who helped with data collection and digitalizing questionnaires along with Dr Alina Diaconescu Statistical analysis was performed by Dr José L. Ramirez-Garcia Luna. The literature review, data analysis and interpretation were performed by Dr Alina Diaconescu and supervised by Drs Maida Sewitch and Nader Sadeghi. Editorial assistance was obtained from the various co-authors. The thesis was written by Dr Alina Diaconescu.

CHAPTER 1: Introduction

1.1 Rationale

Standard of care concurrent chemoradiation (CRT) treatment for oropharyngeal squamous cell carcinoma is well known among clinicians for its short- and long-term side effects. A new experimental therapy that uses neoadjuvant chemotherapy, followed by transoral robotic surgery (NeC+TORS) has been offered as a treatment option to patients at McGill University Health Centre to reduce side effects. To assess if side effect were reduced, this thesis did 2 studies. The first study is a narrative review that aims to investigate the quality of life of OPSCC patients treated with standard of care measured at diagnosis and at 12-month post-treatment using the EORTC questionnaires.

The second study aims to determine how the quality of life of patients, treated by NeC+ TORS alone, is affected by describing QoL change in the 12 months following treatment.

1.2 Thesis Objectives

This thesis aimed (1) to do a narrative review of the literature on the post-treatment QOL of post-standard-of-care treatment OPSCC patients, and (2) to assess the quality of life of patients with locally advanced in HPV+ OPSCC treated at the McGill University Health Centre with neoadjuvant chemotherapy (NeC) followed by transoral robotic surgery (TORS) as definitive treatment. It is hypothesized that pre-treatment and 12-month post-treatment quality of life scores are not significantly different from each other.

1.3 Thesis Organization

The thesis is organized into chapters to provide context and present the findings as well as comparison with historical data. The current chapter, Chapter 1, provides an introduction, stating the thesis rationale, objectives, and thesis organization. Chapter 2 presents background information. Chapter 3 is a narrative review of the literature on the quality of life of oropharyngeal cancer patients with unspecified HPV status from diagnosis to 12-months post-treatment. Chapter 4 is a manuscript that analyzes the evolution of the quality of life of patients with HPV positive oropharyngeal cancer treated with neoadjuvant chemotherapy followed by transoral robotic surgery, as measured by patient reported EORTC surveys on QOL. Chapter 5 presents an overall discussion and conclusion that respond to the research question. Appendices and References follow.

CHAPTER 2: Background

2.1 Epidemiology

Head and neck malignancies may affect all anatomic sites from the skull base to the thoracic inlet. In 2018, the World Health Organization reported 657,438 cases of head and neck cancer, accounting for 3.6% of all cancers worldwide. In Canada, head and neck cancers are diagnosed in about 4,300 individuals each year. Head and neck malignancies can develop from the mucosa of the oral cavity, pharynx, larynx and paranasal sinuses, as well as from salivary gland (major and minor), [1]. Because the most common type of mucosa in these areas is stratified squamous epithelium, the most common malignant neoplastic tumour that has epithelial tissue origin is squamous cell carcinoma.

Anatomically, the oropharynx includes the soft palate, palatine tonsils, lingual tonsils, the base of the tongue and pharyngeal wall as described in Figure 2.1. [2, 3]The interest in this writing is centred on oropharyngeal squamous cell carcinoma cancer, referred to as OPSCC. In 2017 The American Cancer Society reported 49670 news cases of head and neck cancers and 9700 deaths as a result of this disease with 5-year overall survival of 64.7%. [2] The

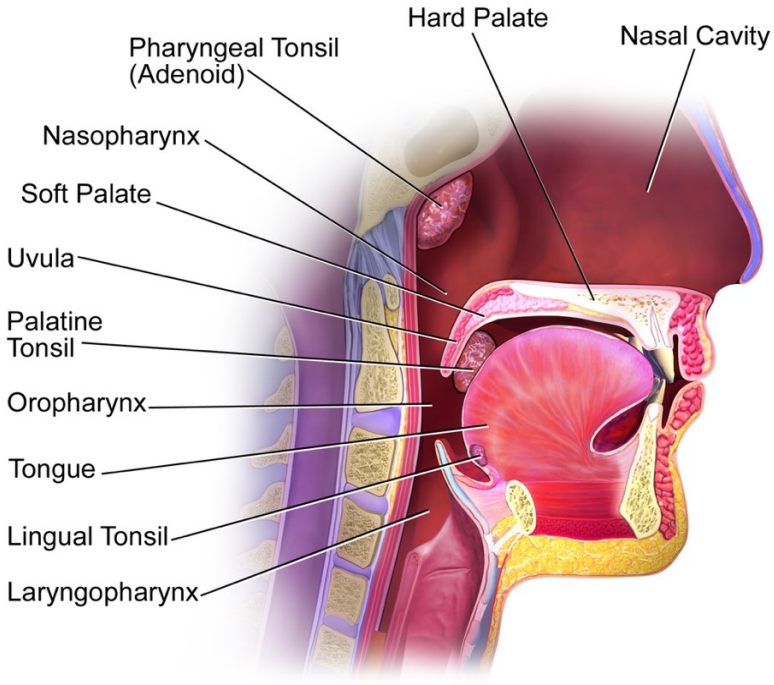


Figure 2.1: Anatomy of the Oropharynx

incidence of OPSCC associated with tobacco and alcohol has decreased in the last decade by approximately 3% per year, whereas the incidence of OPSCC associated with HPV infection has increased approximately 3.6 % per year. [1]

2.2 Aetiology and risk factors

The link between OPSCC and human papillomavirus (HPV) was first made in 1983 by Syrjänen et al. [4] and has been studied and discussed by many authors since, trying to understand better how a virus can cause cancer. HPV is an epitheliotropic, double-stranded DNA oncovirus that affects discontinuous basement membranes such as the oropharyngeal one.[5] Human papillomavirus has 120 different strains; the oncogenic types are HPV 16 and HPV 18. The oncogenic capacity of transforming mucosal tissue is due to its ability to stop the natural life cycle of a cell, stop the apoptosis and have the function of tumour suppressor P16 lost.[6]

The main difference in the epidemiology of HPV negative and HPV positive oropharyngeal cancer is that the leading risk factor for HPV positive OPSCC is sexual behaviour and lifetime number of oral sexual partners. OPSCC patients are predominantly men, around 50, with more than 5 women they performed oral sex on; without risk factors as tobacco or alcohol consumption [7, 8,9].

2.3 Diagnosis, symptoms and clinical exam

Every patient that presents to Otolaryngology-Head and Neck Surgery specialist must be initially assessed using all the information from the history along with the physical examination. Even if the location of the potential cancer is well known because of the main complaint of a patient, all head and neck anatomic sites are examined to look for synchronous cancers and the extent of the index cancer. Diagnosis starts with corroborating the patient's complete and detailed history with

clinical examination and radiologic images.[10] The physician observes the patient's general appearance and looks for signs of oropharyngeal cancer such as a painless neck mass, drooling or recent onset of stertor. Stertor is an inspiratory sound that is due to obstruction above the larynx and may be present in different pathologies; therefore, it is not a pathognomonic sign of oropharyngeal cancer.

The clinical exam includes inspection and palpation of the oropharyngeal anatomic parts: palatine tonsils, tonsillar pillars, soft palate, uvula, posterior pharyngeal wall, tongue base and the tissue that surrounds these structures described in Figure 2.2. While this disease has minimal symptomatology and two-thirds of the patients present with a painless neck mass according to

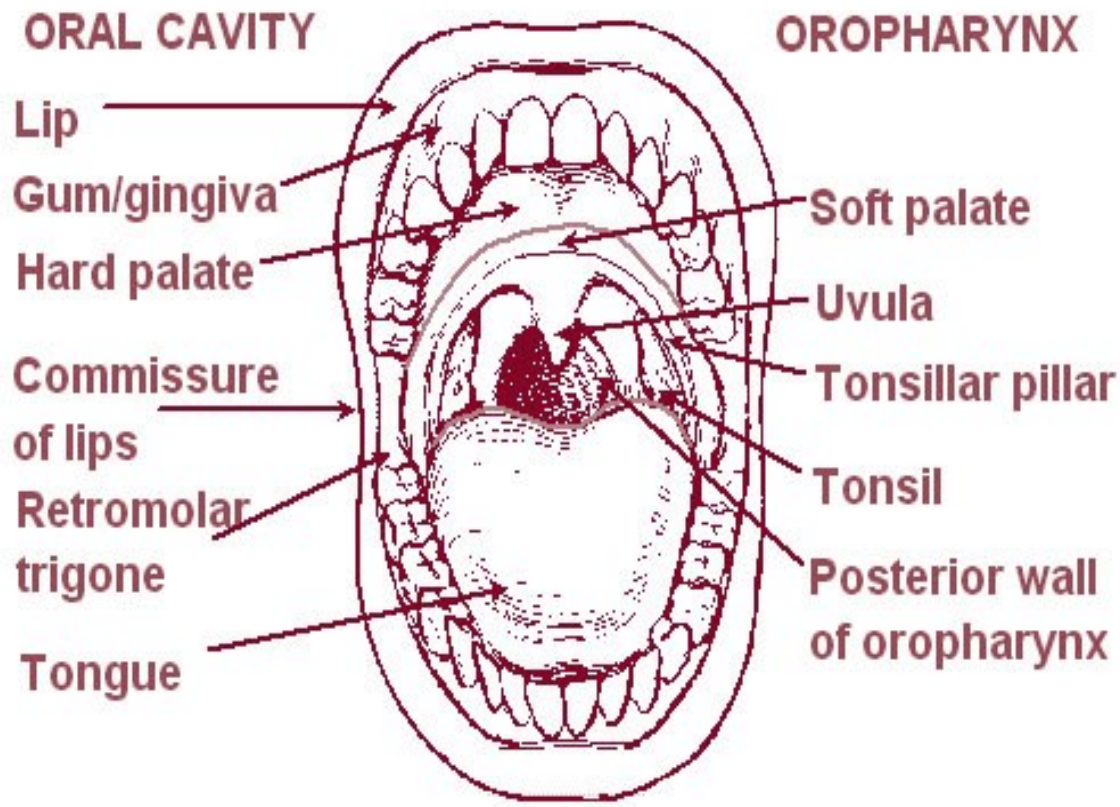


Figure 1.2: Anatomic sites of Oropharyngeal cavity vs Oral cavity

Georgopoulos et al. [10], they are usually diagnosed with locally advanced stages III or IV (AAJC 7TH edition) at presentation.

2.4 Patient management-staging the disease

Imaging and histopathologic assessment

The histopathologic exam is performed before or after the image assessment. It represents a crucial step in the management of an oropharyngeal cancer patient to allow decision by the physician regarding the treatment.

Usually, fine needle aspiration (FNA) is the first step required for a preliminary cytologic diagnosis when a patient presents with neck mass and the primary cancer cannot be visualized. If FNA is positive, a thorough search is undertaken to find the primary cancer that may include an exam and a biopsy under anaesthesia. HPV status is tested through the presence of a P16 marker during the histopathological exam.

When a primary lesion is discovered during the clinical exam a biopsy of the primary lesion is done for histopathological confirmation. Then a cross-sectional imaging is required for further evaluation of the extent of cancer and staging. Both computed tomography (CT) scan of neck and thorax and/or magnetic resonance imaging (MRI) of the primary site are mandatory for a complete staging of cancer [11].

Staging

According to AJCC 7th edition stage III is represented clinically by stage T1-T3(N1) or T3N0, and stage IVa includes T1-T3(N1-N2) or T4a(N0-N2) as described in *Table 2.1*[12].

Table 2.1: Summary of Oropharyngeal Cancer staging Included in AJCC 7th Ed Cancer Staging Manual[13]

Stage 0	**Tis**	**N0**	**M0**
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

In 2017, a new version of the AJCC staging was introduced for HPV positive OPSCC, and all patients diagnosed after January 2018 staging is to be in accordance to the newest AJCC 8th edition staging manual[14]. The significant change involves the necessity of a tumour to be tested for HPV using immunohistochemistry for overexpression of the tumour suppressor protein P16. This test is inexpensive and readily available worldwide.

AJCC 8th Edition major changes

All cancer staging must characterize three aspects in order to be specific and universally understood: tumour(T) classification, node (N) classification and metastasis(M) classification.

The changes that AJCC 8th edition brought to HPV positive OPSCC are detailed below and presented in *table 2.2*.

T classification changed with the removal of Tis (because the cancer is indolent for an extended period) and T4a/b is now T4 only since there was no notable difference in prognosis between the T4a and T4b.

In terms of N classification, N1 is considered ipsilateral lymph nodes smaller than 6 cm, regardless of the number; N2 is represented by bilateral lymph nodes smaller than 6 cm, regardless of the number; and N3 is any lymph node greater than 6 cm, regardless of the number.

M classification remained unchanged.

Table 1.2 Summary of Oropharyngeal Cancer HPV + staging Included in AJCC 8th Ed Cancer Staging Manual[14]

Stage	T and N staging
Stage I	T0-T2N0-N1
Stage II	T0-T2N2 or T3N0-N2
Stage III	T4(any N) or N3(any T)
Stage IVA	M1
Stage IVB	NA
Stage IVC	NA

2.5 Biomarkers of OPSCC

A *biomarker* is defined as a measurable medical sign that is directly related to pathology. For biomarkers to be considered adequate, they must meet relevance and validity criteria. The relevance of a biomarker is represented by its clinical significance, therefore the quality of information that the biomarkers can provide on a particular pathology.[15] The validity of a biomarker is its usage as a surrogate endpoint, and because the endpoint is not clearly defined, usually it is accepted as a spectrum of values.

As described *by M. Mena et al.* in 2018, the most accurate biomarker for HPV positive OPC is the presence of HPV-DNA and p16ink4a. [16] The double positivity, p16 and presence of HPV DNA, is considered to be the only combination that has the diagnostic accuracy and prognostic value. However, in clinical practice p16 positivity in oropharyngeal cancer is considered an accurate surrogate for HPV positivity. This is not the case for other head and neck sites.

As described by the systematic review performed by Sacks et al., even though it is well-known and accepted that HPV positive oropharyngeal tumours have a better response to treatment, up to now, no biomarker can be successfully used to predict the patients' response to different treatments. [17] this being a topic of interest and research in the medical field.

2.6 Treatment options

Standard of care

The current standard of care for advanced stages (III and IV) OPSCC- including HPV related OPSCC- includes high doses chemotherapy (usually cisplatin-based) and radiotherapy that is given concomitantly. The treatment has been considered gold standard since 2003 when Adelstein et al. published a study with strong evidence that this combination offered the best

outcome for locally advanced oropharyngeal cancer.[18] However, clinical practice showed that these approaches leave the survivors with significant and lifelong morbidity, such as difficulties with breathing, swallowing and eating.[19-24]

Most of the toxicity and chronic treatment-related sequelae of OPSCC are due to hypoxic fibrosis of the upper aerodigestive tract caused by radiotherapy. These include loss of salivary function, dry mouth, sticky saliva, dental loss, poor oral health, dysphagia, feeding tube dependency, neck muscle dystonia, fibrotic loss of lower cranial nerve function, pharyngeal and laryngeal stenosis, soft tissue necrosis, chronic mucosal ulcerations, chronic feeding tube dependency, muscle atrophy, and osteoradionecrosis.

Experimental treatment options centred on HPV+ OPSSC

Since the pathogenesis, presentation, tumour prognosis, natural history, and response to treatment differ in HPV+ *versus* HPV- OPSCC, and standard of care is highly toxic, investigations are being carried out to de-escalate the treatment for HPV+ OPSCC in order to improve the functional outcome while optimizing the cancer cure rate.[25, 26]

In 2009 TORS was approved by FDA as an accepted treatment for OPSCC. Since then, there has been a continuous development of treatment protocols in which, preserving the curative aspect of the treatment, attempts are made to reduce the toxicity of the treatment while using this surgical approach.[27]

There have been studies of different de-escalating treatments. These include the ongoing trials, ORATOR2 and Quarterback and completed trials such as E1308, RTOG-1016 and ORATOR trial.

