Longitudinal and comprehensive quality of life in patients with locally advanced human papillomavirus-associated oropharyngeal squamous cell carcinoma

by

Jennifer A Silver, MD

Department of Otolaryngology, Head and Neck Surgery
Faculty of Medicine and Health Sciences
McGill University
Montreal, Canada

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Abstract

Background:

Rates of human papillomavirus-associated oropharyngeal squamous cell carcinoma (OPSCC) are increasing in prevalence, however, prognosis is favourable. Patients are generally younger and healthier at the time of diagnosis and five-year survival statistics are above 80%. Treating human papillomavirus (HPV)-related OPSCC with standard treatments for traditional OPSCC, i.e. chemoradiation therapy, leads to post-treatment toxicities and complications that worsen over time. Efforts are underway searching for alternative therapy regimens or de-escalation strategies to preserve high overall survival and disease-free survival while also aiming to maintain the patient's quality of life (QOL).

Clinical trials are now incorporating patient-reported QOL surveys to assess subjective impacts of the disease and the therapies. However, not all QOL surveys are equal, because different questionnaires focus on different issues and patient outcomes. A patient's QOL is multifactorial, and thus, it is important to consider all QOL components when assessing the benefit or efficacy of treatment regimens.

Objectives:

The objectives of this thesis are (1) to describe the options of treatment regimens for HPV-associated OPSCC, (2) to explore the psychosocial patient-reported QOL outcome data for HPV-associated OPSCC patients, and (3) to assess the longitudinal and multifactorial outcomes of patients currently enrolled in a de-escalation trial (neoadjuvant chemotherapy followed by transoral robotic surgery (TORS) and neck dissection, with radiation therapy reserved for salvage) within our centres.

Thesis Organization:

Three studies aimed to meet the three thesis objectives. A first study is a comprehensive narrative review of treatment trials and studies of de-intensification strategies for HPV-associated OPSCC patients. A second manuscript is a scoping review of studies reporting results of psychosocial QOL assessments in OPSCC patients assessed by validated patient-reported

outcome measures. Finally, a third study explores longitudinal and multifactorial QOL outcomes of HPV-associated OPSCC patients treated with neoadjuvant chemotherapy followed by TORS and neck dissection between 2017-2022.

Results:

The first study identified and categorized the de-escalation strategies into six different groups, with different doses, orders, and use of surgery, chemotherapy, and radiation therapy. It was a challenge to compare these protocols or to determine the best approach. This suggested that patient preference should be a driver of choice in future clinical trials, and that assessment of the QOL of these patients would be essential for understanding true side effect profiles and outcomes. The second study explored four components of patient-reported psychosocial QOL within published papers on OPSCC patients: mental health and emotional wellbeing, social wellbeing and function, stress, and relationship and sexual behavior. It was found that research is limited in all domains. The third study established that neoadjuvant chemotherapy followed by TORS and neck dissection effectively managed AJCC 7th edition stage III/IVa HPV-related OPSCC, while also preserving QOL in all multidimensional domains.

Conclusions:

This thesis explores and expands upon research on patients with HPV-associated OPSCC. Patients treated with neoadjuvant chemotherapy followed by TORS and neck dissection demonstrated a comprehensive QOL assessments that were maintained after completion of treatment.

Résumé

Contexte :

La prévalence du carcinome épidermoïde oropharyngé (OPSCC) associé au virus du papillome humain augmente, mais le pronostic est favorable. Les patients sont généralement plus jeunes et en meilleure santé au moment du diagnostic et le taux de survie à cinq ans est supérieur à 80 %. Le traitement de l'OPSCC lié au VPH par les traitements standard de l'OPSCC traditionnel, c'est-à-dire la chimioradiothérapie, entraîne des toxicités et des complications post-traitement qui se multiplient avec le temps. Des efforts sont actuellement déployés pour mettre. En place des plans thérapeutiques alternatifs ou des stratégies de désescalade afin de préserver un taux élevé de survie globale et de survie sans maladie, tout en mettant l'accent sur le maintien de la qualité de vie.

Les études cliniques intègrent désormais des enquêtes sur la qualité de vie (QV) rapportée par les patients pour évaluer les effets subjectifs de la maladie ainsi que les thérapies administrées. Les questionnaires sur la qualité de vie ne sont pas tous valables les un que les autres, donc il faut tenir compte des questions posées et des résultats rapportés par chacun d'eux. La qualité de vie d'un patient est multifactorielle et il est donc important de prendre en compte toutes les composantes lors de l'évaluation des avantages ou de l'efficacité des traitements.

Objectifs :

Les objectifs de cette thèse sont (1) de décrire les options de traitements pour les OPSCC associés au VPH, (2) d'explorer les données psychosociales relatives à la qualité de vie des patients pour les OPSCC associés au VPH, et (3) d'exprimer les résultats longitudinaux et multifactoriels des patients actuellement inscrits dans un essai de désescalade (chimiothérapie néoadjuvante suivie d'une chirurgie robotique transorale (TORS) et d'une évidemment cervicale, la radiothérapie étant réservée au sauvetage) au sein de notre centre.

Méthodes :

La première étude est une revue narrative complète des études sur les stratégies de désintensification pour les patients atteints d'OPSCC associé au VPH. L'article suivant est une

revue des études rapportant les résultats de la qualité de vie rapportée par les patients atteints d'OPSCC, évalués avec l'aide de questionnaires validés. Enfin, le troisième article démontre les résultats longitudinaux et multifactoriels de la QV rapportée par les patients atteints d'OPSCC associés au VPH, traités par chimiothérapie néoadjuvante suivie d'une TORS et d'une dis évidemment cervicale entre 2017 et 2022.

Résultats :

La première publication a identifiée et classée les stratégies de désescalade en six groupes différents, avec les doses variés, l'utilisation de la chirurgie, de la chimiothérapie ou de la radiothérapie, ainsi que par les ordres différents de l'administration de traitements. Il est difficile de comparer ces protocoles ou de déterminer la meilleure approche. Par conséquent, la préférence du patient est probablement le déterminant du choix – donc de futures études cliniques portant sur la qualité de vie de ces patients sont essentielles pour comprendre les véritables profils d'effets secondaires et les résultats cliniques. Le second manuscrit a exploré quatre composantes psychosociales de la qualité de vie rapportée par les patients atteints de OPSCC : la santé mentale et le bien-être émotionnel, le bien-être social et la fonction, le stress, et les relations et le comportement sexuel. Ce rapport note que les données sont insuffisantes dans tous les domaines. La troisième étude a établie que la chimiothérapie néoadjuvante suivie d'une TORS et d'une évidemment cervicale cou est une approche pour la prise en charge de l'OPSCC lié au VPH de stade III/IVa selon la 7e édition de l'AJCC qui conserve avec succès la qualité de vie dans tous les domaines multidimensionnels.

Conclusions :

Cette thèse explore et approfondit la recherche sur les patients atteints d'OPSCC associé au VPH. Les patients traités par chimiothérapie néoadjuvante suivie d'une TORS et d'une évidemment cervicale soumis à une évaluation complète démontrent que la qualité de vie se maintient après la fin du traitement.

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Contribution of authors

Idea for project: Dr. Jennifer A Silver, Dr. Melissa Henry, and Dr. Nader Sadeghi. Project supervisors: Dr. Melissa Henry and Dr. Nader Sadeghi.

Chapters 1,2,6,7,8: Written by Dr. Jennifer A Silver

Chapter 3: Dr. Jennifer A Silver performed the literature review, narrative review, and manuscript redaction. Drs. Sena Turkdogan, Catherine F Roy, and Thava Subramanian, helped review the manuscript. Dr. Melissa Henry and Dr. Nader Sadeghi supervised the review, reviewed the manuscript, and approved the manuscript.

Chapter 4: Dr. Jennifer A Silver performed the scoping review and manuscript redaction. Dr Russell Schwartz participated as a second independent reviewer. Dr. Catherine F Roy assisted in reviewing the manuscript. Dr. Melissa Henry and Dr. Nader Sadeghi supervised the review, reviewed the manuscript, and approved the manuscript.

Chapter 5: Dr. Jennifer A. Silver helped conceive/design the study; did initial data review and analysis; drafted the manuscript; and revised it. This was all done under the supervision of Dr. Melissa Henry and Dr. Nader Sadeghi. Drs Nathaniel Bouganim, Keith Richardson, Marco A Mascarella, Alex M Mlynarek, Anthony Zeitouni, Michael P Hier, Derin Caglar, Khashayar Esfahani, and Nader Sadeghi contributed in trial participation, patient recruitment, and manuscript revision. Ms Nahid Golabi was essential in patient recruitment, patient communication, and data acquisition. Dr. Jose Ramirez-GarciaLuna performed the statistical analysis and reviewed the manuscript.