ORATOR2 is a randomized phase II trial that aims to de-escalate HPV-associated OPSCC treatment with de-escalated radiotherapy vs trans-oral surgery.[28]

Quarterback is a randomized phase III trial that compares two doses of definitive radiation therapy given with induction and concurrent chemotherapy in HPV-positive oropharynx, unknown primary, or nasopharynx cancer -NCT01706939.

RTOG 1016 was a randomized, multicentre, non-inferiority trial that assessed whether radiotherapy plus cetuximab has better overall survival and progression-free survival than radiotherapy plus cisplatin (standard of care). The results suggested that patients with HPV-positive OPSCC treated with radiotherapy plus cetuximab had lower overall survival and progression-free survival compared with radiotherapy plus cisplatin.[29]

E1308 was a phase II trial of induction chemotherapy (Paclitaxel and Cisplatin) followed by cetuximab (Erbitux) with low dose vs standard-dose intensity modulated radiotherapy (IMRT). The results suggested that reducing radiation dose significantly improved swallowing and permitted an oral diet [30].

ORATOR trial used non-de-escalated radiotherapy ± chemotherapy versus TORS ± RT/CRT. The results showed that patients treated in radiotherapy arm showed superior swallowing related QOL scores one year after treatment, although the difference did not represent a clinically meaningful change.[31] Furthermore in the TORS arm 70% of the patients received adjuvant RT/CRT.

2.7 Risk factors for poor prognosis

The overall 5-year survival rate for patients diagnosed with oral or oropharyngeal cancer is 65%.[32] However, various risk factors influence prognosis, including the stage of cancer at diagnosis, HPV status, marijuana or tobacco use, and race.[6]

Stage of cancer at diagnosis

A more advanced stage of cancer at diagnosis provides a worse prognosis than stages I and II. Also, the treatment strategy differs from one stage to another. In a locally advanced OPSCC, the treatment is more aggressive and has more severe side effects than an early stage disease.

HPV status

OPSCC includes HPV-positive and HPV-negative cancers. As shown by Ragin et al. patients with HPV-positive OPSSC have a lower risk of dying (meta HR: 0.85, 95% CI: 0.7–1.0), and a lower risk of recurrence (meta HR: 0.62, 95%CI: 0.5–0.8) compared to HPV-negative OPSCC patients due to their different response to treatment. [33]

Marijuana or Tobacco Use

Marijuana or tobacco usage is an essential risk factor for head and neck cancer. Some studies showed that the risk of recurrence and death for a tobacco user is 1% higher for each pack-year (number of pack of cigarettes smoked every day * number of years the person smoked) of tobacco use. The risk of death doubles if there is usage during radiotherapy.[34]

For HPV positive OPSCC, as described by (Ang, Harris et al. 2010) the overall three-year rates of survival were split into two risk groups: low risk (93.0%, 95% CI 88.3 to 97.7), intermediate-risk (70.8%, 95% CI 60.7 to 80.8).[35] HPV positive OPSCC patients that smoked less than ten

packs-year were considered low risk while those that smoked more than ten pack-year were low risk if had nodes involvement of N0-N2a and intermediate-risk if N2b-N3. Therefore, a detailed smoking history should be included in HPV-positive OPSCC patients' overall prognosis as a notable risk factor.

Race

Several studies showed a difference in prognosis between white and African American patients. There is a dramatic increase in mortality and recurrence among the last category. However, the mechanism is still studied and explored by researchers and maybe due to socioeconomics and health care access disparity.[36, 37] In a study of over 20000 head and neck cancer patients, Molina et al. reported that median survival time was 40 months for white patients and 21 months for African American patients.[36]

2.8 What influences the quality of life of OPSCC patients diagnosed and treated in stage III and IV

While treatment-related toxicity and functional loss can negatively impact survivors, quantifying and comparing the patient-reported outcome measures and functional outcomes of standard and novel treatments are essential components to consider in the development of better therapies. Patients with locally advanced OPSCC are predominantly treated with concomitant chemotherapy and radiotherapy. Chemotherapy side effects include nausea and/or vomiting, peripheral neuropathy, changes in appetite and loss of taste, diarrhoea, anaemia, hearing loss, tinnitus, and increased infection risk. Radiotherapy side effects are mainly: dry mouth, mouth and gum sores, dysphagia, stiffness in the jaw, nausea, hair loss (in the exposed area), lymphedema, tooth decay.

Radiation-related sequelae are due to hypoxic fibrosis of the upper aerodigestive tract from radiation-related treatment. They include loss of salivary function, dental loss, poor oral health, dysphagia, feeding tube dependency, fibrotic loss of lower cranial nerve function, pharyngeal and laryngeal stenosis as described in Figure 2.3.[38]

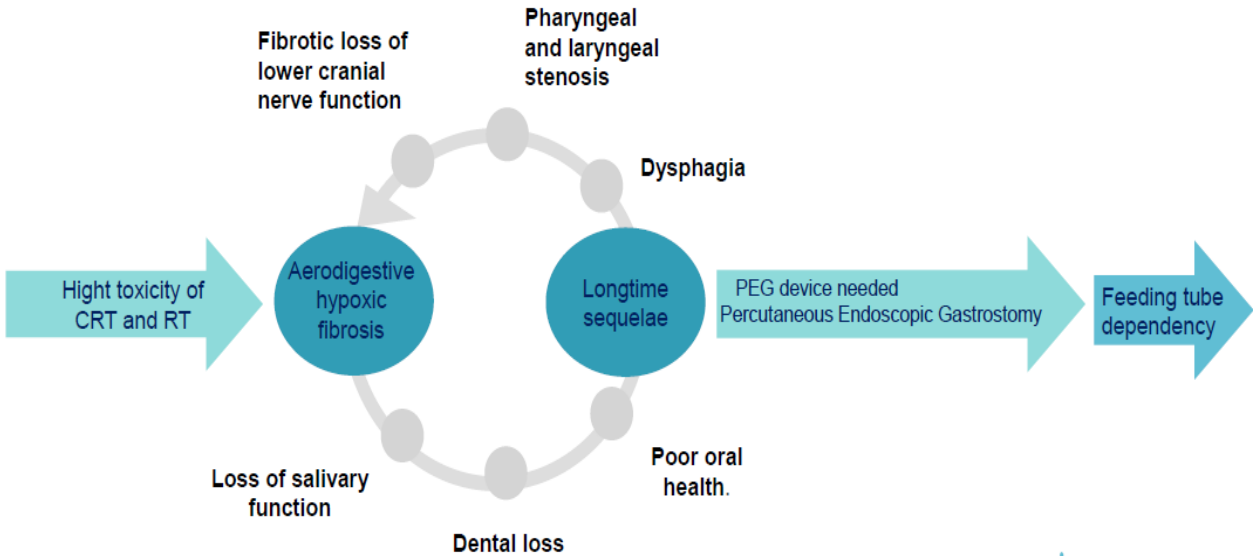


Figure 2.3: Head and neck radiotherapy related toxicity
Figure 2.3: Head and neck radiotherapy related toxicity

Long term side effects of the treatment may include breathing problems and swallowing difficulties needing surgical intervention through procedures like tracheostomy or percutaneous endoscopic gastrostomy (PEG). The impact that those therapies have on patients' lives is especially significant because at diagnosis their quality of life is not majorly influenced by the disease. A high survival should ideally correspond to a high quality of life and a high functional outcome for a treatment to be considered successful treatment.

2.9 Quality of life measures

Worldwide, quality of life of oropharyngeal cancer patients is assessed by self-administered validated questionnaire and patient-reported at different time points from the therapy. At present, there are three questionnaires recognized as the best tools for assessing quality of life by field specialists.

The **University of Washington Quality of Life Questionnaire (UW-QoL)** has scores that range from 0 to 100, with higher scores being favourable, is used in North America.[39]

The **M. D. Anderson Dysphagia Inventory (MDADI)** assesses the effect of dysphagia on quality of life in head and neck cancer patients with scores ranging from 20 to 100, with higher scores being favourable. [40] This questionnaire is new in the medical field and not yet validated in many languages.

The **European Organisation for Research and Treatment of Cancer (EORTC)** questionnaire is the self-administered questionnaire most used worldwide, translated, and validated in 110 languages, including French and English, that had proven as a reliable tool for over 27 years. (See Appendix). The EORTC core questionnaire was validated using patients treated at the Kingston Regional Cancer Centre in Canada, where it was compared to four other scales: The Sickness Impact Profile, the McGill Pain Questionnaire, the General Health Questionnaire and the Cancer Rehabilitation Evaluation, coughing and feeling ill.[41-43]

The **EORTC core questionnaire (QLQ-30**) is a 30-item generic measure of the quality of life. The questionnaire includes five function scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/emesis and pain), six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact) and one global health and QoL scale.

Subscales are scored from 0 to 100. Higher scores for functional or global health scales are favourable, whereas higher scores for symptom scales are unfavourable.

The **EORTC Quality of Life Questionnaire Head and Neck-35 (QLQ-H&N35)** questionnaire evaluates the impact of head and neck cancer on QoL. It has 14 symptom scales (pain, swallowing, sense problems, trouble with social eating, trouble with social contact, teeth, speech problems, coughing, dry mouth, sticky saliva, less sexuality, weight loss, weight gain, and feeding tube dependency), and scores range from 0 to 100.[44] A high score represents more problems and is unfavourable.

Functional outcome is evaluated objectively by the return to an oral diet. Patients with OPSCC who receive standard of care CRT may require percutaneous endoscopic gastrostomy (PEG) to provide a means of feeding when oral intake is not adequate due to oropharyngeal cancer treatment while going through the treatment of after the treatment.[45, 46] This is an endoscopic medical procedure in which a tube is placed into the stomach of a sedated patient through the abdominal wall.

2.10 Link statement

The current standard of care concurrent CRT for patients with locally advanced OPSCC is known to be toxic with long term sequela. Several studies have demonstrated the negative impact of CRT on quality of life at different time-points. The following manuscript is a narrative review of four relevant articles in the otolaryngology head and neck surgery literature in terms of quality of life of OPSCC patients measured at diagnosis and 12-month post-treatment using the EORTC questionnaires.

CHAPTER 3: Manuscript 1: Literature review of OPSCC patients assessed with EORTC QLQ-30 EORTC H&N-35

Alina Diaconescu[1], Nader Sadeghi[1,2] Maida J Sewitch[1,3]

1-Department of Otolaryngology – Head and Neck Surgery, McGill University.
2-Department of Oncology, McGill University.
3 Department of Medicine, McGill University

Research article to be submitted

Part of a Master of Science Thesis
in the Department of Otolaryngology, Head and Neck Surgery
McGill University, Montreal

3.1 ABSTRACT

Background. The current standard of care treatment for advanced oropharyngeal squamous cell carcinoma (OPSCC) is known to be highly toxic and associated with significant and lifelong morbidity. The purpose of this review is to summarize quality of life data from studies that used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ30 and H&N35) in patients with OPSCC at diagnosis and at 12-months post-treatment.

Methods. A literature search was performed with the help of a librarian to locate studies that measured quality of life with the EORTC at diagnosis and 12-months post-treatment for patients diagnosed and treated for OPSCC. The Medline and Cochrane databases were searched for studies from 1999 to December 2019. Data were extracted by the lead author and included author and year of publication, country, sample size, age, sex, cancer stage, treatment and quality of life at diagnosis and 12-months post-treatment.

Results. Four studies with a total of 343 patients met inclusion criteria. Patients with OPSCC treated with standard of care- that includes surgery followed by radiation/chemoradiation (RT/CRT), or concurrent chemoradiation (CRT)- have a lower quality of life at 12-months post-treatment compared with pre-treatment. Most problems were related to long term side effects of radiotherapy, such as xerostomia, sticky saliva, trismus and problems with teeth. Patients also reported lower role functioning scores. A possible cause is the presence of a PEG that impedes oral diet in daily life situations.

Conclusion. Standard of care treatment for OPSCC produced chronic side effects, such as xerostomia, poor oral and dental health, dysphagia, feeding tube dependency, and other fibrotic changes likely caused by radiotherapy or combination of surgery and radiotherapy.

3.2 Introduction

In 2017 the American Cancer Society reported 49,670 new cases of, and 9700 deaths from head and neck cancers respectively, with a 5-year overall survival of 64.7%. [1, 2] While the proportion of oropharyngeal squamous cell carcinoma (OPSCC) was approximately 20% of head and neck cancer in 1980s in the US, it currently represents 70% of head and neck squamous cell carcinomas of head and neck.[3] The incidence of OPSCC associated with tobacco and alcohol has decreased in the last decade by approximately 3% per year, whereas the incidence of OPSCC associated with HPV infection has increased approximately 3.6 % per year.[1] The current standard of care treatment for locally advanced OPSCC- including HPV related OPSCC- is high dose chemotherapy and radiotherapy, which is known to be highly toxic and associated with significant and lifelong morbidity.[4-7]

The short-term and long-term sequelae of OPSCC treatment impact survivors' quality of life. The sequelae include loss of salivary function, dry mouth, sticky saliva, dental loss, poor oral health, dysphagia, feeding tube dependency, neck muscle dystonia, fibrotic loss of lower cranial nerve function, pharyngeal and laryngeal stenosis, soft tissue necrosis, chronic mucosal ulcerations, chronic feeding tube dependency, muscle atrophy, and rarely osteoradionecrosis. These sequelae, in turn, have social, economic and emotional impacts, which are permanently changed after the cancer is cured. Even minimal damage to swallowing, talking, eating and respiration are known to diminish patients' quality of life. [8, 9]

Quality of life is influenced by multiple factors in multiple health dimensions that influence well being of a patient. Patient-centered and patient-reported quality of life assessment has the capacity to measure both objective and subjective quality of life outcomes from a patient perspective. Hence a useful quality of life questionnaire needs to evaluate multiple dimensions of life that are of importance to the patients and represent patient perspective and not the perspective of the treating team. The European Organisation for Research and Treatment of Cancer (EORTC-QLQ30 core) is a self-administered questionnaire that is most used worldwide and has been translated in 110 languages including French and English. There are two components to the EORTC. The core questionnaire **(QLQ-30**) is a 30-item generic measure of

quality of life. The questionnaire includes five function scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/emesis and pain), six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial impact) and one global health and QoL scale. Subscales are scored from 0 to 100. Higher scores for functional or global health scales are favourable, whereas higher scores for symptom scales are unfavourable. The EORTC core questionnaire was validated using patients treated at the Kingston Regional Cancer Centre in Canada, where it was compared to four other scales: The Sickness Impact Profile, the McGill Pain Questionnaire, the General Health Questionnaire and the Cancer Rehabilitation Evaluation, coughing and feeling ill. [10-12] The EORTC Head and Neck-35 (QLQ-H&N35) evaluates the impact of head and neck cancer on QoL. It has 14 symptom scales (pain, swallowing, sense problems, trouble with social eating, trouble with social contact, teeth, speech problems, coughing, dry mouth, sticky saliva, less sexuality, weight loss, weight gain, and feeding tube dependency), and scores range from 0 to 100.[13] A high score represents more problems and is unfavourable.

The purpose of this review is to summarize the literature on the 1-year evolution of quality of life after diagnosis in patients treated for oropharyngeal cancer. The review focuses on the studies that used the EORTC QLQ30 and H&N35 at diagnosis and at 12-month post-treatment. Findings will provide insight on how the current standard of care treatment for OPSCC impacts patients in the year following initial treatment.

3.3 Materials and methods

Search Strategy

With the help of a librarian, we performed an extensive literature search through Medline and Cochrane database for studies from 1999 to December 2019. We used the following terms "oropharynx", "oropharyngeal"," cancer"," neoplasm", "tumour"," quality of life" with databased- specific coding and combinations. Mesh headings were used in different combinations. Inclusion criteria were analytical studies (case-control, cross-sectional, cohort, randomized control trials, qualitative studies, systematic reviews, and meta-analyses) that used the EORTC assessment tool at diagnosis and 12 months after treatment in OPSCC patients.

Articles published in English were included with no intention of searching unpublished literature. Additional limits were set for rejecting results that involved animals or children. HPV status could not be used as a search criterion because there was no clear separation in any study.

3.4 Results

In total, 206 papers were identified. After initial review of the titles followed by the abstracts of these papers, only four met the inclusion criteria. We extracted the following data from the four studies: author and year of publication, country, sample size, age, sex, cancer stage, treatment and quality of life at diagnosis and 12-months post-treatment.