Disclosures

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Chapter 1: Introduction

Rationale

The prevalence of oropharyngeal squamous cell carcinoma (OPSCC) has been increasing in North America due to human papillomavirus (HPV)-associated disease[1]. Standard of care therapy for locally advanced OPSCC, both HPV and smoking-related subtypes, is typically treated with concurrent chemoradiation (CRT) to avoid large disfiguring surgical procedures[2-5]. However, patients with HPV-associated OPSCC have a more favorable prognosis and they live long lives with the sequelae of their treatment regimen[6-8]. As a result, there is a need to identify alternative therapy regimens, or appropriate de-escalation strategies, to minimize negative secondary effects while maintaining high overall survival and disease-free survival[9,10] This thesis will explore how this might best be achieved

First, there is a need to review the recent surge in treatment strategies and modalities for HPV-associated OPSCC and their effectiveness. This thesis will do this in Chapter 3 below.

Many of the previous trials and studies treating OPSCC have used patient-reported quality of life (QOL) questionnaires to document post-therapy secondary outcomes. Despite QOL being multifactorial, most of these trials focus only on physical QOL outcomes[11,12]. There is a need to extend the definition of QOL beyond physical and functional dimensions by including psychosocial outcomes to better understand the whole-person experience[13]. This thesis will explore this by broadly assessing the landscape of published literature focusing on psychosocial QOL in OPSCC patients using patient-reported outcome measures (PROMs). This will be done in Chapter 4 below.

Within our institution at McGill, the treatment regimen of neoadjuvant chemotherapy followed by TORS and neck dissection (NECTORS), which reserves radiation therapy for salvage, has yielded excellent oncologic outcomes that have previously been described[14-16]. However, the overall and multi-faceted QOL of the patients treated within this trial has not yet been fully

explored. To address this need, a third study in Chapter 5 will longitudinally examine a more comprehensive assessment of QOL in patients enrolled in the NECTORS trial.

Thesis Objectives

The main objective of this thesis is to describe the many treatment regimens for HPV-associated OPSCC and the lack of psychosocial patient-reported data for HPV-associated OPSCC patients, while examining the longitudinal and multifactorial outcomes of patients currently enrolled in a de-escalation trial within McGill centres.

Thesis Organization

This thesis is organized into chapters to provide background information and to present the findings of a longitudinal study. Chapter 2 reviews the background of oropharyngeal cancer. Chapters 3, 4, and 5 contain published manuscripts. Chapter 3 is a comprehensive narrative review of treatment strategies and modalities for HPV-associated OPSCC patients. Chapter 4 is a scoping review of the results of psychosocial QOL assessments in OPSCC patients assessed by validated patient-reported outcome measures. Chapter 5 reports the longitudinal QOL outcomes of HPV-associated OPSCC patients treated with neoadjuvant chemotherapy followed by TORS and neck dissection. Chapter 6 contains an overall discussion and conclusions. Chapter 7 is an overall conclusion and contribution to original knowledge. Chapter 8 lists the tables from this thesis. Chapter 9 lists references.

Chapter 2: Background

Epidemiology

Approximately 7,400 head and neck cancers are diagnosed annually in Canada, representing 4.2% of all new cancers[17]. Head and neck malignancies are mainly located in the upper aerodigestive tract, from skull base to thoracic inlet and are predominantly squamous cell carcinomas[18]. The major risk factors, historically, have been tobacco exposure and alcohol use[19,20]. Prevalence of head and neck malignancies has been decreasing globally over the last several decades due to lowered rates of smoking and drinking[1,21]. However, despite decreasing cigarette and alcohol consumption and a decline in head and neck cancers in general, oropharyngeal cancer prevalence has been rising[1]. Oropharyngeal squamous cell carcinoma (OPSCC) related to the human papillomavirus (HPV) has increased in incidence, and is now the most prevalent head and neck cancer in the western world[1,22]. Following the current trends in the rise of HPV-related OPSCC, the United States estimates that HPV-associated OPSCC will make up 47% of all head and neck cancers by 2030[1].

Clinical presentation

Anatomically, the oropharynx spans from the hard palate-soft palate junction superiorly to the hyoid bone and vallecula inferiorly, connecting the superior nasopharynx to the oral cavity anteriorly and the hypopharynx inferiorly. Cancers of the oropharynx are found within the lateral pharyngeal walls/tonsils, base of tongue, soft palate, and the posterior pharyngeal wall.

Patients with HPV-associated OPSCC are younger and healthier at baseline than the typical HPV-negative OPSCC cohort[6,7]. They often have minimal or no tobacco exposure but a more extensive sexual history[1,23]. Patients often have subtle symptoms, including sore throat, foreign body sensation, dysphagia, or unilateral otalgia making early diagnosis less common. Approximately one third of patients with OPSCC present to a clinician after identification of a neck mass and are diagnosed with locally advanced disease[24].

HPV-positive malignancies have smaller primary tumours with larger nodal disease[6,25]. Although advanced nodal stage is a poor prognostic factor for HPV-negative disease, the same adverse prognosis does not apply in HPV-associated disease[26,27]. When planning how to address the neck, whether it be by radiotherapy or surgically, understanding of the lymphatic spread from the primary tumor is essential. The primary echelon of lymphatic drainage from oropharyngeal cancers is in the upper jugular chain, or level II[28]. Level IIB lymph nodes are rarely positive in isolation without level IIA metastases, large size, or tonsillar primary[29]. Along with level II, retropharyngeal and parapharyngeal lymph nodes are also primary drainage sites for tonsil, soft palate, and posterior pharyngeal wall tumors. From these locations, cervical metastases can secondarily spread to levels I, III, and lower cervical nodes (IV) if the disease is extensive[28].

HPV pathophysiology

HPV is the most common sexually transmitted infection in North America[30]. The human papillomaviruses are a family of non-enveloped, double-stranded, circular DNA viruses that has an affinity for squamous epithelium. There are over 100 identified types of HPV with different risk-levels associated. The main subtypes of interest to otolaryngologists include HPV-6 and HPV-11, low-risk subtypes which induce proliferation of epithelium causing papillomas and warts, and HPV-16 and HPV-18, high-risk subtypes implicated in cervical, anogenital, and head and neck cancers. The rates of HPV-related OPSCC varies by location, however, North American studies have identified approximately 70% of OPSCC cases to be due to HPV[31-34].

HPV transmission occurs through direct skin-to-skin or mucosal contact during vaginal, anal, or oral sex[30]. Individuals who are asymptomatic or symptomatic can transmit the virus[30,35]. After transmission to another individual, HPV can spread from the primary area to another site[36]. Oral infection with the high-risk HPV subtype, HPV-16, is responsible for the majority of HPV-associated OPSCCs[37]. A cross-sectional study conducted by the National Centre for Health Statistics identified oral HPV infection in 6.9% of men and women aged 14-69, of which 1.0% were HPV-16[38]. There is a bimodal age distribution, with peaks between 30-34 years and 60-64 years, and men had higher infection rates than women (10.1% vs 3.6%, $p<0.001$)[38]. This study

also identified increased high risk HPV infection prevalence with greater numbers of lifetime sexual partners[38].

The HPV genome contains E6 and E7 oncogenes, which are responsible for carcinogenesis[39,40]. E6 binds to and breaks down the p53 tumor suppressor gene and also acts to prolong the lifespan of infected epithelial cells to further propagate the virus[39,41]. The E7 oncogene binds to and degrades the retinoblastoma protein, a product of the tumor suppressor retinoblastoma gene, and causes chromosomal disruption and genomic instability[42]. With the breakdown of the retinoblastoma protein, there is greater expression of the p16 protein[40,43].

The natural history of HPV is not entirely understood. Most information about HPV epidemiology stemmed first from research on HPV-related cervical cancer[44]. Viral load is a balance of viral acquisition and clearance, where persistence of the virus can lead to cancer development[45]. While infection of oral high-risk HPV subtypes is less common than genital infection, the infections seem to clear at approximately the same rates[46,47]. Studies have demonstrated that there is viral clearance in most cases within one year in individuals with a negative oral HPV test at baseline[45,46]. However, a study following male patients for longer than seven years found that 18% of patients with HPV-16 infections were still positive after 24 months, which explains why this is a high-risk subtype[48]. Usually, development of HPV-related OPSCC occurs many years after incident infection.