	Author (year)	Country	N=343	Age (mean)	Male (%)	Stage (% distribution)	Treatment - (number of patients)
1	Petruson et al. (2005) [14]	Sweden	60	57	78%	I+II (13%) III+IV (87%)	Surgery +Radiotherapy -2. Chemoradiotherapy -48 Radiotherapy -10.
2	Nordgren et al. (2006) [15]	Sweden	50	58	72%	I+II (25%) III+IV (75%)	Surgery and radiotherapy -14. Chemoradiotherapy -16 Radiotherapy -19
3	Oates et al. (2008) [16]	Australia	27	NA	NA	N/A	Surgery and radiotherapy -10. Surgery-2. Chemoradiotherapy- 13. Radiotherapy -2
4	Al-Mamgani et al. (2013) [17]	The Netherlands	207	<65=69%. >65=31%	69%	N/A	Surgery and radiotherapy -77 Chemoradiotherapy - 62 Radiotherapy-68

Table 2 Summary of QoL in OPSCC patients using the EORTC

As described in *table 1,* 343 patients from three countries were included in this review. Mean age ranged between 57 and 64 in 3 studies; in the fourth study, 69% of patients were under 65 years of age. All studies had more male than female patients. Treatment included surgery alone, surgery followed by radiotherapy, surgery and chemoradiotherapy or radiotherapy alone. Only one study described the presence of a PEG at 12-month time-point. There was no information on the HPV status of the tumour.

Table 2 shows the EORTC OLQ-C 30 values at diagnosis (Dx), and 12-months post-treatment in the four included studies as well as those of the general male population aged 50–59.

The Global quality of life improved in all the studies from diagnosis to 12-month post-treatment.

STUDY	PETRUSON [14]		NORDGREN [16]		OATES [16]		AL-MAMGANI [17]		GENERAL MALE POPULATION 50-59 *[18]
N	60	36	37	27	27	27	207		
	at Dx	at 12-mo	at Dx.	at 12-mo at Dx		at 12-mo	at Dx	at 12-mo	
EORTC QLQ-C30									
FUNCTIONING SCALES									
PHYSICAL	N/A	N/A	81	81	N/A	N/A	87.1	83.4	93
ROLE	N/A	N/A	80	74	N/A	N/A	81.8	82	88.5
EMOTIONAL	N/A	N/A	73	81	N/A	N/A	71	80.8	84.2
COGNITIVE	N/A	N/A	88	80	N/A	N/A	87.8	86.4	91.3
SOCIAL	N/A	N/A	88	80	N/A	N/A	87.3	88.5	91.2
GLOBAL QUALITY OF LIFE	61	69	65	72	64	59	72.1	74	76
SYMPTOM SCALES									
FATIGUE	N/A	N/A	29	23	24	37	22.4	25	17.2
NAUSEA/VOMITING	N/A	N/A	5	7	N/A	N/A	3.2	4.9	2.3
PAIN	31	19	28	19	N/A	N/A	21.6	14.1	16.7
SINGLE ITEMS									
DYSPNEA	N/A	N/A	20	19	N/A	N/A	10.8	12.5	10.5
SLEEP DISTURBANCES	N/A	N/A	32	14	N/A	N/A	25.6	15.4	14.2
APPETITE LOSS	N/A	N/A	19	26	N/A	N/A	13	17.3	3.3
CONSTIPATION	N/A	N/A	15	10	N/A	N/A	7.1	7.3	3.3
DIARRHOEA	N/A	N/A	7	2	N/A	N/A	5.1	5.8	5.7
FINANCIAL DIFFICULTIES	N/A	N/A	14	9	N/A	N/A	10.7	15	6.5
EORTC QLQ-H&N35									
SYMPTOM SCALES									
PAIN H&N	38	29	31	24	42	27	21.4	23.3	
SWALLOWING	25	25	23	22	28	17	31.1	23.6	
SENSES	N/A	N/A	11	28	N/A	N/A	11.2	19.6	
SPEECH	16	16	12	10	18	8	13.5	10.7	
SOCIAL EATING	N/A	N/A	17	26	N/A	N/A	13.9	16.6	
SOCIAL CONTACT	N/A	N/A	8	9	N/A	N/A	4.7	5.7	
SEXUALITY	N/A	N/A	10	30	43	60	21.8	24.6	
SINGLE ITEMS									

PROBLEMS WITH TEETH	**15**	**19**	**7**	**14**	**N/A**	**N/A**	**15.6**	**22.4**
PROBLEMS OPENING MOUTH	**N/A**	**N/A**	**21**	**20**	**N/A**	**N/A**	**16.1**	**24.6**
DRY MOUTH	**26**	**80**	**23**	**75**	**24**	**61**	**21.8**	**48.4**
STICKY SALIVA	**N/A**	**N/A**	**27**	**15**	**N/A**	**N/A**	**16.7**	**41.8**
COUGHING	N/A	N/A	28	14	N/A	N/A	19.4	23.3
FEELING ILL	N/A	N/A	24	14	N/A	N/A	12.4	13.2

Table 3 EORTC Quality of life scores in the four studies in the literature review and in the general male population

As per *Table 2* General population scores were comparable to scores at diagnosis of patients in all four studies. Some studies reported degradation of quality of life in different scales. At 12 months, post-treatment Nordgren et al. reported deterioration in social functioning, an increase in loss of appetite, senses problems, social eating problems, sexuality problems, as well as remarkable worsening of problems with teeth and dry mouth compared to diagnosis.[16] Petruson et al. reported an increase in problems with teeth and dry mouth at 12-month post-treatment compared to diagnosis.[14] Al-Mamgani et al. reported worse scores in appetite, pain related to head and neck, senses problems, social eating, sexuality, and remarkable worsening in problems with teeth, problems opening the mouth, dry mouth and sticky saliva.[17] Oates reported increases in fatigue and dry mouth at 12-month post-treatment compared with values at diagnosis.[16]

Oates et al. was the only study that determined the presence of a PEG at 12 months, which was reported in 25% of patients.

3.5 Discussion and Conclusions

In summary, this brief literature review showed that patients with OPSCC treated with standard of care- that includes surgery followed by RT/CRT, or chemotherapy and radiotherapy in different combinations- have a QoL at 12-month post-treatment that is lower compared with pre-treatment one. Most problems were related to long term side effects of radiotherapy, such as xerostomia, sticky saliva, trismus and problems with teeth. Patients also reported lower role, functioning scores, and a possible cause for that is the presence of a PEG that impedes oral diet in daily life situations, and likely deterioration in other scales. For now, there are no data in the literature to assess the impact of HPV positivity on the quality of life of OPSCC patients following treatment as these studies included all OPC irrespective of HPV status, However, the treatment is the major determinant of the QOL and that being the same irrespective of HPV status, these results likely apply to HPV positive OPC. Given the known higher prevalence of HPV positive oropharyngeal cancer compared to HPV negative OPSCC (75% vs 25%), likely most patients in these studies had HPV positive OPSCC.

In conclusion the current standard treatment of OPSCC that includes radiotherapy either in adjuvant setting after surgery or as concurrent with chemotherapy in definitive treatment setting has significant negative impact on the quality of life of survivors. Hence, a future direction for improving the quality of cancer care for this patient population should focus on preservation of the quality of life in addition to improvement is survival outcomes.

References

1. Cohen, N., S. Fedewa, and A.Y. Chen, *Epidemiology and Demographics of the Head and Neck Cancer Population.* Oral Maxillofac Surg Clin North Am, 2018. **30**(4): p. 381-395.
2. Timbang, M.R., et al., *HPV-related oropharyngeal cancer: a review on burden of the disease and opportunities for prevention and early detection.* Hum Vaccin Immunother, 2019. **15**(7-8): p. 1920-1928.
3. Marur, S. and B. Burtness, *Oropharyngeal squamous cell carcinoma treatment: current standards and future directions.* Curr Opin Oncol, 2014. **26**(3): p. 252-8.
4. Rieger, J.M., J.G. Zalmanowitz, and J.F. Wolfaardt, *Functional outcomes after organ preservation treatment in head and neck cancer: a critical review of the literature.* Int J Oral Maxillofac Surg, 2006. **35**(7): p. 581-7.
5. Fung, K., et al., *Voice and swallowing outcomes of an organ-preservation trial for advanced laryngeal cancer.* Int J Radiat Oncol Biol Phys, 2005. **63**(5): p. 1395-9.
6. Nguyen, N.P., H.J. Smith, and S. Sallah, *Evaluation and management of swallowing dysfunction following chemoradiation for head and neck cancer.* Curr Opin Otolaryngol Head Neck Surg, 2007. **15**(2): p. 130-3.
7. Jensen, K., K. Lambertsen, and C. Grau, *Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: frequency, intensity and correlation with dose and volume parameters.* Radiother Oncol, 2007. **85**(1): p. 74-82.
8. Deantonio, L., et al., *Dysphagia after definitive radiotherapy for head and neck cancer. Correlation of dose-volume parameters of the pharyngeal constrictor muscles.* Strahlenther Onkol, 2013. **189**(3): p. 230-6.
9. Dorr, W. and J.H. Hendry, *Consequential late effects in normal tissues.* Radiother Oncol, 2001. **61**(3): p. 223-31.
10. Bjordal, K. and S. Kaasa, *Psychometric validation of the EORTC Core Quality of Life Questionnaire, 30-item version and a diagnosis-specific module for head and neck cancer patients.* Acta Oncol, 1992. **31**(3): p. 311-21.
11. Niezgoda, H.E. and J.L. Pater, *A validation study of the domains of the core EORTC quality of life questionnaire.* Qual Life Res, 1993. **2**(5): p. 319-25.
12. Epstein, J.B., et al., *Quality of life and oral function following radiotherapy for head and neck cancer.* Head Neck, 1999. **21**(1): p. 1-11.
13. Bjordal, K., et al., *A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group.* Eur J Cancer, 2000. **36**(14): p. 1796-807.
14. Petruson, K., et al., *Longitudinal evaluation of patients with cancer in the oral tongue, tonsils, or base of tongue--does interstitial radiation dose affect quality of life?* Brachytherapy, 2005. **4**(4): p. 271-7.

15. Nordgren, M., et al., *Health-related quality of life in patients with pharyngeal carcinoma: a five-year follow-up.* Head Neck, 2006. **28**(4): p. 339-49.
16. Oates, J., et al., *Integration of prospective quality of life and nutritional assessment as routine components of multidisciplinary care of patients with head and neck cancer.* ANZ journal of surgery, 2008. **78**(1-2): p. 34-41.
17. Al-Mamgani, A., et al., *A prospective evaluation of patient-reported quality-of-life after (chemo)radiation for oropharyngeal cancer: which patients are at risk of significant quality-of-life deterioration?* Radiotherapy & Oncology, 2003: p. 359-63.
18. Hinz, A., S. Singer, and E. Brahler, *European reference values for the quality of life questionnaire EORTC QLQ-C30: Results of a German investigation and a summarizing analysis of six European general population normative studies.* Acta Oncol, 2014. **53**(7): p. 958-65.

3.6 Link statement

The previous manuscript showed that standard of care treatment produces chronic side effects, such as xerostomia, poor oral and dental health, dysphagia, feeding tube dependency in, and other fibrotic changes likely caused by radiotherapy or combination of surgery and radiotherapy. The following manuscript is a study that assessed the 1-year evolution of quality of life in HPV+ positive OPSCC in stage III and IV, according to AJCC 7th edition, who were treated with NeC+TORS. Data were collected at diagnosis, 1-, 3-,6-, and 12-month post-treatment.

CHAPTER 4: Manuscript 2: Quality of life in locally advanced HPV positive oropharyngeal cancer treated with neoadjuvant chemotherapy followed by transoral robotic surgery and neck dissection

Alina Diaconescu[1], Maida J Sewitch[1,3,5] Marco Mascarella[1], Jose Garcia Luna[2], Nahid Golabi[1], Keith Richardson[1], Nathaniel Bouganim[3], Reza Forghani[4], Alex Mlynarek[1], Michael Hier[1,3], Nader Sadeghi[1,3, 5]

1-Department of Otolaryngology – Head and Neck Surgery, McGill University.

2-Division of Experimental Surgery, McGill University.

3-Department of Oncology, McGill University.

4-Department of Diagnostic Radiology, McGill University.

5- Research Institute of McGill University Health Centre

Research article to be submitted to JAMA Otolaryngology-Head and Neck Surgery

Part of the Master of Science Thesis in Department of Otolaryngology, Head and Neck Surgery

McGill University, Montreal

4.0 Abstract

Background: Chronic treatment-related toxicity and functional loss following standard of care chemoradiation (CRT) has a significant impact on the quality of life (QoL) of survivors of oropharyngeal squamous cell carcinoma (OPSCC). Neoadjuvant chemotherapy followed by transoral robotic surgery and selective neck dissection has been shown to be effective definitive treatment for HPV-related OPSCC with competitive survival compared to CRT.

Objective: This study aimed to assess the quality of life in human papillomavirus positive (HPV+) OPSCC patients with locoregionally advanced disease treated under a new paradigm of neoadjuvant chemotherapy (NeC) followed by transoral robotic surgery (TORS) as definitive treatment.

Design, Setting, and Participants: An ambidirectional cohort study took place at McGill University Health Centre in Montreal, Canada. Patients were diagnosed with stage III and IV (AAJC 7th edition) HPV+ OPSCC and treated with NeC (docetaxel and cisplatin) followed by TORS and selective neck dissection, between January 2017 and July 2018.

Main Outcomes and Measures: Patient-reported quality of life was assessed using the EORTC QLQ-30 and H&N35 at pre-treatment, 1-, 3-, 6, and 12-month following completion of the treatment. The functional outcome was assessed by the presence of a percutaneous endoscopic gastrostomy (PEG) feeding tube at each follow-up. Repeated-measures mixed-effects models were used to assess the impact of baseline measurements on the scores over time, and the score change over time.

Results: Of 23 patients recruited, 19 met eligibility criteria. Of these, (90.5%) were male, the median age was 58 years Seven patients had cancer localised in the base of tongue and 12 in the palatine tonsils. EORTC- H&N35 scores showed that values at 12-month post-treatment do not significantly differ from pre-treatment values for any of the scales including the scales known as most affected by the standard of care's toxicity, swallowing ($p = 0.38$), social eating problems ($p = 0.70$), dry mouth ($p = 0.98$), and sticky saliva ($p = 0.87$). No patient required a gastrostomy tube (PEG) at any time point assessed.

Conclusions

In patients treated NeC and TORS, quality of life at 12 months post-treatment returned to baseline on the symptom scales that are most negatively affected by the current standard of care CRT treatment. QoL also returned to baseline on all other scales. Patients had a rapid return to an oral diet not requiring PEG for feeding. Findings suggest that NeC followed by TORS provides maintenance of QoL and improvement in some of the functional scales of EORTC-H&N35 compared to pre-treatment levels.

4.1 Introduction

In Canada, head and neck cancers are diagnosed in 4,300 individuals each year.(1) The most prevalent subtype of head and neck cancer in western world is oropharyngeal squamous cell carcinoma (OPSCC), and approximately 90% of OPSCC are related to human papillomavirus (HPV).(2) HPV infection is of particular interest in the management of OPSCC since the risk factors, pathogenesis, tumour prognosis, and survival are different in HPV positive versus HPV negative OPSCC.(3) The epidemiology of HPV positive OPSCC patients describes them as predominantly men , in their 50s, with more than 5 female oral sex partners, and often without other risk factors such as tobacco or alcohol.(4, 5) While two-thirds of patients present with minimal symptoms like neck mass , and sore throat, they are usually diagnosed with a later stage of the disease when regional spread has occurred (stage III or IV in accordance with AJCC 7th edition).(6) Indeed, before treatment, most HPV positive patients are almost asymptomatic. The majority are otherwise healthy at presentation, hence with expected long-life expectancy if they survive the cancer.