Pathological diagnosis

In the oropharynx, the virus often enters at the epithelium at the base of the tonsillar crypts[49]. The HPV DNA virus preferentially infects the basal epithelium.

On light microscopy, the HPV-positive and HPV-negative squamous cell carcinomas appear similar. While HPV-positive samples having a greater likelihood to be non-keratinizing, poorly differentiated or basaloid in nature, this is insufficient to be diagnostic[49-52]. The gold standard pathological test to detect HPV-related disease is polymerase chain reaction. Although it is extremely sensitive and specific given it has the ability to detect a single copy of viral DNA, its

high cost limits its use (NCCN guidelines). Another option is detection via in situ hybridization for HPV DNA which has a high specificity for HPV-associated disease but is more technically challenging to perform[53]. A technique commonly used is the assessment of p16 on immunohistochemistry, used as a surrogate biomarker for HPV as HPV infection leads to increased nuclear p16 expression, and has high sensitivity[50,53]. The standard criterion for a positive p16 immunohistochemistry staining is staining of more than 70% cells with nuclear and cytoplasmic expression with at least moderate to strong intensity[54].

Pathological differentiation of HPV-positive and HPV-negative disease is essential when prognosticating and counseling patients[50]. Some studies report pathologists suggesting a two-step diagnostic system, where screening is performed with immunohistochemistry, followed by in situ hybridization as a confirmatory test[50,55,56]. The National Comprehensive Cancer Network Cancer of the Oropharynx guideline state the p16 expression is highly correlated with HPV status, that several tests are available for use, including those listed above. These guidelines refer to testing recommendations published by the College of American Pathologists in 2018. As per the College of American Pathologists, there is a clear recommendation for testing by p16 immunohistochemistry staining for all oropharyngeal tissue analyzed, and they note that additional HPV-testing can be performed at the discretion of the pathologist or treating team[54].

Prognosis

HPV-associated OPSCC has a more favorable prognosis than HPV-unrelated disease[6,7]. The improved survival rate of HPV-associated OPSCC with standard treatments lead the American Joint Committee on Cancer (AJCC) to update the OPSCC staging system by separating HPV-positive and HPV-negative OPSCC into two distinct entities. In 2017, the eighth edition categorized oropharyngeal cancers by p16 status, the surrogate marker for HPV status, downstaging the p16 positive OPSCC from the prior edition[57].

Chapter 3: De-Escalation Strategies for Human Papillomavirus-Associated Oropharyngeal Squamous Cell Carcinoma—Where Are We Now? (Manuscript 1)

Jennifer A. Silver[1,2] , Sena Turkdogan[1,2], Catherine F. Roy[1,2], Thavakumar Subramaniam[1,2], Melissa Henry[2,3,4,5] and Nader Sadeghi[1,2,6]

1. Department of Otolaryngology—Head and Neck Surgery, McGill University Health Centre, Montreal, Quebec, Canada
2. Department of Otolaryngology—Head and Neck Surgery, McGill University, Montreal, Quebec, Canada
3. Gerald Bronfman Department of Oncology, McGill University, Montreal, Quebec, Canada
4. Lady-Davis Institute for Medical Research, Montreal, Quebec, Canada
5. Segal Cancer Centre, Jewish General Hospital, Montreal, Quebec, Canada
6. Research Institute of McGill University Health Center, McGill University, Montreal, Quebec, Canada

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Abstract:

The prevalence of oropharyngeal squamous cell carcinoma has been increasing in North America due to human papillomavirus-associated disease. It is molecularly distinct and differs from other head and neck cancers due to the young population and high survival rate. The treatment regimens currently in place cause significant long-term toxicities. Studies have transitioned from mortality-based outcomes to patient-reported outcomes assessing quality of life. There are many completed and ongoing trials investigating alternative therapy regimens or de-escalation strategies to minimize the negative secondary effects while maintaining overall survival and disease-free survival. The goal of this review is to discuss the most recent advancements within the field while summarizing and reviewing the available evidence.

Keywords:

oropharyngeal squamous cell carcinoma; human papillomavirus; de-escalation; transoral surgery

1. Introduction

Worldwide, there were 900,000 new diagnoses of head and neck cancers and 400,000 deaths from their cancers in 2020 [1]. In the United States, the overall incidence of head and neck cancers has been decreasing due to lower rates of tobacco consumption, however, not all subtypes are following this trend [2,3]. The prevalence of oropharyngeal squamous cell carcinoma (OPSCC) has been increasing in North America due to human papillomavirus (HPV)-associated disease [2]. Recent studies have found that approximately 60–70% of OPSCC cases in the United States are associated with HPV, in contrast to traditional tobacco- and alcohol-related OPSCC [2,4–9].

Patients with HPV-associated OPSCC are molecularly and clinically distinct as com- pared with those with conventional OPSCC. The etiology arises from the double-stranded DNA viruses E6 and E7 oncogenes that inactivate the p53 tumor suppressor gene and the retinoblastoma protein which lead to release of transcription factors causing cell cycle progression [10]. Patients with HPV-associated OPSCC are younger, healthier at baseline, often with minimal or no tobacco exposure, and have a more favorable prognosis with standard treatment, demonstrated in retrospective and prospective research [6,8,11]. The improved survival rate of HPV-associated OPSCC has resulted in important changes to the American Joint Committee on Cancer (AJCC) staging system. In 2017, the eighth edition categorized oropharyngeal cancers by p16 status, a surrogate marker for HPV status, downstaging the p16 positive OPSCC from the prior edition [12].

Historically, OPSCC treatments have primarily consisted of radiation-based therapies, which were favored over the invasive and often disfiguring open surgical approaches with high morbidity and mortality [13]. It has been shown that treatment intensification with concurrent chemoradiation (CRT) improves overall survival of head and neck cancer patients as compared with radiotherapy alone [14–17]. The first meta-analysis on this subject was performed in 2000 and was updated in 2009. The versions both concluded that concomitant CRT provided a five-year overall survival benefit as compared with locoregional treatment with radiotherapy alone at 4% and 4.5%, respectively. In analyses based on tumor subsite, they concluded that there was a

benefit for concurrent CRT for OPSCC. Blanchard et al. conducted another meta-analysis and concluded that OPSCC patients had a five-year survival benefit of 5.3% and that concomitant chemotherapy to locoregional treatment was the most efficacious timing of administration [14].

The standard treatment regimens for OPSCC patients currently consists of surgery with a preference for minimally invasive transoral surgery, radiation therapy (RT), and chemotherapy as either single modality or multimodality based on TNM staging. For stages I and II OPSCC, treatment often consists of surgery or RT, while stages III and IV OPSCC are often treated with concomitant CRT or surgery with adjuvant RT or CRT based on pathological features [18].

With a five-year survival rate greater than 80%, the younger and healthier patients in remission from HPV-associated OPSCC are living longer with post-treatment toxicities [8,19]. The three treatment modalities, i.e., radiation therapy, chemotherapy, and surgery, have specific benefits and both short-term and long-term side effects to consider.

1.1 Radiation

As described above, early stage OPSCC can be treated with single modality RT. More advanced cancers are treated with multimodality treatment which includes RT. Early complications include dermatitis of varying degrees, pain, mucositis, dysphagia, and infection. However, it is the late post-RT consequences that are often debilitating and affect quality of life in the decades after treatment. These are well described in the literature, and include xerostomia due to damage to the salivary glands, trismus from contraction and fibrosis of the masticator muscles, and less frequently osteoradionecrosis which may lead to infection, fracture and fistula formation, rare ischemic stroke, and second primary radiation- induced malignancy [20,21]. The radiation toxicities have been proven to be augmented in patients also receiving concurrent chemotherapy [8,22]. Efforts have been made to reduce RT-based adverse effects with newer technologies such as intensity-modulated radiotherapy (IMRT) or intensity-modulated proton therapy (IMPT), sparing swallowing and salivary gland structures, and lowering doses of RT with some success [23].

1.2 Chemotherapy

Chemotherapy can be administered as induction prior to definitive therapy, concomitantly with RT, or as an adjuvant systemic therapy. Neoadjuvant chemotherapy has potential benefits, including tailoring which definitive treatment to offer the patient if there is response to chemotherapy (radical surgery or concomitant CRT), facilitating organ preservation, providing systemic therapy for micro-metastases, and providing initial locoregional treatment while preparing for radiation [24–26].

Chemotherapy toxicity is mediated by anti-mitotic, cytotoxic, or photosensitizing properties, as well as their myelo- and immuno-suppressive effects. Haematologically, chemotherapy agents inducing neutropenia puts patients at risk of systemic infections caused by viral, bacterial, and fungal organisms, where chemotherapy-induced significant mucositis and stomatitis may be the site of entry [27]. Anemia and thrombocytopenia may additionally increase the risk of bleeding complications. In head and neck cancer of all sites, neoadjuvant chemotherapy followed by CRT has been shown to not have any added benefit for overall survival over concurrent CRT in the DeCIDE study [28]. However, a sub-analysis in this study showed a trend towards improved survival for patients with HPV-associated OPSCC. The neoadjuvant chemotherapy regimen used in the DeCIDE study included 5-florouracil (5-FU) along with docetaxel and cisplatin. Furthermore, the concomitant chemotherapy included docetaxel, hydroxyurea, and 5-FU, significantly adding to the intensity and toxicity of the treatment which was not warranted in HPV-associated OP- SCC. A common regimen for HPV-associated OPSCC is docetaxel and cisplatin, which is generally well tolerated [29]. Relatively recently, 5-fluorouracil has been eliminated in the chemotherapy regimen as it brought significant toxicity. Without it, there has been better patient tolerance while maintaining the oncological effect [29]. The significance of good oncological efficacy of chemotherapy has been demonstrated in studies by Sadeghi et al. where neoadjuvant chemotherapy was administered in HPV-associated OPSCC patients and demonstrated pathologic complete response in 72% and 57%, respectively, for the primary tumor and the cervical nodal disease [29,30].

1.3 Surgery

The great benefit of surgery is histopathological assessment of the tumor to guide further treatments. Analysis of the specimen can identify perineural invasion, extracapsular spread, angioinvasion, microscopic disease, and positive margins. Depending on the risk stratification, observation, adjuvant RT or adjuvant CRT may be recommended to the patient [31].

Surgical resection can be further divided into open or transoral approaches and have different advantages, risks, and long-term morbidities associated with them. Open surgical approaches include trans-mandibular and trans-pharyngeal routes and often require microvascular free flap reconstruction based on the defect size. A complication rate of 50% or more has been reported in the literature in open approaches [32,33]. Potential complications include damage to nerves and vessels, disfigurement, scarring, dysphagia and aspiration, speech articulation difficulties, trismus, and malocclusion. A tracheostomy is required in the vast majority of patients for airway protection, and time to decannulation and time to adequate oral intake is lengthened often requiring permanent or transitory tracheostomy and percutaneous gastrostomy feeding at home.

Transoral surgical techniques include both transoral laser microsurgery (TLM) and transoral robotic surgery (TORS). The limiting factors for transoral surgery are difficult exposure causing poor visualization of the primary tumor to obtain adequate margins; surgeon-dependent training and skills for these techniques; and availability or access to the necessary equipment, lasers, or robotic surgical systems. However, when possible, it is used in T1 and T2 tumors, and resections in difficult-to-reach areas such as the base of tongue and vallecula are now attainable [34,35]. Benefits include less functional disability and dysphagia, no cosmetic deformity, lower tracheostomy and percutaneous gastrostomy rates, and higher rates of decannulation when tracheostomy is necessary [36,37].

2. De-Escalation Strategies

With the rise of HPV-associated OPSCC and its lower mortality rates, younger and healthier patients in remission are living longer with the morbidities afflicted by their treatments. In Ang et al.'s publication of the RTOG 0129 trial, the prognosis of OPSCC patients was sub-analyzed

by HPV status [8]. Patients with HPV-associated disease had higher overall survival rates at three years (82.4% vs. 57.1%) and progression-free survival rates (73.7% vs. 43.4%). The HPV-associated cohort was less likely to smoke and had a lower cumulative pack-years of smoking exposure. This research identified cigarette use as an independent prognostic factor for both HPV-positive and -negative head and neck cancers, with a 1% increase in risk of death or relapse with each additional pack-year of smoking. A history of 10 pack-years has been identified as a cut-off point for impact on survival. Therefore, those with HPV-associated OPSCC without or with minimal tobacco history are considered to be low risk.

The oropharynx is an anatomical region essential for daily functions, such as speech and deglutition, as well as sensation and emotional expression. Different treatments can limit these activities of daily living and greatly affect quality of life. Maintaining or prioritizing functional quality of life can greatly improve a patient's outlook on their cancer diagnosis. Given the improved prognosis of HPV-associated OPSCC, studies have shifted from mortality-based outcomes to patient-reported outcomes assessing quality of life [31]. Therefore, the emphasis has been placed on identifying alternative therapy regimens or de-escalation strategies to minimize negative secondary effects while maintaining overall survival and disease-free survival. This review will explore different de-intensification studies and clinical trials that are seeking to improve the quality of life of post-treatment HPV-associated OPSCC patients without compromising survival (Table 1).

3. Upfront Surgery and Pathology-Based Adjuvant Therapy Approach

Since the advent of TORS, primarily indicated and approved for T1 and T2 oropharynx cancer, there has been a significant shift in the management of early OPSCC towards TORS and neck dissection. This has been followed by risk-based adjuvant RT or CRT based on pathology. The shift in treatment has been based on successful oncologic and swallowing outcomes based on case series [38,39].

ORATOR (NCT01590355 (accessed on 1 January 2022)) is a Canadian-based trial randomizing patients with AJCC 7th edition T1–2, N0–2 OPSCC to either upfront surgical resection via

TORS and neck dissection with risk-based adjuvant CRT (n = 34) or RT at 70 Gy with concurrent chemotherapy if node or margin positive (n = 34). High-dose cisplatin was used; however, patients received cetuximab or carboplatin regimens if not fit for high-dose cisplatin [40,41]. Eighty-eight percent of patients had HPV-associated OPSCC. In the surgical arm, 10 patients underwent primary surgery without adjuvant therapy, 16 patients received adjuvant RT (60 Gy), and 8 patients underwent adjuvant CRT (64 Gy RT and 5 cisplatin, 3 carboplatin). Among the 34 patients in the RT group, two withdrew from the study, 9 patients received RT alone, and 23 patients underwent concurrent CRT, with 4 patients requiring salvage surgery. The main endpoint studied was swallowing-related quality of life, as measured by the MD Anderson Dysphagia Inventory (MDADI) standardized questionnaire, with other quality of life scales used as well. Their initial results at a median follow-up of 27 months demonstrated a greater swallowing-associated quality of life in the RT group after one year, although this value was not clinically significant, as the threshold of a meaningful difference between groups must be a 10-point score discrepancy [40]. However, a recent update regarding long-term results at median follow-up time of 45 months published in January 2022 demonstrated that this difference between groups in swallowing quality of life decreases over time and the oncological outcomes are similar [41]. Overall, the main differences within the treatment arms are the distinct side-effect profiles. The RT arm patients have greater ototoxicity and neutropenia while the surgical group has greater pain, trismus, and bleeding. In the RT group, one patient required a percutaneous feeding tube at one year, but at two and three years had a total oral diet without restrictions. In the surgical arm, no patients needed a percutaneous feeding tube at one year, however, one patient who underwent post-operative CRT had a decline in swallowing capacity, and at 30 months post-treatment required insertion of a feeding tube. Recurrence rates were similar in each group, at four patients per treatment arm. The authors ultimately concluded that both are reasonable treatment options of T1–2, N0–2 OPSCC and should be discussed openly to allow the patient to weigh the risks and benefits of the different modalities [41]. ORATOR attempted to compare upfront surgery to radiation-based therapy, however, risk stratification and adjuvant treatment allocation lead to 47% of patients in this group requiring adjuvant RT and an additional 24% of patients to requiring CRT post-operatively. This surgery-first approach carries a high risk of post-operative adjuvant therapy, which leads to additional locoregional therapy instead of treatment de-escalation. In essence, patients in this trial were treated with a high rate

of adjuvant therapy (71% of patients), which does not allow for a simplified comparison of surgery versus RT.

This same group conducted ORATOR2 (NCT03210103 (accessed on 1 January 2022)), where they compared de-intensified treatments in early stage disease (T1–2, N0–2, HPV- associated OPSCC, AJCC 8th edition) [42]. Patients were risk-stratified by smoking status and randomized to primary transoral surgery and neck dissection and lowered dose adjuvant RT if needed ± chemotherapy or de-escalated RT at 60 Gy ± chemotherapy [43]. These two treatment arms are based on other trials that will be discussed in this review (*E3311* and *NRG HN002*). The primary endpoint was overall survival and secondary endpoints were progression-free survival, quality of life, and toxicity. 61 patients were recruited (31 in TORS and neck dissection arm and 30 in RT arm) before this trial was closed early due to treatment-related deaths in two patients (bleeding and osteomyelitis after RT, both in the surgical arm). Median follow-up was 17 months. The two-year overall survival estimates in the TORS group versus RT group for were 89.1% and 100% respectively. The two-year progression-free survival estimates were 83.5% and 100%, respectively. In terms of toxicities, 71% of the surgical group had grade II–V toxicities as compared with 67% of patients in the RT arm. Average MDADI scores one year post-treatment were similar between arms and no one required a feeding tube at one year. Overall, this trial demonstrated a mortality risk with the upfront surgery approach but demonstrated that this lowered dose of RT had both positive oncologic outcomes and toxicity profile. This data was drawn from a recently presented abstract as publication is pending.