The worldwide standard of care treatment for locally advanced OPSCC regardless of etiology has been radiotherapy alone or in combination with surgery or chemotherapy. Concomitant CRT has been the dominant standard of care treatment over 2 decades since the intergroup study showing improved survival over radiotherapy alone for advanced head and neck cancer.(7, 8) However, the standard of care treatment often results in significant life-long side effects, including loss of salivary function, dental loss, poor oral health, dysphagia, feeding tube dependency, potential loss of lower cranial nerve function, as well as pharyngeal and laryngeal stenosis.(9) These side effects are a result of hypoxic fibrosis of the upper aerodigestive tract

from radiation-related treatment exacerbated by concomitant chemotherapy or surgery. The standard CRT has evolved for advanced head and neck cancer irrespective of etiology and prior to understanding the role of HPV in OPSCC and its effect on prognosis.

Given the well-established improved survival in HPV+ OPSCC, the standard CRT has come under question for this cancer as too intense. Currently, intense efforts are undertaken across the world through different trials to reduce the intensity and toxicity of treatment of HPV+ OPSCC while maintaining effectiveness. The aim of current trials is to improve and/or maintain the quality of life without compromising cancer cure by a de-escalation of the treatment.

Currently, three de-escalation strategies are in trial: reducing radiotherapy dose-volume in patients that responded to induction chemotherapy (OPTIMA trial), modifying the chemotherapy regimen (TROG 12.01), and surgery with de-escalation of adjuvant treatment (ADEPT, ECOG 3311, PATHOS, ORATOR2). Some of the radiation- based trial have completed include the following: RTOG 1016 was a randomised, multicentre, non-inferiority trial that assessed whether radiotherapy plus cetuximab has better overall survival and progression-free survival than radiotherapy plus cisplatin. The results suggested that patients with HPV+ treated with radiotherapy plus cetuximab had lower overall survival and progression-free survival compared with radiotherapy plus cisplatin.(10) The E1308 trial was a phase II trial of induction chemotherapy (Paclitaxel and Cisplatin) followed by cetuximab (Erbitux) with low dose versus standard-dose intensity modulated radiotherapy (IMRT). The results suggested that reducing radiation dose significantly improved swallowing and permitted an oral diet. (11, 12)

Since 2009, when TORS was approved as a treatment for OPSCC, the efficacy has been assessed and reported as being feasible with good oncologic outcome (10). TORS and neck dissection with or without adjuvant RT/CRT have become a dominant treatment modality in the united states. TORS has been used as initial treatment followed by risk- based adjuvant RT/CRT based on pathology. The functional swallowing outcome of TORS versus RT was evaluated in a randomized clinical trial showing improved swallowing in the radiotherapy group. (13) However, in this trial 70% of the patients in TORS arm received adjuvant RT/CRT. Hence, this strategy is indeed an escalation and not a de-escalation, and the worse swallowing outcome in the TORS group is not surprising. Induction chemotherapy using docetaxel and cisplatin combination followed by transoral surgery and neck dissection as definitive treatment was shown to be feasible and effective as a new strategy of management of HPV positive OPSCC by our group.(14) Subsequent larger series by our group has confirmed the effectiveness of this strategy and competitive survival outcome to chemoradiation.(15, 16)

Our approach is based on paradigm of systemic escalation (neo-adjuvant chemotherapy) and local regional surgical de-escalation (TORS and selective neck dissection) without adjuvant radiotherapy.

In the present study, we report on longitudinal quality of life (QoL) outcomes of a sample of patients with locally advanced HPV+ OPSCC (stage III and IV, AJCC 7th edition) treated with neoadjuvant chemotherapy followed by transoral robotic surgery (NeC+TORS) for definitive management reserving radiotherapy for salvage. Patients were treated at the McGill University Health Centre (MUHC) in Montreal, Canada.

We report the demographic details and quality of life assessed with EORTC QLQ30 and H&N35. Clinical practice suggests that patients that were given this treatment experience a level of quality of life at 12-months that is like their pre-treatment level. The present study aims to examine this notion by describing QoL in the 12 months following treatment with NeC+ TORS alone. Our objective was to compare pre-treatment and 12-month post-treatment QoL scores, as well as to describe the one-year evolution of QoL in patients with Stage III and IV (AJCC 7th Edition) treated with NeC+TORS in an intention to treat analysis.

To our knowledge, this is the first study to look at the quality of life of patients treated with NeC+TORS. It is hypothesised that pre-treatment and 12-month post-treatment quality of life does not differ in patients treated with this strategy.

4.3 Methods

Ethical considerations

Approval for the study was obtained from the MUHC research ethics board REB (MP-37- 2018-3568).

Data source

This study used data from a subset of patients that were previously reported, and on whom quality of life data was collected. (15)

Study design

An ambidirectional cohort study that used both retrospectively and prospectively collected data was conducted. Investigators used the prospectively collected research database and medical records to identify patients and complete the study. At the time of study inception, the QoL data had already been prospectively collected at pre-treatment, and at 1, 3, and 6-month post-treatment. The 12-month post-treatment QoL data were also collected prospectively through surveys for this study.

Setting and Participants

The study took place at the McGill University Health Centre, Department of Otolaryngology-Head and Neck Surgery, in Montreal (Canada). Eligibility criteria were the following: diagnosed with stage III, and IV (AAJC 7th edition) HPV+ OPSCC and treated with NeC+TORS between January 2017 and July 2018, aged at least 18 years, have biopsy-proven HPV+ OPSCC, no distant metastasis, ≤ 5 grossly positive lymph nodes by imaging with CT and/or MRI at presentation, Eastern Cooperative Oncology Group (ECOG) Performance Status <2, fit to undergo TORS surgery or standard of care treatment, and no prior head and neck cancer or any other malignancy in the past five years. After patients were discussed during weekly tumour board meetings, the recommended treatment was proposed to the patient. All study participants gave written informed consent. An additional eligibility criterion specific to the present study objectives was that patients must have completed at least 2 out of 5 quality of life questionnaires, one of which was the baseline QoL before treatment. Not completing the pre-treatment questionnaire was an exclusion criterion.

Methodology

For the baseline, 1-, 3- 6- and 12-month assessments, QoL questionnaires had been given by the investigators to the patient to self-complete during a clinic visit. One patient who did not complete the 12-month questionnaire at the clinic visit was contacted by the research assistant who also administered the questionnaire by phone. After completion of the QoL questionnaires, the values were entered into a template previously configured to perform the calculations of the scales from the raw data according to the EORTC Scoring Manual (17). At a later time-point, two research assistants re-verified the accuracy of the data in the database.

Variables

Variables obtained from the MUHC database included: age, sex, smoking and alcohol use, anatomic location and microscopic description of the tumour, the pathologic tumour margins, P16 status (a surrogate for HPV)), lymph nodes, TNM stage (clinical and image-based), the type of neoadjuvant chemotherapy given, and the surgical treatment. Data from medical charts included duration of usage a feeding tube, presence or absence of use of percutaneous endoscopic gastrostomy (PEG) feeding tube.

Instruments

Quality of life was assessed using the EORTC QLQ-30 core and Head and Neck extension, the EORTC H&N35 questionnaires. EORTC OLQ-30 is available in over 100 languages, including French and English. The EORTC core has 30 questions, and EORTC-H&N35 extension has 35 questions. It takes approximately 20 minutes to complete the entire questionnaire. The EORTC

core questionnaire was also validated with patients treated at the Kingston Regional Cancer Centre in Ontario, Canada.

The QLQ-C30 includes nine different scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (pain, fatigue, and nausea/vomiting); and global health and quality-of-life scale. The QLQ-H&N35 questionnaire consists of seven symptom scales (pain, swallowing, senses, speech, social eating, social contact, and sexuality), eleven single items (problems with teeth, problems with opening mouth, dry mouth, sticky saliva, coughing, felt ill, taking pain killers, taking nutritional supplements, having a feeding tube, weight loss, weight gain). Quality of life questionnaires was collected, starting with January 2017 up to the last time point for collecting 1-year post-treatment questionnaires, July 2019.

Sample size and power

The study size was dictated by the number of patients treated with NeC+TORS for HPV+ OPSCC MUHC between January 2017 and July 2018 who also completed a pre-treatment quality of life and one other during the 12-month post-treatment follow up.

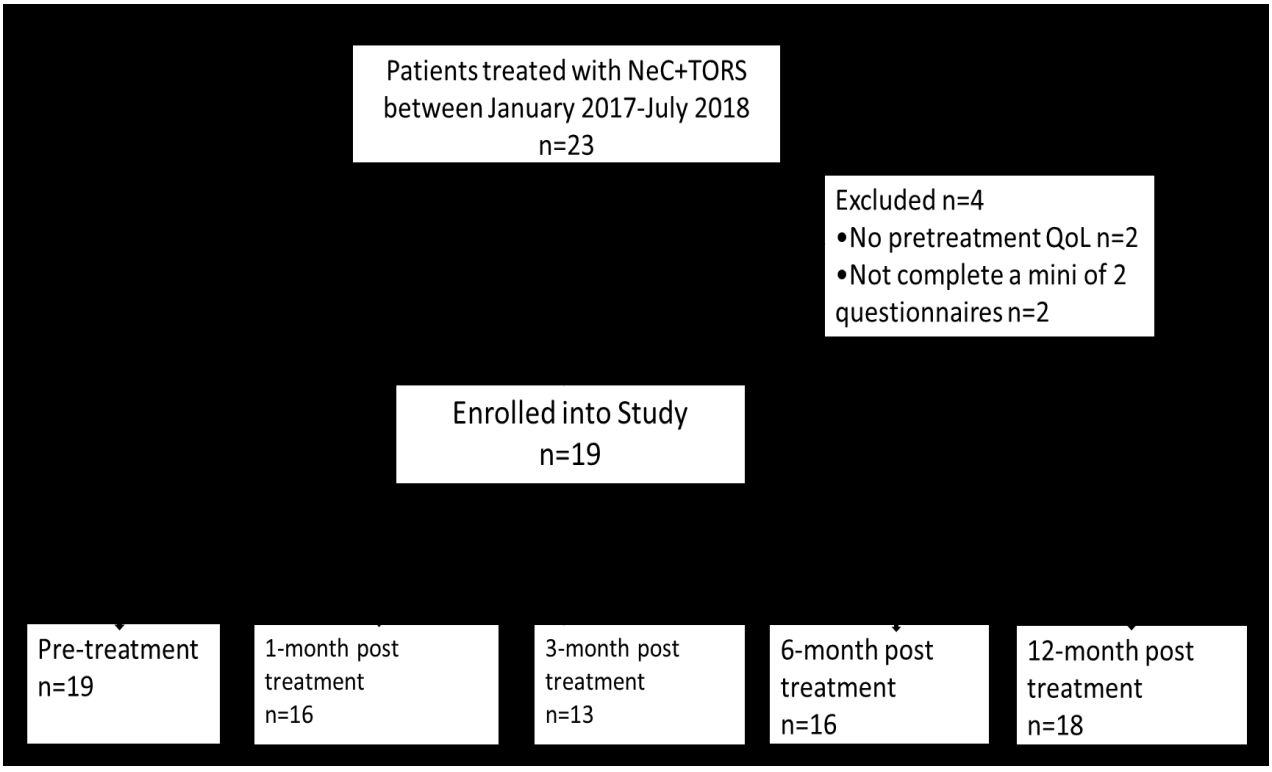
Statistical analysis

Statistical analysis was performed using the R v.3.4.1 software. Descriptive statistics were used to describe the study population. Means and standard deviations, as well as medians and interquartile ranges, were computed for continuous variables. Proportions were calculated for categorical variables. Data are presented as mean and standard deviations or 95% confidence interval (CI). Repeated-measures mixed-effects models were used to assess a) the impact of baseline measurements on the scores over time and b) the score change over time. The analysis

makes use of the individual patients as clusters with a random intercept. Multiple comparisons were adjusted using Tukey posthoc tests. Statistical significance was set at a p-value <0.05.

4.4 Results

Figure 1. Flow diagram of study participants shows patients enrolled in the study and the number of participants who have completed the EORT surveys at each time interval from end of treatment.



Between January 2017 and July 2018, there were 23 patients treated with NeC+TORS at MUHC. Of these, four patients were excluded; two did not complete the pre-treatment questionnaire, and two did not complete a minimum of two questionnaires (*Figure 1*). A total of 87 questionnaires were completed, with an average of 4.1 questionnaires completed per participant. An average of 17.4 questionnaires was filled out at each of the study time points. The missing questionnaires were not completed due to the non-compliance of patients with some follow-ups, excluding 4 patients from the study.

4.4.1 Descriptive data

Table 1 shows that of the 19 patients in this study, 17 (91%) were male, and the median age was 58 years (interquartile range, 48-78 years). Nine (47%) patients were ever-smokers. Seven patients had cancer localised in the base of tongue and 12 in the palatine tonsils. The clinical staging of the patients' tumours was dominated by T2 (68.42%) N2b (57.8%). All patients received neoadjuvant chemotherapy, followed by TORS with unilateral (52.7%) or bilateral (47.3%) neck dissection. Resection margins for the primary tumour were positive in only one case. The margins for this case were revised to negative margins in a second TORS intervention. The mean number of days that patients required a nasogastric feeding tube following surgery was 8.9 days, with a standard deviation of 5.6. No patient required a PEG feeding tube in any of the time-points assessed.

Table 1 Baseline and treatment characteristics of OPSCC HPV+ patients treated with NeC+TORS

Number of patients included in the study n=19	**n**	**%**
Age, median (IQR)		58 (48-78)
Sex		
male	17	91
female	2	10
Smoking history	9	47
Primary site		
Tonsil	12	63.1
Base of tongue	7	36.8
Clinical T stage		
T1	5	26.3
T2	13	68.4
T3	0	0
T4	1	5.2
Clinical N stage		0
N0	2	10.5
N1	4	21
N2a	2	10.5
N2b	11	57.8
Stage (AJCC 7th Edition)		
III	6	31.5
IV	13	68.5
Surgery		0
TORS+ND Unilateral	10	52.7
Tors ND Bilateral	9	47.3
Induction Chemotherapy	19	100
PEG	0	0
NG tube feeding median no of days (SD)		*8.9(5.6)*

Table 2 EORTC QLQ-30 scores of HPV+ OPSCC patients treated with NeC+TORS across the 5-time assessment points

	QLQ-C30				
	Mean (SD)				
	Functional Scale (100=favorable)				
No of respondents	19	16	13	16	18
	Pre-treatment	1-month post-treatment	3-month post-treatment	6-months post-treatment	12-month post-treatment
physical functioning)	95.4(9.6)	85.9(10.4)	90.6(10.6)	95(6.2)	94.7(8.7)
role functioning	88.5(23.6)	74.6(26)	81.1(21.7)	88.5(20.8)	82.4(33)
cognitive functioning	92.9(11.5)	85.1(24.1)	84.4(19.3)	88.5(13.2)	92.1(11.6)
emotional functioning	75(26)	79.1(21.6)	85.5(15.8)	88(20.6)	87.2(12.5)
social functioning	91.2(17.8)	78.7(21.2)	92.2(12.3)	92.7(14.8)	94.7(9.7)
	Symptom Scale(100=unfavorable)				
fatigue	19.1(20.4)	36.4(27.6)	21.4(19.9)	15.9(17.1)	16.3(16.7)
dyspnea	7(17.8)	11.1(25.5)	11.1(20.5)	2(8.3)	5.2(12.4)
pain	14(20.9)	25(20.8)	22.2(22.4)	10.4(17)	14.9(21.4)
sleep	33.3(24.8)	24(29.8)	24.4(29.4)	12.5(16.6)	22.8(22.3)
appetite	10.5(15.9)	18.5(20.5)	11.1(20.5)	10.4(20)	17.5(20.3)
nausea vomiting	6.1(13.8)	4.6(7.6)	1.1(4.3)	0(0)	3.5(8.9)
constipation	8.7(24.4)	12.9(28.3)	8.8(19.7)	6.2(18.1)	7(17.8)
diarrhea	7(17.8)	11.1(25.5)	11.1(20.5)	2(8.3)	5.2(12.4)
financial impact	14(27.9)	18.5(30.7)	11.1(20.5)	14.5(20.9)	8.7(18.7)
global quality of life	80.2(18)	67.1(19)	77.7(15.9)	79.6(17.9)	83.7(13.1)
	QLQ-H&N35				