4. Surgery and Adjuvant Low-Dose Radiotherapy Approach

There are a number of studies that have investigated the role of upfront surgery with de-escalation of adjuvant RT. Those that are completed and those ongoing are discussed further.

The MC1273 trial (NCT01932697 (accessed on 1 January 2022)) was a single-arm phase II trial investigating whether post-operative RT dose reduction, from 60–66 Gy to 30–36 Gy, administered with weekly docetaxel, could reduce toxicity while maintaining both quality of life and high rates of disease-free survival [44,45]. Patients included in this study had HPV-

associated OPSCC staged with the AJCC 7th edition as either stage III or IV with a smoking history of 10 pack-years or less. Those included underwent curative intent primary site surgical resection and neck dissection with negative margins and were subsequently stratified to one of two cohorts based on pathologic analysis. Group A had tumors with no extra-nodal extension (ENE) but had at least one other intermediate- risk factor (lymphovascular invasion (LVI), perineural invasion (PNI), involvement of ≥two regional lymph nodes, any lymph node > 3 cm in size, or ≥T3 primary tumor). Group B were ENE positive. The adjuvant therapy for group A (n = 37) consisted of 30 Gy RT and two cycles of docetaxel, while group B (n = 43) received 36 Gy RT and two cycles of docetaxel; 95% of the patients underwent transoral surgery and all completed their treatment plans. The average follow-up during this study was 35 months. In Group A, one patient had a distant recurrence at 12 months and Group B had nine patients with disease recurrence (three local, one regional, and five distant metastases to either lung or bone). The three patients with local recurrence all required revision margin excision intra-operatively after frozen sections were positive for disease. For the whole cohort, two-year distant metastasis-free survival was 94.9%, progression-free survival was 91.1%, and overall survival was 98.7% (the three deaths were secondary to cardiac or pulmonary causes, not due to their cancer). This study attempted to decrease the RT to a lower dose than other trials while using concurrent adjuvant docetaxel to make the effective dose higher, and still demonstrated locoregional control, progression-free survival, and overall survival rates similar to standard adjuvant therapy [46]. While Group B had a higher rate of negative disease outcomes (21% recurrence needing salvage), this was to be expected based on the ENE found in their disease. This study concluded that this aggressive RT de- intensification achieved similar results as historical controls. The toxicity of this treatment regimen was improved in early and late adverse events as compared with historical controls. Only one patient required percutaneous feeding supplementation which was removed one month post-treatment. Using patient reported outcome measures, pre-RT quality of life metrics were improved at one-year follow-up. It can be noted that intermediate-risk patients in this cohort, those with completely resected disease, between one to four positive lymph nodes, and without ENE, had a very good prognosis with this de-escalated regimen. Worse prognostic factors for progression were larger primary tumor size, greater than four positive lymph nodes, and ENE. These patients were at a greater risk of distant failures. One

hypothesis may be that these high-risk patients require systemic therapy escalation to aid in treatment of micro-metastases for possible distant recurrence.

The AVOID phase II trial (NCT02159703 (accessed on 1 January 2022)) assessed patients with resected pT1–2, pN1–3, M0 HPV-related OPSCC, staged with the AJCC 7th edition, with no primary site risk factors and withheld RT (IMRT or IMPT) to the primary site to improve the toxicity profile [47]. All patients (n = 60) underwent TORS with neck dissection and were included if there were clean surgical margins >2 mm, no PNI, and no LVI. RT was not given to the primary tumor site, and only the involved neck was treated with 60–66 Gy, and the uninvolved neck with 54 Gy. Patients with ENE (n = 13) were treated with adjuvant CRT (nine weekly low-dose cisplatin, two high-dose cisplatin, two cetuximab). In this 60-patient cohort with an average follow-up of 2.4 years, only one patient had primary site recurrence, one patient developed regional neck recurrence, and two patients later presented with distant metastases. The locoregional recurrence patients underwent salvage surgical resection. The two-year local control rate was 98.3% and the overall survival was 100%. No patients required long-term percutaneous feeding tubes, but two patients required post-treatment feeding tubes which were later removed. Two patients had soft tissue necrosis and they had higher RT dose to the primary site than those without soft tissue necrosis (45.8 Gy versus 36.6 Gy). This was treated conservatively in both, and one of the patients used hyperbaric oxygen therapy. With this technique, the average RT dose to the primary site was 36.9 Gy, which was significantly lower than post-operative standard 60–66 Gy. This cohort demonstrated a good safety profile for risk-stratified de-intensified postoperative RT that aimed to avoid the primary resected site.

E3311 (NCT01898494 (accessed on 1 January 2022)) is a multi-institutional phase II trial that assessed the feasibility of reducing the dose of adjuvant RT in patients who underwent transoral surgery [48]. Patients included had stage T1–2, N1–2b HPV-associated OPSCC, as per AJCC 7th edition, and underwent TORS or TLM. In total, 359 patients were assigned one of four adjuvant treatment arms based on their post-operative pathological risk. Group A consisted of low-risk patients (n = 38), including those with T1–2 disease with negative mar- gins >3 mm and N0–1 without ENE, and were given no adjuvant therapy. Group D patients were high-risk patients (n = 113) due to positive margins, >1 mm of ENE, or five or more positive lymph nodes,

and received post-operative chemoradiation therapy. The population of interest of this trial were the intermediate-risk patients (Group B and C). These patients were defined as T1–2 primary tumors with negative margins or margins < 3 mm, N1–2 with ≤1 mm ENE, or up to four positive lymph nodes. Post-operatively, this group was randomized to receive adjuvant RT at either a reduced dose of 50 Gy (group B, $n = 100$), or a standard dose of 60 Gy (group C, $n = 108$). After approximately 35 months of surveillance, there was no significant difference in progression-free survival between groups. Two-year progression-free survival was 96.9% for arm A, 94.9% for arm B (50 Gy), 96.0% for arm C (60 Gy), and 90.7% for arm D. There were 16 deaths in the patient cohort (one in A, two in B, six in C, and seven in D). The two-year overall survival was 100% for arm A, 99.0% for arm B, 98.1% for arm C, and 96.3% for arm D. This trial evaluated treatment-related toxicities and noted a significantly different rate of grade III to V treatment toxicities between arms B and C (14% versus 24%, $p = 0.03$). E3311 utilized 50 Gy as the de-escalated RT dosage, which is still above the dosage tolerated by salivary glands and would be unlikely to improve this adverse event. Deasy et al. reviewed the effect of dose volume on salivary gland function and determined that severe xerostomia can be avoided at lower doses than what patients received in this trial [20]. Specifically, they determined that ideal doses to parotid glands are less than 25 Gy if both parotid glands or less than 20 Gy in at least one of the parotid glands. Another study determined that 39 Gy was the threshold dose for submandibular glands, where gland function may improve gradually over the two years post-RT if this level was not surpassed [49]. A similar study reported the effect of RT on the parotid glands and identified a threshold level of 26 Gy [50]. While it was not a primary endpoint, functional outcomes measured with the MDADI and Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) for both intermediate-risk groups were similar in the E3311 study. This study concluded that a reduced dosage of adjuvant RT was an appropriate therapeutic option when pathological analysis identified intermediate-risk disease due to the progression-free survival, overall survival, and patient reported quality of life measures.

The SIRS phase II trial (NCT02072148 (accessed on 1 January 2022)) risk stratified HPV-associated OPSCC patients after pathological staging post-transoral surgery and neck dissection with AJCC 7th edition staging to receive different adjuvant treatments [51]. Low-risk patients were staged as pT1–2, pN0–2b, and were observed post-operatively. Intermediate-risk patients

were those staged as pT1–2, pN0–2b with negative margins, with LVI and/or PNI, ≤3 lymph nodes (LNs), and <1 mm ENE and received 50 Gy adjuvant IMRT. High-risk patients had significant adverse features (>3 LNs, supraclavicular LNs, contralateral LNs, positive surgical margins, >1 mm ENE, or matted LNs), and therefore, received concurrent cisplatin and 56 Gy RT. There were 75 patients enrolled with 21 withdrawals. Overall, 54 patients were evaluated but 1 patient did not complete RT and was excluded from analysis; 24 patients were in the surveillance group (low risk), 14 patients received RT alone (intermediate risk), and 15 patients received CRT (high risk). Median follow-up was 43 months. Progression-free survival probability was 91.3% for Group 1, 86.7% for Group 2, and 93.3% for Group 3. The Global MDADI QOL scores improved with time and returned to baseline scores. No patients required long-term gastrostomy tube feeding. This trial demonstrated positive outcomes following post-operative risk stratification-based adjuvant treatment allocation in HPV-related OPSCC patients.

Trials without Published Results

The PATHOS trial (NCT02215265 (accessed on 1 January 2022)) is similar to E3311, where T1–3, N0–2b, and M0 HPV-related OPSCC patients undergo minimally invasive transoral surgery and neck dissection with risk stratification based on pathological fac- tors [48,52]. Low-risk patients are observed, intermediate-risk patients are randomized to 50 or 60 Gy RT (just as in E3311), and high-risk patients are randomized to adjuvant 60 Gy RT or 60 Gy RT with concurrent cisplatin.

The ADEPT phase III trial (NCT01687413 (accessed on 1 January 2022)) included T1–4a HPV-related OPSCC who underwent transoral surgery and neck dissection. Patients that were found to be ENE positive on pathological analysis were randomized to 60 Gy IMRT alone or with concurrent weekly cisplatin. The study was terminated due to funding issues and slow accrual in 2020 without publication but preliminary results are available on clinicaltrials.gov.

The Minimalist (MINT) trial (NCT03621696 (accessed on 1 January 2022)) is a phase II study of stage I–III resectable HPV-related OPSCC, staged with the AJCC 8th edition, in which patients undergo transoral surgery and neck dissection with adjuvant therapy determined by

pathological risk. Low-risk patients receive 42 Gy RT, intermediate-risk patients receive 42 Gy RT and one dose of cisplatin, and high-risk patients undergo 60 Gy RT with concurrent cisplatin. There are no published results, but preliminary data are available on clinicaltrials.gov (accessed on 1 January 2022).

DART-HPV (NCT02908477 (accessed on 1 January 2022)) is a follow-up study from MC1273 where patients with resectable T1–3, N0–3, M0 HPV-associated OPSCC are randomized to standard CRT (60 Gy with concurrent cisplatin) versus 30–36 Gy with concurrent docetaxel, the regimen proposed from MC1273.

ADAPT (NCT03875716 (accessed on 1 January 2022)), the phase II trial, utilizes pathologic analysis post transoral surgery and neck dissection to plan adjuvant therapy. Low-risk patients are observed, intermediate-risk patients receive reduced dose RT (46 Gy), and high-risk patients receive adjuvant standard dose RT (60 Gy) without chemotherapy.

The DELPHI phase I trial (NCT03396718 (accessed on 1 January 2022)) includes patients with OPSCC who underwent primary site surgery and neck dissection with indications for adjuvant therapy. Patients with HPV-associated OPSCC are given one of three options of RT dosage with or without chemotherapy as needed and as determined by tumor board discussion and pathological analysis. The three RT dosage options are standard (60/66 Gy), reduced level 1 (54/59.4 Gy), and reduced level II (48.8/55 Gy). Patients with high-risk features were differentiated from those with intermediate-risk characteristics and were treated with the higher dose RT and concurrent chemotherapy.

NCT03729518 (accessed on 1 January 2022) is a phase II study from the Abramson Cancer Center of the University of Pennsylvania currently recruiting patients with pT0–3, N0–2b, M0 HPV-associated OPSCC, staged with the AJCC 7th edition, who have undergone TORS primary site resection and ipsilateral neck dissection. These patients will receive reduced-dose RT (IMRT or IMPT at 50 Gy to ipsilateral high risk neck and 45 Gy to contralateral side). Patients will receive adjuvant chemotherapy as well if criteria are met.

NCT02784288 (accessed on 1 January 2022), a phase II trial from the University of Michigan Rogel Cancer Center, recruited 34 patients who have potentially resectable T1–3, N0–2c, M0 HPV-related OPSCC [53]. The patients underwent up-front neck dissection and used the neck lymphadenopathy pathology results to guide treatment: low-risk patients (single lymph node < 6 cm, no ENE, no PNI, no LVI), will undergo transoral surgery of the primary cancer; intermediate-risk patients (≥2 LNs, without adverse features or a single node with LVI or PNI) will undergo RT; and high-risk patients (ENE positive) will complete transoral surgery and chemoradiation. While not yet fully published, this group explained their preliminary methodology in a parallel study within this same cohort. The preliminary clinical trial methodology is described in their publication on their goal of quantifying the circulating tumor DNA (HPV ctDNA) from plasma in HPV-associated OPSCC patients. This HPV ctDNA will be analyzed within this cohort to assess clearance of HPV ctDNA post-treatment and follow ctDNA for recurrence.

5. Altered Regimen of Chemoradiotherapy Approach

Concurrent CRT is the current standard of care, but is associated with significant side effects. There are studies completed and ongoing that have discussed de-intensifying the chemotherapy and/or the radiation regimen to decrease toxic effects. These are discussed below.

The NRG HN002 (NCT02254278 (accessed on 1 January 2022)) phase II trial included patients with T1–2 N1–2b M0, or T3 N0–2b M0 HPV-associated OPSCC (staging with AJCC 7th edition) and assigned them to concurrent 60 Gy IMRT (over 6 weeks) with cisplatin versus 60 Gy (over 5 weeks) alone [54]. This study of reduced IMRT dosage enrolled 306 patients, 157 patients were randomly assigned to concurrent chemoradiotherapy and 149 patients to IMRT alone group. The primary endpoint was progression-free survival at two years and swallowing quality of life at one-year via the MDADI patient reported outcome measure. Overall, seven patients did not complete the IMRT doses as per the assigned protocol (five patients refused, two received alternative therapy). In the cohort as- signed to receive concurrent chemotherapy, five patients did not receive any and 45 patients terminated the regimen early. The median follow-up was 2.6 years, and 292 patients were followed for at least two years. The estimated two-year

locoregional failure rates were 3.3% and 9.5% in the concurrent versus IMRT alone group, with a significant difference between arms. The overall-survival rates at two years were similar, 96.7% for the CRT group versus 97.3% for the IMRT group. The combination therapy group had higher rates of acute adverse events, however, the MDADI scores at one year were not significantly different from baseline ($p = 0.78$). The IMRT-alone group did not meet acceptability criteria as the progression-free survival rate was just 87.6%. For the chemoradiotherapy cohort, the two-year progression-free survival met acceptability criteria at 90.5%. This treatment arm met the predefined endpoints allowing development into a phase III trial.

NCT00606294 (accessed on 1 January 2022) is a pilot study from the Memorial Sloan Kettering attempting to de-escalate RT in concurrent CRT treatment for patients with T1–2, N1–2b (AJCC 7th edition) with HPV-related OPSCC after assessment of tumor hypoxia with fluorine-18-labeled fluoromisonidazole PET (18F-FMISO PET) [55]. It has previously been demonstrated that hypoxia mediates radiation resistance and is a negative prognostic factor for malignancies [56]. Therefore, in patients with no hypoxia on this nuclear imaging, treatment would consist of chemotherapy and de-intensification of RT to 30 Gy. Patients first underwent primary tumor resection and patients were included even if there were positive margins. Two to four weeks post-operatively, they had a fluorodeoxyglucose PET or computed tomography-based simulation for planning of RT, as well as the 18F- FMISO PET to evaluate pretreatment hypoxia status. Those without hypoxia initially or on pretreatment scanning would receive 30 Gy RT, with two cycles of cisplatin. If there was hypoxia on this first scan, patients were re-assessed approximately one week after starting chemotherapy to determine if there was an intra-treatment change and a possibility for RT dose de-escalation down to 30 Gy. The patients with persistent hypoxia on intra- treatment 18F-FMISO PET were treated with 70 Gy and two cycles of cisplatin. Patients underwent weekly MRIs post-treatment, and neck dissection at four months after CRT to assess pathological response. There were 18 patients who were included and analyzed in this study. Within this cohort, 6 patients had no evidence of hypoxia and 12 patients had pretreatment hypoxia. These six patients received 30 Gy RT with cisplatin. The 12 patients with hypoxia started the RT and cisplatin and at the intra-treatment scan follow up, nine patients had no further evidence of hypoxia. Therefore, these nine patients also received 30 Gy RT and

cisplatin, however, one of the fifteen patients only received one dose of cisplatin. The median follow-up was 34 months. Eleven of these 15 patients had a complete pathological response on post-treatment neck dissection, two patients had minimal foci of residual disease with uncertain viability (without further treatment), and one patient had clinically significant residual disease with tumor regrowth seen on post-treatment MRI. The patient who did not receive his second cycle of cisplatin developed progressive locoregional disease. There were no grade III radiation-related toxicities observed in the de-escalated group. Two-year locoregional control, progression-free survival, and overall survival for the de-escalated cohort per protocol were 100%, 92.9%, and 92.9%, respectively. This pilot study has concluded that using hypoxia as a marker for radiosensitivity and de-escalation using this data is safe in HPV-related OPSCC. NCT03323463 is a phase II clinical trial currently recruiting patients within the same research group to assess this protocol without mandatory post-CRT neck dissection.