	Symptom items(100=unfavorable)				
pain	**17.5(19.7)**	**26.3(18.7)**	**12.7(12.1)**	**17.7(18.4)**	11.8(12.8)
swallowing	9.7(14.9)	11.1(10.6)	5(6.9)	10.9(15.1)	11.4(13.3)
senses problems	15.7(23.8)	14.7(19.4)	15.5(23.1)	22.9(28.4)	10.5(17.7)
speech problems	8.6(12.3)	14.1(14.6)	8.1(14.8)	9.7(11.3)	9.3(13.9)
trouble with social eating	**6.5(10.9)**	**12.9(12.8)**	**1.6(4.6)**	**8.3(12.1)**	7.4(13.5)
trouble with social contact	5.1(11.7)	6.6(10.2)	8(15.5)	4.5(7.9)	1.7(4.8)
less sexuality	14.9(25.3)	27.7(30.7)	10.7(19.1)	10.4(25.7)	9.6(18.6)
problem with teeth	3.7(10.7)	5.5(12.7)	4.4(11.7)	6.2(13.4)	3.5(10.5)
problem opening mouth	**16.6(20.6)**	**11.1(19.8)**	**8.8(15.2)**	**4.1(11.3)**	1.7(7.6)
dry mouth	**11.1(16.1)**	**33.3(30.2)**	**13.3(16.9)**	**16.6(27.2)**	10.5(15.9)
sticky saliva	**14.8(20.5)**	**25.9(29.2)**	**11.1(20.5)**	**14.5(29.7)**	12.2(27.6)
coughing	20.3(20.2)	35.1(31.2)	20(21)	25(19.2)	17.5(25.7)
felt ill	**9.2(22.3)**	**12.9(16.7)**	**8.8(19.7)**	**10.4(15.9)**	8.7(15)
using pain killers	31.5(47.7)	50(51.4)	26.6(45.7)	6.2(25)	26.3(45.2)
taking nutritional supplement	42.1(50.7)	27.7(46)	26.6(45.7)	18.7(40.3)	5.2(22.9)
using feeding tube	0(0)	0(0)	0(0)	0(0)	0(0)
weight loss	21(41.8)	27.7(46)	13.3(35.1)	6.2(25)	10.5(31.5)
weight gain	10.5(31.5)	22.2(42.7)	33.3(48.7)	18.7(40.3)	15.7(37.4)

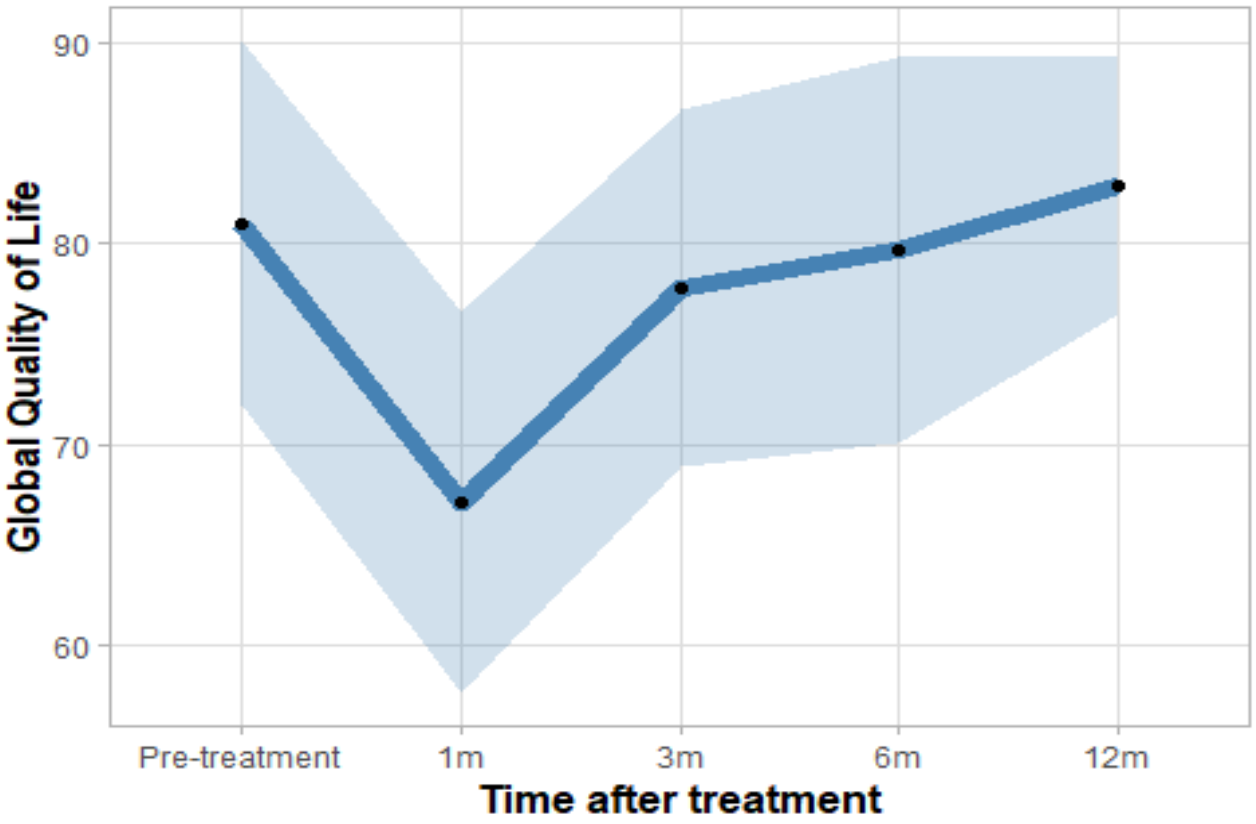
The EORTC- H&N35 results in symptom scales known as most negatively affected by the standard of care concomitant CRT, from pre-treatment to 12 months post-treatment scores were as follows: pain from a mean (SD) of 17.5(19.7) to 11.8(12.8, problem opening the month from a mean(SD) of 16.6(20.6) to 1.7(7.6, dry mouth from a mean(SD) of 11.1(16.1) to 10.5(15.9, sticky saliva from a mean(SD) of 14.8(20.5) to 12.2(27.6)).

4.4.2 Longitudinal results in main scales: comparison of values at diagnosis & 12-month post-treatment

Global quality of life (GQL)

Figure 2. EORTC QLQ-30 Global quality of life (GQL) change over time of OPSS HPV + treated with NeC+TORS

Note: shaded area in graphs represents 95%CI



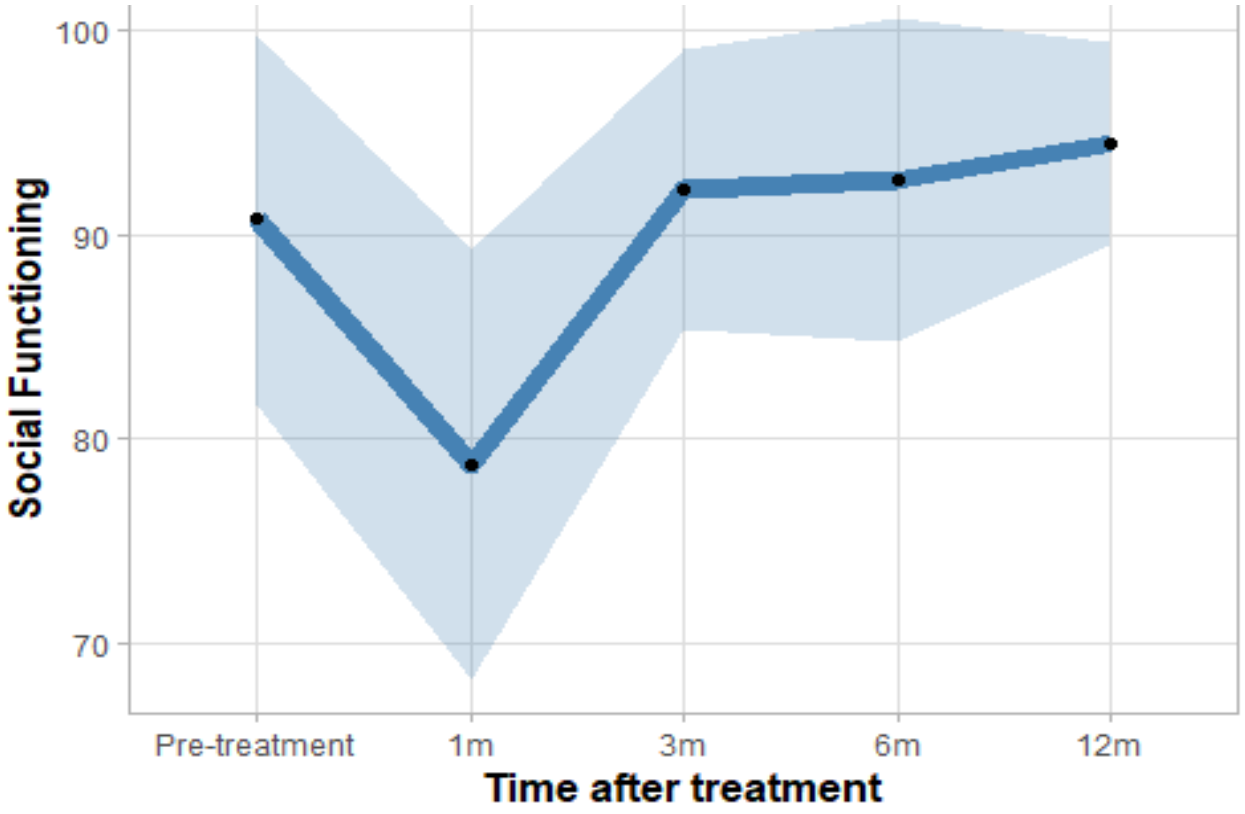
There were significant differences between global quality of life (GQL) values over time ($p < 0.001$). GQL values at 1-month post-treatment are significantly lower than pre-treatment values (-15.3, 95%CI -27.4 to -3.2, $p = 0.004$), as expected given the acute side effects of the

treatments. However, 12-month post-treatment values did not differ from pre-treatment values (p =0.9931). (Figure 2)

***Soci*al Functioning (SF)**

Figure 3. Social Functioning (SF) of HPV+ OPSS treated with NeC+TORS over time

Note: shaded area in graphs represents 95%CI



Significant differences were found in social functioning (SF) over time (p = 0.008). SF at 1-month post-treatment is significantly lower than values at 12 months post-treatment (-16.1,

95%CI -29.4 to -2.95, p = 0.007) as expected given the acute side effects of the treatments.

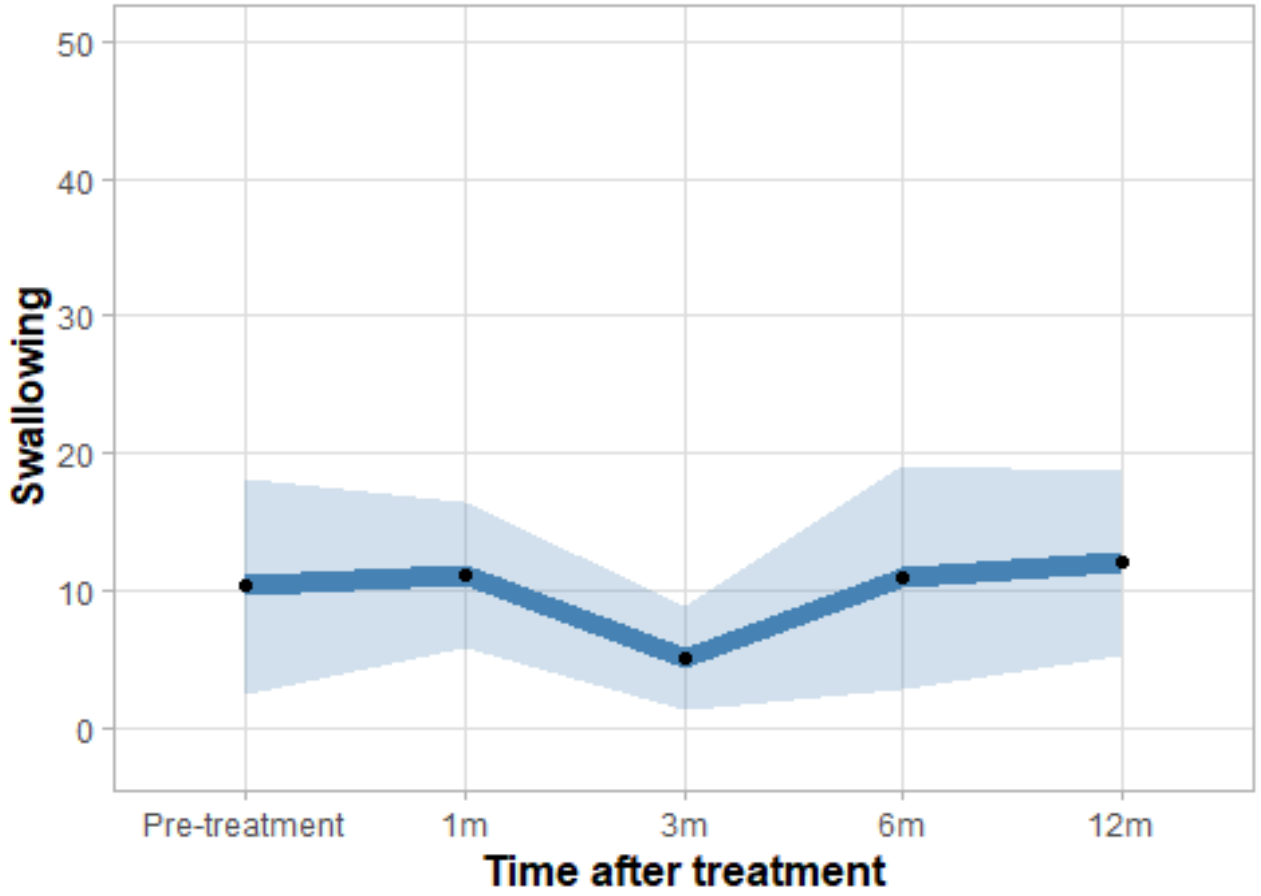
However, 12-month post-treatment values did not differ from pre-treatment values (p=0.9380).

(Figure 3

Swallowing difficulties (SW)

Figure 4. EORTC H&N-35 Swallowing (SW) of OPSCC HPV+ patients treated with NeC+TORS over time

Note: shaded area in graphs represents 95%CI

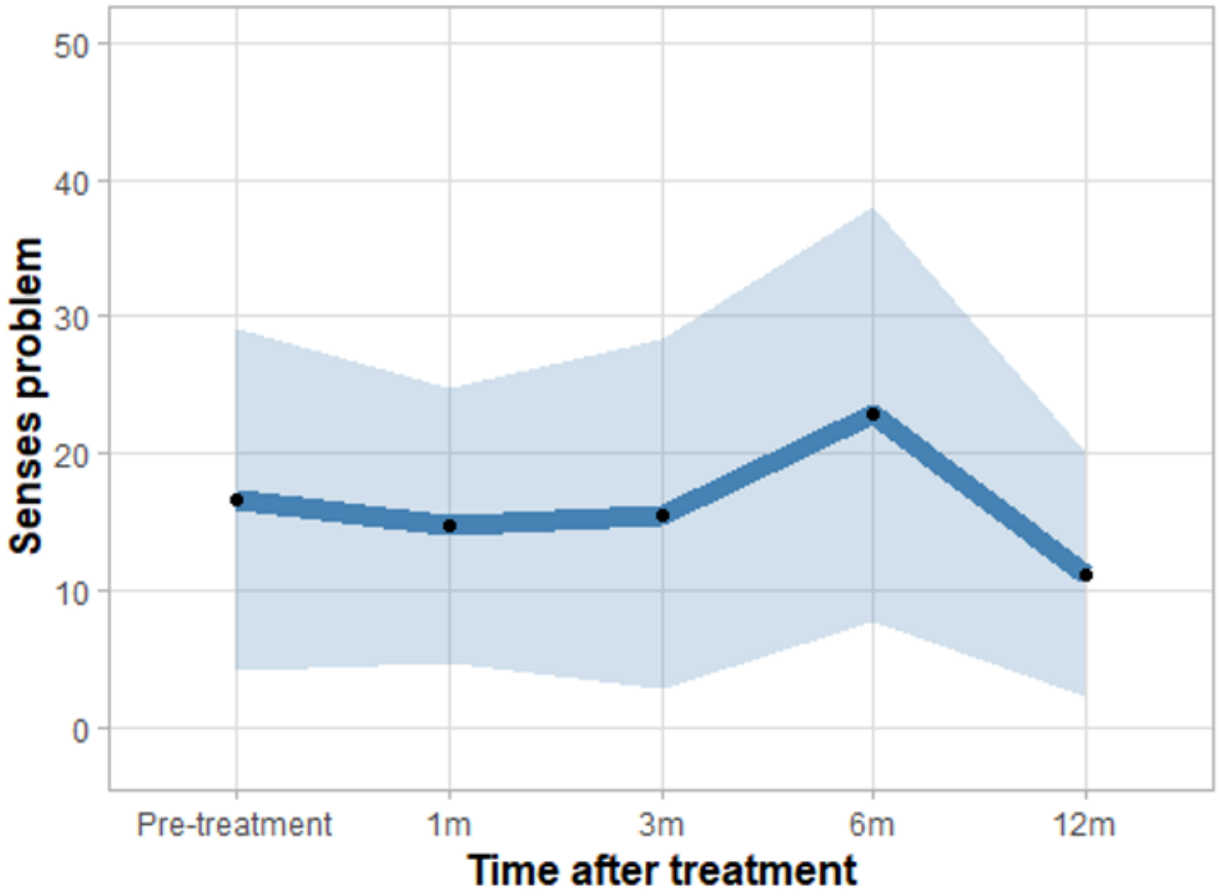


No significant differences were found on swallowing difficulties (SW) over time values (p = 0.38); 12-month post-treatment values did not differ from pre-treatment values (p=0.99). (Fig. 4)

Senses problem (SE)

Figure 5. EORTC H&N-35 Senses problems (SE) of OPSCC HPV+ treated with NeC+TORS over time

Note: shaded area in graphs represents 95%CI

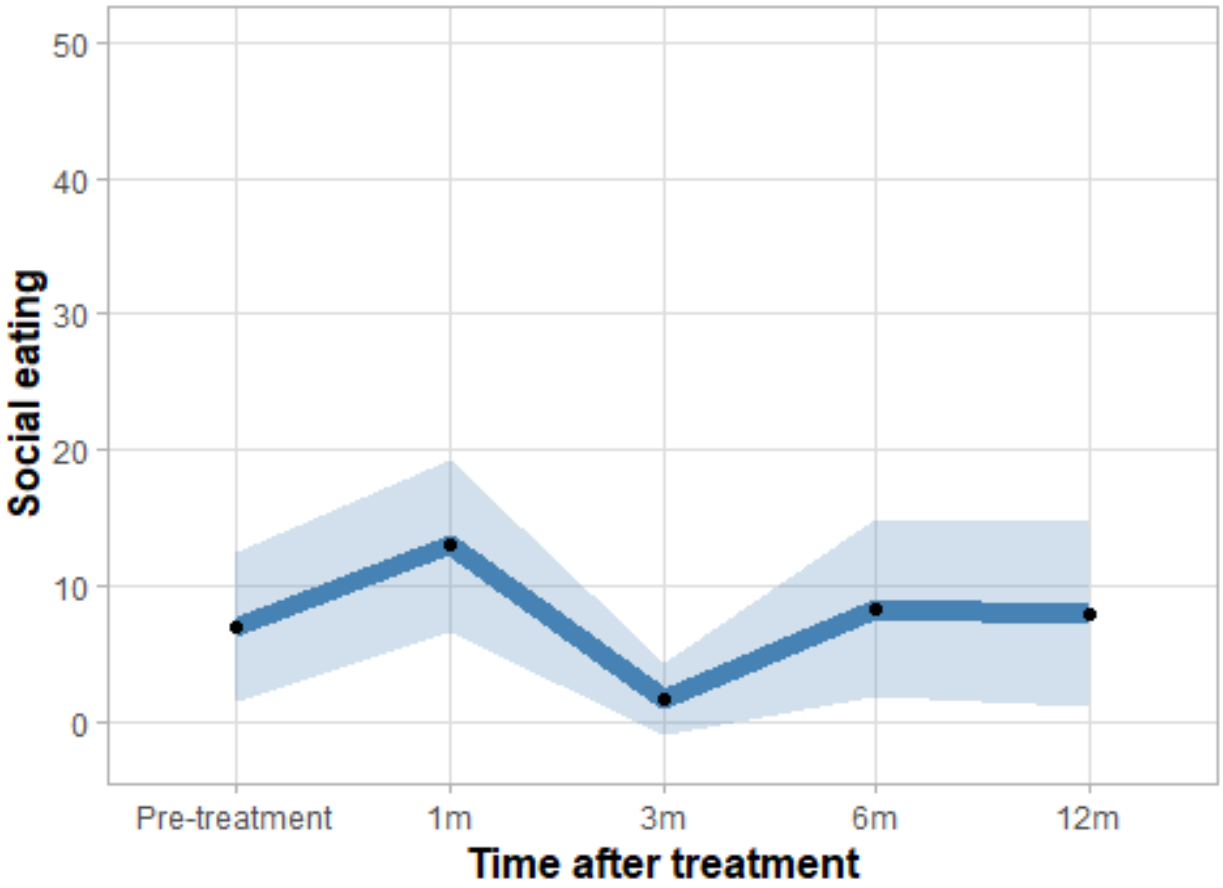


There were no significant differences between sense problem (SE) values over time (p = 0.64), and no significant differences between the SE pre-treatment & post-treatment. (p=0.94). (Fig. 5)

Social eating (SO)

Figure 6. EORTC H&N-35 Social eating (SO)of OPSCC HPV+ treated with NeC+TORS over time

Note: shaded area in graphs represents 95%CI

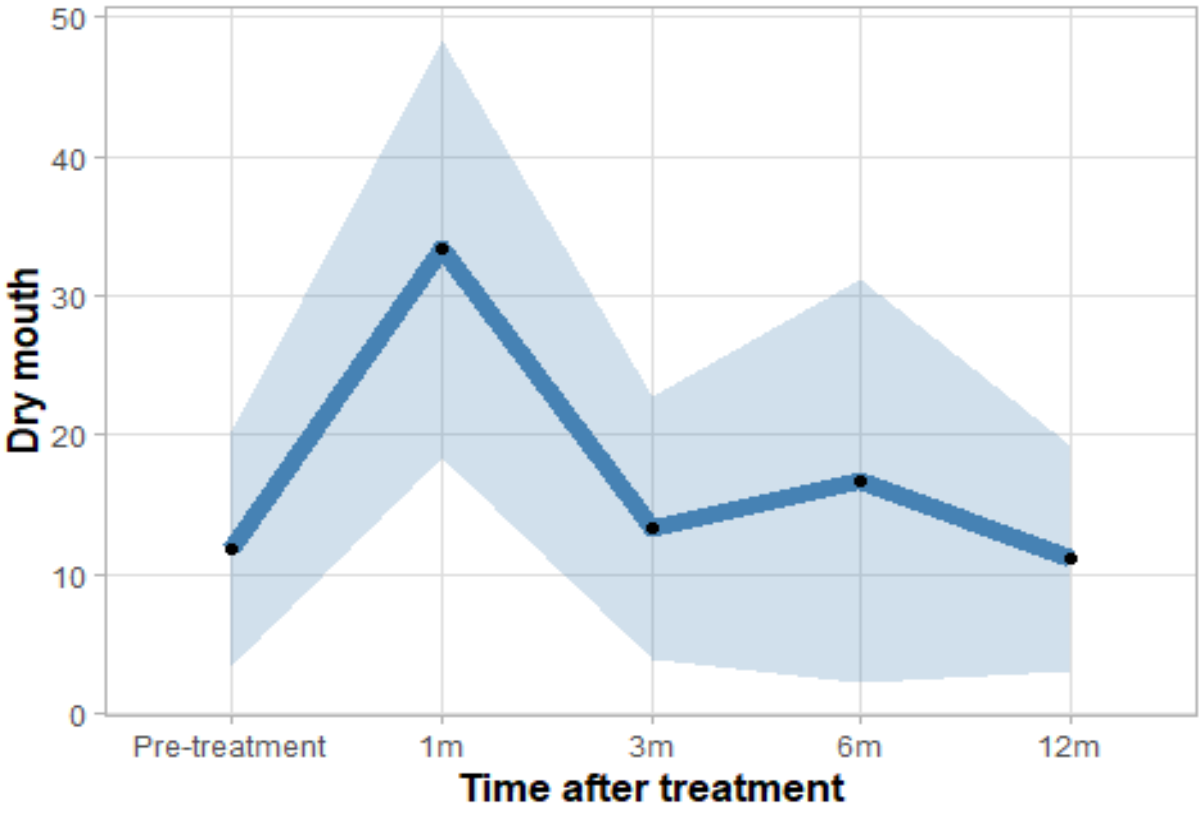


There was no significant statistical association (p = 0.70) between pre-treatment social functioning (SO) values and SO values over time. Values from pre-treatment did not significantly differ from values at 12 months post-treatment (p=0.999). (Figure 6)

Dry mouth (DM)

Figure 7. EORTC H&N-35 Dry mouth (DM)of OPSCC HPV+ treated with NeC+TORS over time

Note: shaded area in graphs represents 95%CI



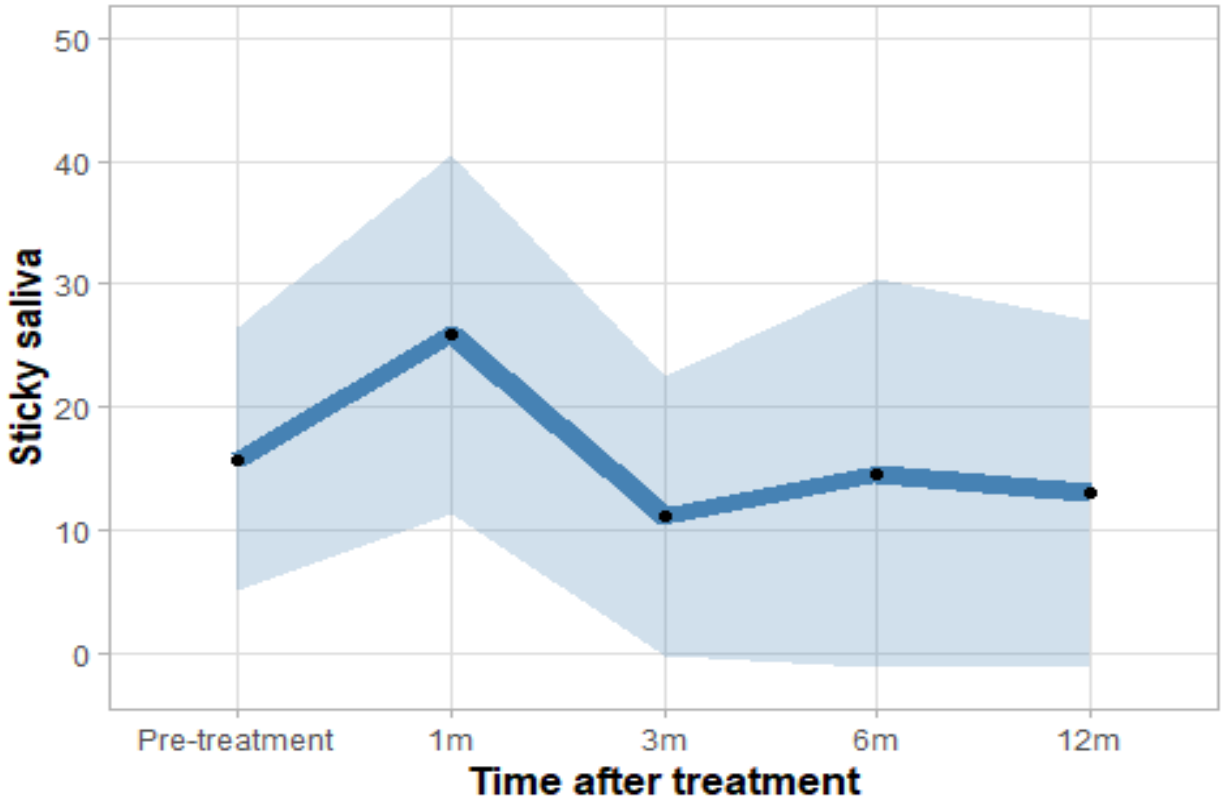
There were significant differences between DM values over time (p = 0.013). DM values at 1-month post-treatment were significantly higher than pre-treatment values (21.3, 95%CI 1.47 to 41.1, p = 0.028). Initial dry mouth from acute treatment effects resolved by three months post-

treatment. Value from pre-treatment did not significantly differ from values at 12 months post-treatment (p=0.98). (Figure 7)

Sticky Saliva (SS)

Figure 8. EORTC H&N-35 Sticky saliva (SS) of OPSCC HPV+ treated with NeC+TORS over time

Note: shaded area in graphs represents 95%CI



There was no significant association (p = 0.87) between pre-treatment SS values and SS values over time. There were no significant differences between SS values over time (p = 0.50). (Fig. 8)

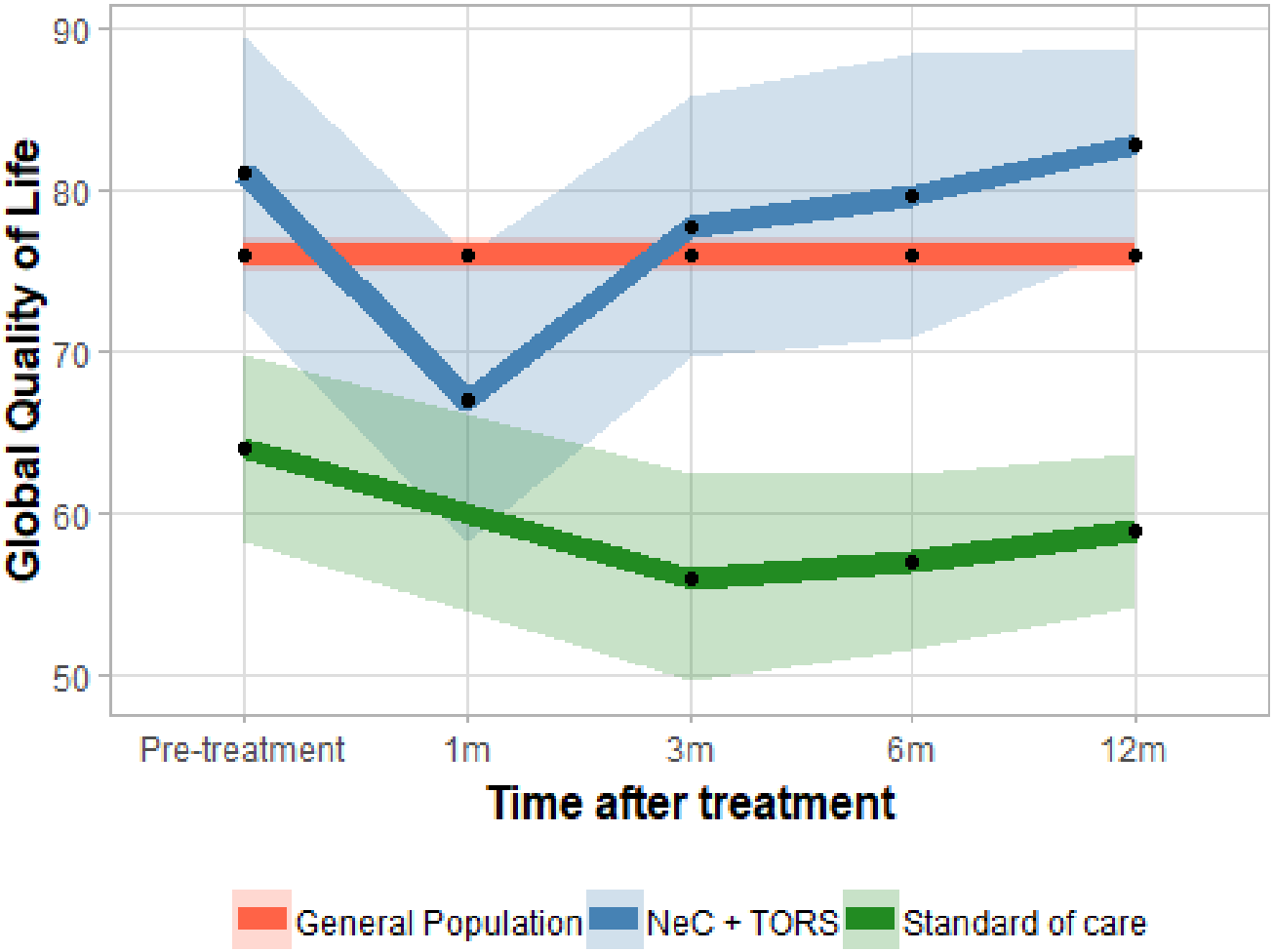
4.4.3 Comparison against historical controls