LCCC1120 (NCT01530997 (accessed on 1 January 2022)) is a completed phase II trial of patients with T0–3, N0–2c, M0 HPV-associated OPSCC (7th edition) who underwent concurrent CRT at de-escalated doses [57]. Patients received a six-week course of IMRT at 60 Gy with six weekly low doses of cisplatin (30 mg/m2), as opposed to standard 70 Gy and three cycles of high-dose cisplatin (100 mg/m2). Clinical and radiologic responses were assessed post-completion of CRT. If there was a complete clinical response at the primary site, patients underwent evaluation under anesthesia and primary site directed biopsies. In cases of partial primary site response post-CRT, transoral surgery was performed to resect the remaining disease. Finally, any non-N0 patient on clinical or radiologic exam underwent selective neck dissection (SND), to remove at least all previously involved nodal levels [58]. The primary endpoint of this trial was pathologic complete response (CR), using the benchmark value of 87% locoregional control as this is the quoted three-year locoregional control rate with standard dosing CRT [8]. There were 45 patients recruited and 43 patients completed the planned protocol and were included in the analysis. At a median 14-month follow-up from onset of treatment, there was no measurable tumor present on physical and radiologic examination in 64% of the patients. Post-operatively, the pathological CR rate was 86% (37/43). There were 17 patients who required a feeding tube for an average of 15 weeks, but no patient required long-term supplemental feeding. This was a great improvement as compared with the PARADIGM study, where 85% of head and

neck cancer patients receiving two cycles of high-dose cisplatin and 72 Gy RT required feeding tube placement [59]. In 2018, this group published updated results of their cohort after a median 36-month follow-up, reporting a three-year locoregional control, distant metastasis-free survival, and overall survival rates were 100%, 100%, and 95%, respectively [60]. The six patients with incomplete pathological response were all alive with no evidence of disease. At three years post-treatment, this cohort's global quality of life returned to baseline and patients did not suffer from significant swallowing dysfunction. This favorable toxicity profile even noted a continued improvement of the acute onset xerostomia that peaked in patients at around six to eight weeks. This group has been working towards identifying the optimal CRT de-escalation regimen, and therefore moved, forward with LCCC1413.

LCCC1413 (NCT02281955 (accessed on 1 January 2022)) is a follow-up to NCT01530997 (study above) and utilized the same inclusion criteria [61]. The same de-escalated treatments were used but the protocol did not necessitate post-treatment surgical evaluation. Instead, they used positron emission tomography-computed tomography (PET-CT) to assess need for surgical evaluation. All patients received 60 Gy IMRT (n = 114), 80% of the patients staged to receive chemotherapy completed at least four cycles of cisplatin, and 11% of patients received cetuximab upfront due to contraindications to cisplatin. The median follow-up was 31 months and 81% of patients were followed for at least two years. The post- treatment complete response on PET-CT was 93% (n = 8 residual disease) at the primary site and 80% in the neck. Of the eight patients with residual disease at the primary site on imaging, six patients were observed with no local recurrence at two years, two patients were biopsied, and one patient had local persistent disease and died. Of eleven patients who had a neck dissection for residual neck disease, four patients had pathological residual disease. All are alive and with no evidence of disease at follow-up. One patient died of neutropenic sepsis. Two-year locoregional control, progression-free survival, and overall survival were as follows: 95%, 86%, and 95%, respectively. Additionally, 38 of 113 patients required a feeding tube for a median duration of 10.5 weeks, but none were permanent. Patient-reported outcome measures demonstrated decreases in quality of life and a higher symptom burden after completion of treatment, but all returned to baseline after 6 months.

Trials without Published Results

LCCC1612 (NCT03077243 (accessed on 1 January 2022)) is a follow-up study to LCCC1120 and LCCC1413 after learning that the de-escalation regimen is efficacious in these two studies (6-week course of IMRT at 60 Gy with 6 weekly low doses of cisplatin (30 mg/m2), Within this trial, they will identify smoking history and p53 mutational status. Patients with a significant smoking history who are wild-type p53 will be de-escalated, however, those with mutated p53 will not receive the de-escalated therapy. The goal of this trial is to identify who can safely be de-escalated.

NCT01088802 (accessed on 1 January 2022) is a phase II clinical trial from the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins consisting of HPV-associated T1–3, N0–2c, M0 OPSCC reducing IMRT dosage from 70 Gy to 63 Gy with concurrent cisplatin therapy.

EVADER (NCT03822897 (accessed on 1 January 2022)) is a phase II clinical trial of HPV-associated OPSCC AJCC 8th edition T1–3, N0–1 investigating an experimental RT with altered RT volume for the neck. This study is assessing whether omitting RT from specific low-risk lymph node areas is safe and efficacious. The two groups will both receive experimental RT, but one will also have standard cisplatin chemotherapy while the other will not.

6. Targeted Therapy with EGFR Inhibitor versus Cisplatin Approach

The trials that have investigated targeted therapy with the monoclonal anti-EGFR antibody cetuximab as a potential replacement to standard cisplatin-based chemotherapy are discussed below.

RTOG1016 (NCT01302834 (accessed on 1 January 2022)) was a phase III randomized, prospective clinical trial exclusive to patients diagnosed with T1–2, N2a–3 or T3–4, N0–3 HPV-positive OPC (AJCC 7th edition staging) investigating whether replacing cisplatin with cetuximab would maintain high efficacy and reduce toxicities [62]. Cetuximab, an epidermal growth factor receptor inhibitor, was proposed as previous studies comparing IMRT alone with

IMRT and cetuximab in patients with locally advanced head and neck cancer had improved control and mortality rates without greater toxicity burden [63]. All patients in the RTOG1016 trial received standard 70 Gy IMRT over six weeks and were randomized to weekly cetuximab (n = 399) or two cycles of high-dose cisplatin on Days 1 and 22 of radiotherapy (n = 406). The median follow-up was 4.5 years and there were 133 deaths recorded; 78 and 55 patients died in the cetuximab and cisplatin groups, respectively. The rate of grade III–IV acute adverse events was similar between the two groups, but the side effect profiles were different with rash being more common with cetuximab and myelosuppression, kidney injury, and hearing impairment occurring more commonly with cisplatin. Progression-free survival was significantly decreased in the cetuximab group (67.3 vs. 78.4%, p = 0.0002). Most importantly, when assessing the cohort for overall survival outcomes, radiotherapy and cetuximab did not meet the criteria for non-inferiority as compared with cisplatin. Therefore, cetuximab is not an appropriate substitute for cisplatin for patients with HPV-related OPSCC.

The De-ESCALaTE HPV trial (NCT01874171 (accessed on 1 January 2022)) was another phase III clinical trial that compared cetuximab to cisplatin chemotherapy in patients with T3–4, N0 or T1–4, N1–3 HPV-related OPSCC staged with AJCC 7th edition [64]. Patients received 70 Gy radiotherapy and were randomized to concurrent seven weekly doses of cetuximab (n = 152) or three cycles of high-dose cisplatin on Days 1, 22, and 43 of radiotherapy (n = 152). The results were similar to ROTG1016 where the overall mean number of toxicity events was similar between the two cohorts. However, there was a significant difference in two-year overall survival of 97.5% for cisplatin versus 89.4% for cetuximab, p = 0·001, and two-year recurrence rate of 6.0% for cisplatin versus 16.1% for cetuximab, p = 0·0007. Therefore, this study also concluded that cetuximab is inferior to cisplatin and should not be used in these patients.