Global quality of life data from NeC+TORS was compared against general population reference values and against the standard of care reference values obtained from Michaelsen et al. 2017 (18), and from Oates et al. 2008 respectively (19). Data were compared for the values in the present study by estimating their 95% confidence interval and t-distribution of the data. Reference values of the general population were assumed constant over time. Where appropriate, multiple comparisons were adjusted using Bonferroni correction. (Figure 9)

Global quality of life (GQL)

Figure 9. EORTC QLQ-30 Global quality of life outcomes for OPSCC in NeC+TORS, Standard of care and patients and general population

Note: shaded area in graphs represents 95%CI



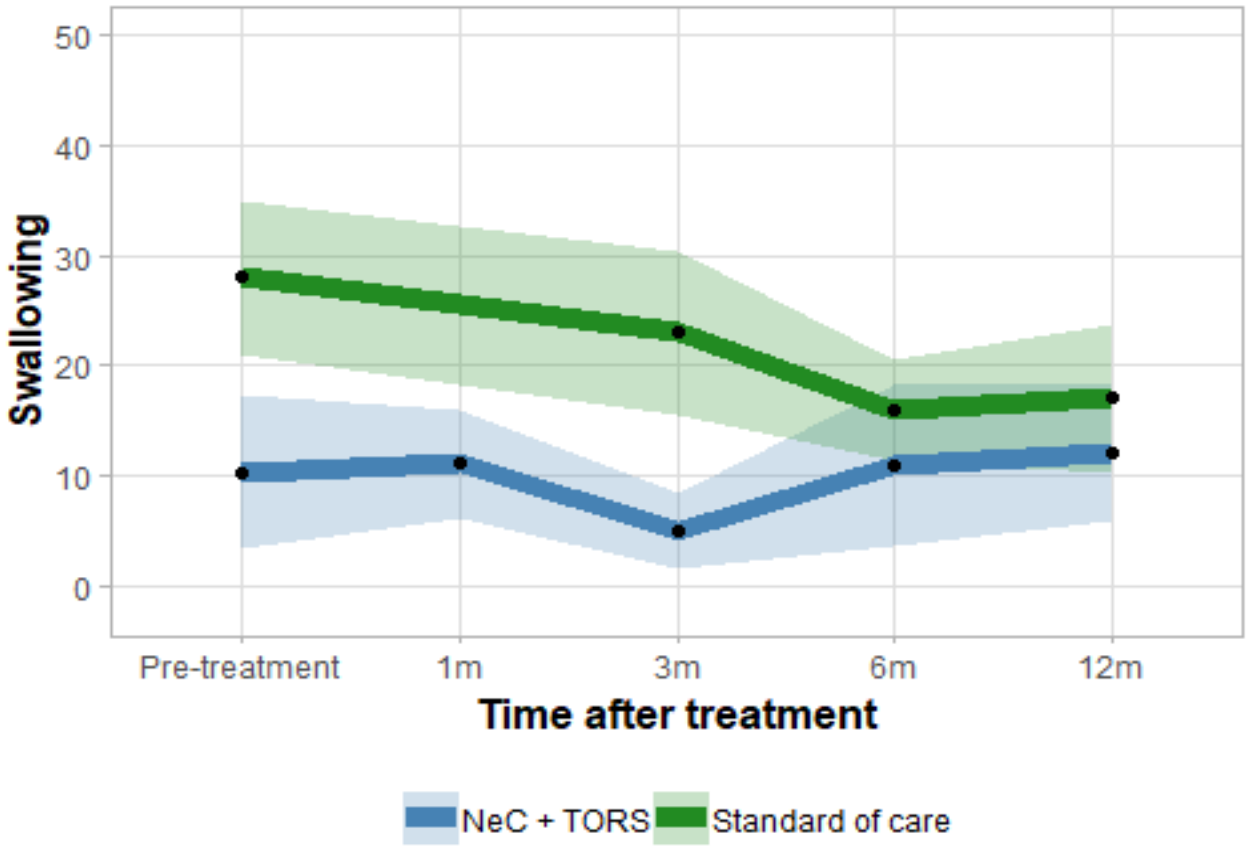
There was a significant difference between GQL scores of NeC+TORS patients and GQL scores of the general population at 12-month post-treatment. (p=0.02), with the NeC+TORS group having higher scores. There was a highly significant statistical difference between GQL scores in the standard of care patients and GQL scores of the general population at 12-month post-

treatment (p= 9.961*10^-9), with the standard of care patients having worse scores. There was a highly significant difference between GQL scores of NeC+TORS patients and GQL scores of standards of care patients at 12-month post-treatment (p=5.53*10^-6) with better scores in NeC+TORS group. (Figure 9)

Swallowing difficulties (SW)

Figure 10. EORTC-H&N-352 Swallowing (SW) over time, comparison between NeC+TORS and standard of care OPSCC patients

Note: shaded area in graphs represents 95%CI

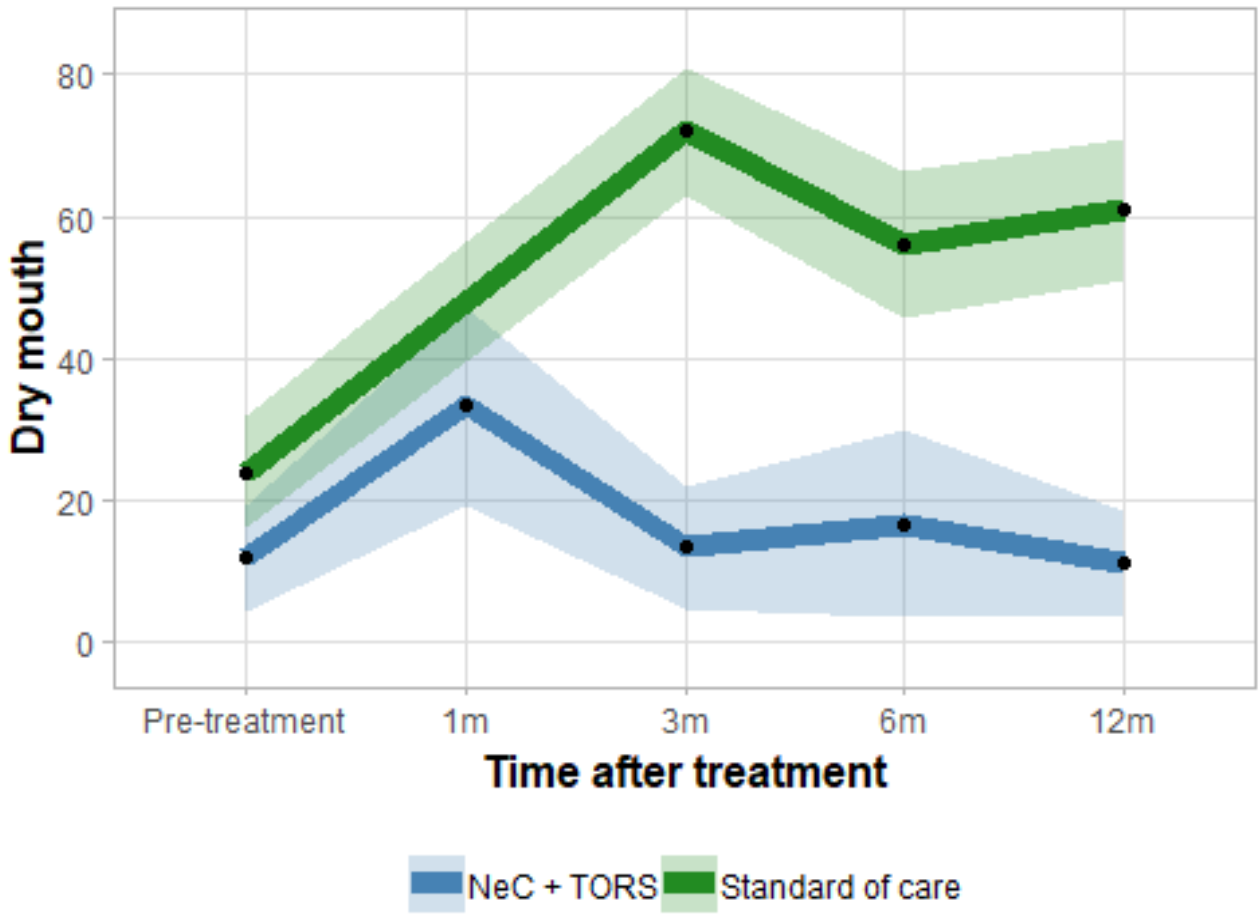


There was no statistical difference between the standard of care scores for swallowing difficulties and that of NeC+TORS patients' scores at 12 months after treatment (p=0.15). (Figure 10)

Dry Mouth (DM)

Figure 11. EORTC-H&N-35 Dry mouth (DM) over time, comparison between OPSCC patients treated with NeC+TORS and Standard of care

Note: shaded area in graphs represents 95%CI



There was a highly significant statistical difference between DM scores of NeC+ TORS patients and standard of care patients at 12 months after treatment with better results in NeC+TORS group (p= =2.37*10-7). (Figure 11)

4.5 Discussion

This study sought to investigate the evolution of the quality of life of locally and regionally advanced HPV positive OPSCC patients treated with NeC+TORS from diagnosis to 12-month post-treatment. To our knowledge, this is the first report of quality of life of HPV+ OPSCC patients treated with NeC+TORS with patient-reported data collected at baseline, 1-,3-,6-, and 12-month post-treatment.

In patients with locoregionally advanced stage III and IV HPV+ OPSCC, treated with NeC+TORS as definitive treatment, there was no statistically significant difference between pre-treatment and 12 months post-treatment in the QoL across all scales assessed. This shows that the quality of life in this group of patients returns to baseline following treatment with NeC+TORS. Within the sample that we had, there was a change over time in global quality of life, social functioning, senses problems and dry mouth. In all these scales, we observed a statistically significant drop in quality of life at 1-month post-treatment that returns to pre-treatment baseline in 3 months. This shows, as expected that it takes about 6-8 weeks to fully recover from the acute side effects of chemotherapy followed by TORS.

Previously reported quality of life studies on OPSCC patients treated with standard of care RT/CRT showed at 12-month post-treatment significant increase of symptoms of xerostomia, sticky saliva, swallowing and senses problems. (18)

We performed a comparison of NeC+TORS with historical data from OPSCC patients treated with standard of care RT/CRT as reported by Oates et al.(19) This showed a statistically

significant difference between the values of Global Quality of life (GQL), at 12-month post-treatment with NeC+TORS patients having a higher GQL. Notably, patients included in the Oates et al. study had lower scored of GQL at diagnosis. This baseline difference may explain the difference at 12 months post treatment GQL outcomes between NeC+TORS versus standard of care. Oates study included OPSCC patients in the study regardless of their tumour HPV status. This may also account for the differences in baseline GQL with that of NeC+TORS group.

We also compared our sample's Global Quality of life scores with scores of general populations (20) from a comparable age group and gender distribution. Regarding the comparison performed, there were notable differences in global quality of life scores of the three different groups at baseline and at 12 months. The general population had lower scores in comparison to NeC+TORS and higher than the standard of care patients; statistically significant in both cases. For general population estimates of the GQL, participants were included in the original study regardless of their comorbidities or other malignancies. (20) This may explain the lower quality of life of the general population than the baseline of our sample. Our sample had minimal symptomatology related to OPSCC and did not have any other major health problems. What is clear is that the GQL of NeC+TORS patients return to baseline, where as a deterioration of GQL is noted in patients reported by Oates et al, receiving standard of care treatment.

Moreover, it is known from the literature that patients with HPV negative have more comorbidities and a higher mean of age at diagnosis. Hence, we cannot draw definite conclusions for comparison of GQL between NeC+TORS and standard of care CRT. It has been shown in multiple studies that HPV+ patients have different risk factors, are younger and have a better

response to treatment with a higher 5-year year survival. (21) This may explain the better baseline and post treatment GQL in these patients.

In dry mouth scores, there was a notable difference at 12-month post-treatment, with lower (better) scores of NeC+TORS patients compared with historical controls as reported by Oates et al. This is evidently explained by the fact that NeC+TORS patients do not receive radiotherapy, the treatment component in standard of care that is known to be responsible for dry mouth. No difference between the standard of care and NeC+TORS was observed in swallowing scale.

Head and neck cancer patients have a percutaneous gastrostomy tube at 12-month post-treatment in the proportion of up to 15%. (22) In the NeC+TORS sample used; percutaneous gastrostomy was not necessary for any patient in any time-point. As known from clinical practice and literature, returning to an oral diet is extremely important for the quality of life and functional outcome of patients. A previous study showed that relying on a feeding tube to live among inpatients was considered the same or worse than death in 55% of the patients questioned. (23)

Several limitations restrict the generalizability of this study. Firstly, the sample size was dictated by the number of patients treated at MUHC in the specific timeframe. While the data comes from a uniform group of HPVs+ OPSCC cohort treated with NeC+TORS, eligibility restricted the study population to stage III and IV-a patients. Patients with stage IVb as well patients with T4 disease were excluded. Hence it is not be generalizable for more advanced HPV+ OPSCC with T4 and N3 disease. Secondly, all patients were operated by the same surgeons highly experienced in TORS. There was only one patient that had a microscopic positive margin and required a re-operation. No patient needed adjuvant radiotherapy based on the criteria established

for NeC+TORS. The data needs to be reproduced in a multi-institutional setting. The early stage I and II patients are excluded, and this is a strength. These early stage patients are effectively treated with unimodality surgery or radiotherapy alone.

Additionally, to our knowledge, there are no prior studies that analysed data on QoL as measured by EORTC QLQ-30 and H&N35 of exclusively HPV positive OPSCC patients with stage III and IVa (AJCC 7th edition) disease treated with standard of care using EORTC at baseline and 12-month post-treatment. And our own series did not include a cohort of similar patients treated with CRT and having QoL surveys. Hence, we could not make a direct and more accurate comparison.

4.6 Conclusion

In the small sample of patients, this study confirmed the clinical observation that patients with locally advanced HPV positive treated with NeC+TORS return to their baseline quality of life they had before treatment. In the symptom scales that are recognised in the field as most negatively affected by the current standard CRT, we observed a return to baseline, following treatment of HPV positive OPSCC with NeC+TORS. Patients in the study had a rapid return to an oral diet as measured by the absence of a PEG and short use of nasogastric feeding tube. We conclude that NeC followed by TORS provides overall maintenance of the patient-reported quality of life from the pre-treatment levels.

4.7 Access to data and data analysis

The first author and principal clinical investigator had full access to all the data in the study and take responsibility for the integrity of the data.

References

1. Public Health Agency of C, Statistics C, Canadian Cancer S, provincial/territorial cancer r. Release notice - Canadian Cancer Statistics 2019. Health Promot Chronic Dis Prev Can. 2019;39(8-9):255.
2. Rebecca L. Siegel MKDM, MPH2; Ahmedin Jemal, DVM, PhD3. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30. 2017.
3. Timbang MR, Sim MW, Bewley AF, Farwell DG, Mantravadi A, Moore MG. HPV-related oropharyngeal cancer: a review on burden of the disease and opportunities for prevention and early detection. Human vaccines & immunotherapeutics. 2019;15(7-8):1920-8.
4. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294-301.
5. Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B, et al. Annual Report to the Nation on the Status of Cancer, 1975-2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst. 2013;105(3):175-201.
6. Georgopoulos R, Liu JC. Examination of the patient with head and neck cancer. Surg Oncol Clin N Am. 2015;24(3):409-21.
7. Adelstein DJ, Li Y, Adams GL, Wagner H, Jr., Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003;21(1):92-8.
8. Sher DJ, Adelstein DJ, Bajaj GK, Brizel DM, Cohen EEW, Halthore A, et al. Radiation therapy for oropharyngeal squamous cell carcinoma: Executive summary of an ASTRO Evidence-Based Clinical Practice Guideline. Practical radiation oncology. 2017;7(4):246-53.
9. Vainshtein JM, Moon DH, Feng FY, Chepeha DB, Eisbruch A, Stenmark MH. Long-term quality of life after swallowing and salivary-sparing chemo-intensity modulated radiation therapy in survivors of human papillomavirus-related oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2015;91(5):925-33.
10. Weinstein GS, O'Malley BW, Jr., Magnuson JS, Carroll WR, Olsen KD, Daio L, et al. Transoral robotic surgery: a multicenter study to assess feasibility, safety, and surgical margins. Laryngoscope. 2012;122(8):1701-7.
11. Marur S, Li S, Cmelak AJ, Gillison ML, Zhao WJ, Ferris RL, et al. E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx-ECOG-ACRIN Cancer Research Group. J Clin Oncol. 2017;35(5):490-7.
12. Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. The Lancet. 2019;393(10166):40-50.

13. Nichols AC, Theurer J, Prisman E, Read N, Berthelet E, Tran E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. Lancet Oncol. 2019;20(10):1349-59.
14. Sadeghi N, Li NW, Taheri MR, Easley S, Siegel RS. Neoadjuvant chemotherapy and transoral surgery as a definitive treatment for oropharyngeal cancer: A feasible novel approach. Head Neck. 2016.
15. Sadeghi N, Mascarella MA, Khalife S, Ramanakumar AV, Richardson K, Joshi AS, et al. Neoadjuvant chemotherapy followed by surgery for HPV-associated locoregionally advanced oropharynx cancer. Head Neck. 2020;42(8):2145-54.
16. Sadeghi N, Khalife S, Mascarella MA, Ramanakumar AV, Richardson K, Joshi AS, et al. Pathologic response to neoadjuvant chemotherapy in HPV-associated oropharynx cancer. Head Neck. 2020;42(3):417-25.
17. Fayers P, Aaronson, N. K., Bjordal, K., Groenvold, M., Curran, D., & Bottomley, A. EORTC QLQ-C30 Scoring Manual. (3rd ed.) 2001.
18. Hoxbroe Michaelsen S, Gronhoj C, Hoxbroe Michaelsen J, Friborg J, von Buchwald C. Quality of life in survivors of oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients. Eur J Cancer. 2017;78:91-102.
19. Oates J, Clark JR, Read J, Reeves N, Gao K, O'Brien CJ. Integration of prospective quality of life and nutritional assessment as routine components of multidisciplinary care of patients with head and neck cancer. ANZ journal of surgery. 2008;78(1-2):34-41.
20. Hinz A, Singer S, Brahler E. European reference values for the quality of life questionnaire EORTC QLQ-C30: Results of a German investigation and a summarizing analysis of six European general population normative studies. Acta Oncol. 2014;53(7):958-65.
21. Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. Oral Oncol. 2014;50(6):565-74.
22. Cheng SS, Terrell JE, Bradford CR, Ronis DL, Fowler KE, Prince ME, et al. Variables associated with feeding tube placement in head and neck cancer. Arch Otolaryngol Head Neck Surg. 2006;132(6):655-61.
23. Rubin EB, Buehler AE, Halpern SD. States Worse Than Death Among Hospitalized Patients With Serious Illnesses. JAMA Intern Med. 2016;176(10):1557-9.

CHAPTER 5: DISCUSSION AND CONCLUSION

Patients diagnosed with OPSCC usually present with a painless neck mass that does not interfere majorly with their quality of life. Most of them are in advanced stages of their disease, and they require aggressive treatment, represented by the current standard of care, which is surgery, chemotherapy, and radiotherapy in different combinations. Current treatment of OPSCC tends to reduce the side effects of these therapies while maintaining the cancer cure rate. However, different de-escalations methods are being tested in trials all over the world. NeC+TORS represent an experimental treatment that does not include radiotherapy.

The first manuscript reviewed the literature on quality of life of OPSCC patients treated with standard of care therapy, comparing baseline to 12-month post-treatment scores. EORTC QLQ30 and H&N 35 scores at 12-month post-treatment showed worsening in scales like appetite, pain related to head and neck, senses problems, social eating, sexuality. The scores of problems with teeth, problems opening the mouth, dry mouth, and sticky saliva, compared to pre-treatment scores showed that these symptoms are present at 12-month post-treatment and interfere negatively with the quality of life. Standard of care for OPSCC produced side effects that modify in a negative way the quality of life reported by patients.

The second manuscript, a small ambidirectional study, included OPSCC HPV+ patients that were treated with NeC+TORS. We presented the one-year evolution and the comparison between pre-treatment and 12-month post-treatment scores of EORTC QLQ and H&N35. We also performed comparisons with the standard of care of similar patients and with the general population with similar characteristics (age group and sex) as OPSCC HPV+ patients. In patients

treated with NeC+TORS, 12-month scores on global quality of life, social functioning, social eating, dry mouth, swallowing and sticky saliva, had returned to baseline values. The comparison of NeC+ TORS with the standard of care showed important differences in global quality of life and dry mouth in 12-month post-treatment, with the standard of care patients reporting lower quality of life. The finding that the general population had a worse global quality of life than NeC+TORS patients at 12-month post-treatment may be due to the inclusion of people with different comorbidities in the general population. Although we compared NeC+TORS patients to both standard of care and the general population, the populations are not directly comparable. Our findings, therefore, highlight the need for a randomized controlled trial that compares the self-reported quality of life in patients treated with standard of care and NeC+TORS at different time-points after treatment.

In conclusion, patients treated with NeC+TORS suggest a new treatment option for locally advanced OPSCC HVP+ with few side effects and quality of life that was comparable to pre-treatment. NeC+TORS is a promising treatment option that deserves to be tested in a randomized clinical trial.[47].

Appendix

APPENDIX A

Inclusion Criteria:

- Age at least 18 years
- p16 positive (HPV+)
- Biopsy proven OPSCC (tonsil, base of tongue, vallecula, soft palate),
- AJCC-7 stage III (T1N1, T2N1, T3N0, T3N1) and stage IVA (T1N2, T2N2, T3N2) disease not previously treated with any method (Surgery, RT, CRT)
- No distant metastatic disease
- Fit for surgery, and primary tumor assessed to be surgically resectable with negative margins (by PI) via transoral approach
- KPS > 60%, or ECOG < 2
- ANC > 2,000, platelets > 100,000 and calculated creatinine clearance >50
- Signed study specific consent form
- No other malignancies except cutaneous basal or squamous cell cancer within the last 5 years
- Patients must have measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST). Baseline measurements and evaluations of all site of disease must be obtained within 3 weeks of starting study treatment.
- Men and women of childbearing potential must agree to use effective contraception while on the study. In addition, a woman of childbearing potential must have a negative pregnancy test, and not be lactating.

Exclusion Criteria:

- Patients with advanced T4 cancer unresectable without glossectomy, laryngectomy or major disability.
- p16 negative tumor
- Patients with N3 disease (Stage IVB).
- Patients with 5 or more positive cervical lymph nodes on presentation.
- Patients with distant metastatic disease
- Radiologically positive neck nodes with evidence of gross extracapsular nodal tumor invasion into soft tissue.
- Anatomy not allowing transoral access and exposure (Judged by the surgical PI)
- Patients with prior head and neck cancer at any time (other than basal or squamous cell cancer of the skin)
- Coexistent second malignancy or history within 5 years of prior malignancy
- Peripheral neuropathy ≥ grade 1
- Prior Taxanes or Cisplatin
- Any concurrent infections. All patients must be afebrile for at least 3 days prior to start of therapy unless due to tumor.
- Any coexisting medical illness of a severity that might interfere with treatment or follow-up
- Inability to give informed consent
- Prior radiation therapy, surgery and chemotherapy for the current tumor
- Patients must not be receiving any other investigational agent

Appendix B 1

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

REFERENCES

1. Cohen, N., S. Fedewa, and A.Y. Chen, *Epidemiology and Demographics of the Head and Neck Cancer Population.* Oral Maxillofac Surg Clin North Am, 2018. **30**(4): p. 381-395.
2. Timbang, M.R., et al., *HPV-related oropharyngeal cancer: a review on burden of the disease and opportunities for prevention and early detection.* Hum Vaccin Immunother, 2019. **15**(7-8): p. 1920-1928.
3. You, E.L., M. Henry, and A.G. Zeitouni, *Human papillomavirus-associated oropharyngeal cancer: review of current evidence and management.* Curr Oncol, 2019. **26**(2): p. 119-123.
4. Syrjanen, K., et al., *Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis.* Int J Oral Surg, 1983. **12**(6): p. 418-24.
5. Berman, T.A. and J.T. Schiller, *Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases.* Cancer, 2017. **123**(12): p. 2219-2229.
6. Kobayashi, K., et al., *A Review of HPV-Related Head and Neck Cancer.* J Clin Med, 2018. **7**(9).
7. Chaturvedi, A.K., et al., *Human papillomavirus and rising oropharyngeal cancer incidence in the United States.* J Clin Oncol, 2011. **29**(32): p. 4294-301.
8. D'Souza, G., T.S. McNeel, and C. Fakhry, *Understanding personal risk of oropharyngeal cancer: risk-groups for oncogenic oral HPV infection and oropharyngeal cancer.* Ann Oncol, 2017. **28**(12): p. 3065-3069.
9. *Annual Report to the Nation on the Status of Cancer, 1975–2009, Featuring the Burden and Trends in Human Papillomavirus (HPV)–Associated Cancers and HPV Vaccination Coverage Levels*. Journal of the National Cancer Institute.
10. Georgopoulos, R. and J.C. Liu, *Examination of the patient with head and neck cancer.* Surg Oncol Clin N Am, 2015. **24**(3): p. 409-21.
11. Mehanna, H., et al., *Oropharyngeal cancer: United Kingdom National Multidisciplinary Guidelines.* J Laryngol Otol, 2016. **130**(S2): p. S90-S96.
12. SB Edge, D.B., CC Compton, AG Fritz, FL Greene, A Trotti,, *AJCC Cancer Staging Manual 7th edition.* Springer, 2010.
13. Edge, S.B. and C.C. Compton, *The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM.* Ann Surg Oncol, 2010. **17**(6): p. 1471-4.
14. MB Amin, S.E., FL Greene, et al, *AJCC Cancer Staging Manual 8th edition.* New York: Springer, 2017.
15. Strimbu, K. and J.A. Tavel, *What are Biomarkers?* Current opinion in HIV and AIDS, 2010. **5**(6): p. 463-466.
16. *Double positivity for HPV-DNA/p16ink4a is the biomarker with strongest diagnostic accuracy and prognostic value for human papillomavirus related oropharyngeal cancer patients.*

17. Sacks, P.-L., et al., *Prognostic biomarkers of human papilloma virus (HPV)-positive neoplasia of the upper aerodigestive tract: a systematic review.* Australian Journal of Otolaryngology, 2018. **1**(6).
18. DJ, A., et al., *An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer.* - J Clin Oncol. 2003 Jan 1;21(1):92-8. doi: 10.1200/JCO.2003.01.008., 2003(- 0732-183X (Print)): p. - 92-8.
19. Dorr, W. and J.H. Hendry, *Consequential late effects in normal tissues.* Radiother Oncol, 2001. **61**(3): p. 223-31.
20. Rieger, J.M., J.G. Zalmanowitz, and J.F. Wolfaardt, *Functional outcomes after organ preservation treatment in head and neck cancer: a critical review of the literature.* Int J Oral Maxillofac Surg, 2006. **35**(7): p. 581-7.
21. Fung, K., et al., *Voice and swallowing outcomes of an organ-preservation trial for advanced laryngeal cancer.* Int J Radiat Oncol Biol Phys, 2005. **63**(5): p. 1395-9.
22. *Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected.*
23. Nguyen, N.P., H.J. Smith, and S. Sallah, *Evaluation and management of swallowing dysfunction following chemoradiation for head and neck cancer.* Curr Opin Otolaryngol Head Neck Surg, 2007. **15**(2): p. 130-3.
24. Jensen, K., K. Lambertsen, and C. Grau, *Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: frequency, intensity and correlation with dose and volume parameters.* Radiother Oncol, 2007. **85**(1): p. 74-82.
25. Bossi, P., et al., *Treatment-related outcome of oropharyngeal cancer patients differentiated by HPV dictated risk profile: a tertiary cancer centre series analysis.* Ann Oncol, 2014. **25**(3): p. 694-9.
26. *Quality of Life in Patients with Oropharynx Carcinomas: Assessment after Accelerated Radiotherapy with or without Chemotherapy versus Radical Surgery and Postoperative Radiotherapy.*
27. Windon, M.J., G. D'Souza, and C. Fakhry, *Treatment preferences in human papillomavirus-associated oropharyngeal cancer.* Future Oncol, 2018. **14**(24): p. 2521-2530.
28. Nichols, A.C., et al., *Treatment de-escalation for HPV-associated oropharyngeal squamous cell carcinoma with radiotherapy vs. trans-oral surgery (ORATOR2): study protocol for a randomized phase II trial.* BMC Cancer, 2020. **20**(1): p. 125.
29. Gillison, M.L., et al., *Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial.* The Lancet, 2019. **393**(10166): p. 40-50.
30. Marur, S., et al., *E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx— ECOG-ACRIN Cancer Research Group.* Journal of Clinical Oncology, 2016. **35**(5): p. 490-497.
31. Nichols, A.C., et al., *Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial.* Lancet Oncol, 2019. **20**(10): p. 1349-1359.

32. Rebecca L. Siegel, M.K.D.M., MPH 2 ; Ahmedin Jemal, DVM, PhD 3, *Cancer statistics, 2019.* 2019.
33. Ragin, C.C. and E. Taioli, *Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis.* Int J Cancer, 2007. **121**(8): p. 1813-20.
34. *The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas.*
35. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer.* The New England journal of medicine, 2010. **363**(1): p. 24-35.
36. Molina, M.A., et al., *African American and poor patients have a dramatically worse prognosis for head and neck cancer: an examination of 20,915 patients.* Cancer, 2008. **113**(10): p. 2797-806.
37. Weinberger, P.M., et al., *Human papillomavirus-active head and neck cancer and ethnic health disparities.* Laryngoscope, 2010. **120**(8): p. 1531-7.
38. Broglie, M.A., et al., *Quality of life of oropharyngeal cancer patients with respect to treatment strategy and p16-positivity.* Laryngoscope, 2013. **123**(1): p. 164-70.
39. Rogers, D.L.S.N., *University of Washington Quality of Life Questionnaire (UW-QOL v4)* 2012.
40. Chen, A.Y., et al., *The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory.* Arch Otolaryngol Head Neck Surg, 2001. **127**(7): p. 870-6.
41. Bjordal, K. and S. Kaasa, *Psychometric validation of the EORTC Core Quality of Life Questionnaire, 30-item version and a diagnosis-specific module for head and neck cancer patients.* Acta Oncol, 1992. **31**(3): p. 311-21.
42. Niezgoda, H.E. and J.L. Pater, *A validation study of the domains of the core EORTC quality of life questionnaire.* Qual Life Res, 1993. **2**(5): p. 319-25.
43. Epstein, J.B., et al., *Quality of life and oral function following radiotherapy for head and neck cancer.* Head Neck, 1999. **21**(1): p. 1-11.
44. Bjordal, K., et al., *A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group.* Eur J Cancer, 2000. **36**(14): p. 1796-807.
45. Rogers, S.N., et al., *Health-related quality of life and clinical function after primary surgery for oral cancer.* Br J Oral Maxillofac Surg, 2002. **40**(1): p. 11-8.
46. Hoxbroe Michaelsen, S., et al., *Quality of life in survivors of oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients.* Eur J Cancer, 2017. **78**: p. 91-102.
47. N, S., et al., *Neoadjuvant chemotherapy followed by surgery for HPV-associated locoregionally advanced oropharynx cancer.* Head and Neck, 2020(- 1097-0347 (Electronic)): p. T - aheadofprint.