TROG12.01 (NCT01855451 (accessed on 1 January 2022)) investigated cetuximab to weekly cisplatin chemotherapy [65]. Using the AJCC 7th edition, patients with HPV- associated OPSCC stage III (except T1–2, N1) or stage IV (except T3, N3, or M1) with less than 10 pack-year smoking history, or if greater than 10 pack-year smoking exposure must be N0–2a were included. Patients received standard-dose 70 Gy RT and were randomized to receive concurrent cetuximab (n = 90) or weekly cisplatin (n = 92). The symptom severity was similar between the

two groups. However, the three-year failure-free survival rates were 80% in the cetuximab arm and 93% in the cisplatin group (hazard ratio 3, p = 0.015). Therefore, cisplatin remains superior to cetuximab as the standard of care in non-surgical management of this disease.

Trial without Published Results

NRG HN005 (NCT03952585 (accessed on 1 January 2022)) is a phase II/III trial of T1–2, N1, M0, or T3, N0–1, M0 HPV-associated OPSCC (AJCC 8th edition). Patients are randomized to one of three arms: (1) concurrent CRT with two cycles of cisplatin and 70 Gy IMRT, (2) two cycles of cisplatin with concurrent 60 Gy IMRT, or (3) two cycles of cisplatin 60 Gy IMRT with the addition of nivolumab. Patients can receive IMRT or image-guided radiotherapy. This study is assessing whether reduced dose RT with nivolumab is as efficacious as standard dose radiation therapy and cisplatin in this cohort.

7. Neoadjuvant Chemotherapy with Consolidation Surgery Approach

The NeCTORS (NCT02760667 (accessed on 1 January 2022)) phase II clinical trial utilized neoadjuvant chemotherapy and TORS to de-escalate the treatment of stage III and IVa (AJCC-7) HPV-associated OPSCC, reserving radiotherapy for salvage. It was based on the efficacy of the approach shown previously [29,30,66]. The neoadjuvant chemotherapy approach has been shown to be highly effective to downstage the cancer and decrease the tumoral burden in the neck and the primary site to allow definitive surgical consolidation of treatment with negative margins without adjuvant RT/CRT. It also has the added benefit of providing systemic treatment to prevent metastatic spread of disease, which is a concern in patients with advanced neck disease and accounts for half of the mortalities despite locoregional control with standard CRT. The approach combines systemic escalation with more radical locoregional de-escalation on the premise that most of the late toxicity of the treatment of OPC comes from locoregional adverse therapy effects. The surgical margin of the primary tumor is immediately outside the pre-chemotherapy tumor margin. Mucosal margins of the primary tumor are tattooed, when it extends outside of the tonsillar fossa or base of tongue (BOT), before starting chemotherapy in order to map out the subsequent surgical resection. Patients undergo three cycles of neoadjuvant

chemotherapy with cisplatin and docetaxel, and then TORS with SND is performed. The SND is unilateral for tonsillar fossa cancers, unless they extend into the BOT or the soft palate beyond 1 cm. This trial aimed to avoid RT to the head and neck altogether, which is thought to be the main driver of post-treatment morbidity in OPSCC patients. In a prior case series based on NeCTORS, a cohort of 55 patients (T1–2, N1–2c, T3N0–2c, with any number of nodes, AJCC 7th edition) were compared to a propensity T and N-matched cohort from a historical control of 142 patients who underwent concurrent CRT. In the NeCTORS group only 2/55 patients required adjuvant CRT due to unresectable positive margins following TORS, and none required salvage RT for recurrence. The five-year disease-free survival was 96.1% in trial participants and 67.6% in the historical CRT controls. There were seven (12.7%) severe toxicity events without permanent sequelae in the neoadjuvant chemotherapy and surgery group as compared with 35 (24.6%) events in the control group. While a nasogastric feeding tube was inserted for immediate post-operative nutritional support for a median duration of six days, no patients required gastrostomy tube placement in the NeCTORS group, as opposed to 24.5% of the control group who remained gastrostomy tube dependent at 12 months post-treatment. Distant metastases are the main reason for failure of HPV- associated OPSCC post-treatment [67,68]. Given the proven efficacy of the neoadjuvant chemotherapy and no patient developing distant metastases in prior studies, it is believed that this is an effective method against undetectable possible micro-metastases [30]. The aim of this trial was to change the customary treatment from radiation-based, to surgery-based approaches in hopes of limiting chronic RT-based adverse events. RT was reserved for pathologic adverse findings including >three nodes with persistent tumor, ENE > 2 mm, positive margins, as salvage for recurrences, and for management of second primaries.

8. Neoadjuvant Chemotherapy and Low-Dose Radiotherapy Approach

The next studies investigate induction chemotherapy and low-dose adjuvant RT. These completed studies are described below.

The E1308 (NCT01084083 (accessed on 1 January 2022)) phase II clinical trial aimed to study neoadjuvant chemotherapy and reduced-dose IMRT with cetuximab in stage III and IV HPV-associated OPSCC (7th edition staging) [69]. Enrolled patients (n = 80) underwent induction

chemotherapy with three cycles of cisplatin, paclitaxel, and loading dose followed by weekly cetuximab and concurrent IMRT. Radiological (CT or MRI) and clinical reassessment was performed within 14 days of induction chemotherapy. In cases of complete response, patients were treated with reduced-dose IMRT (54 Gy in 27 fractions), while cases of partial or no response received a standard 69 Gy in 33 fractions. Fifty-six (70%) of the enrolled patients had a complete clinical response, and 51 patients underwent reduced-dose IMRT and weekly cetuximab (five protocol deviations treated with 69 Gy); 18 patients had incomplete response to induction chemotherapy, 10 patients proceeded with 69 Gy IMRT, and 8 patients with protocol deviations were treated with 54 Gy. With regards to grade III toxicity, the cohort receiving 54 Gy of RT and concurrent cetuximab, and the most frequent adverse events experienced were mucositis (30%) and dysphagia (15%). In the 69 Gy RT arm, there were higher rates of these same adverse events, with 47% of the patients suffering from mucositis and 29% of the patients having dysphagia. The two-year progression-free survival and overall survival for the 51 patients with complete clinical response receiving 54 Gy RT was 80% and 94%, respectively. All patients with treatment failures within two years had a greater than 10 pack-year smoking history. In a post-hoc analysis including only those with ≤10 pack-year smoking history, <T4, and <N2c, the two-year progression-free survival and overall survival increased to 96% and 96%, respectively.

The Quarterback trial (NCT01706939 (accessed on 1 January 2022)) was a phase III clinical trial of HPV-related stage III or IV OSPCC without distant metastases, staged with the 7th edition [70]. Patients (n = 22) received three cycles of docetaxel, cisplatin, and fluorouracil. Patients were evaluated post-induction chemotherapy and if there was partial or complete response, they were randomized to standard CRT (n = 8, 70 Gy) or reduced CRT (n = 12, 56 Gy), with carboplatin. The goal of the RT regimen is to lower the mean dose to the parotids to under 26 Gy and under 50 Gy to the pharyngeal constrictors, when possible. When evaluating the primary site of the whole cohort after induction chemotherapy, 16 patients had complete responses and four patients had partial responses. At the nodal basin, 16 patients had complete responses, three patients had partial responses, and one patients was unable to be evaluated. After CRT, all patients had primary site complete clinical and radiologic responses, and 19/20 had neck complete responses. The one remaining patient underwent a salvage neck dissection for residual disease. The median follow-up period was 56 months. The three-year progression-free and

overall survival rates were 87.5% for standard CRT (7/8) and 83.3% for reduced CRT (10/12 patients) (same rates for both endpoints). Non-inferiority of reduced CRT dosages could not be demonstrated given the limited number of enrolled participants. However, it should be noted that there was clinical response in all participants and all treatment failures were within four months of treatment completion, with no further recurrences in long-term follow-up. The Quarterback II trial (NCT02945631 (accessed on 1 January 2022)) is a follow-up trial to the aforementioned study, also testing RT dose reduction (56 Gy) after induction chemotherapy (docetaxel, cisplatin, 5-fluorouracil) and is currently recruiting.

The OPTIMA trial (NCT02258659 (accessed on 1 January 2022)) was a phase II clinical trial of patients with HPV-associated T1–4, N2–3, M0, or T3–4, any N, M0 OPSCC (AJCC 7th edition). Enrolled patients were first risk stratified based on baseline characteristics as low-risk patients (≤T3, ≤N2B, ≤10 pack-year smoking history) or high-risk patients (T4 or ≥N2C or >10 pack-year smoking history), and all were treated with induction chemotherapy (three cycles of carboplatin and nab-paclitaxel) [71]. Baseline risk status and response to induction chemotherapy then guided therapy: (1) low-risk patients with >50% response received 50 Gy RT alone (RT50), (2) low-risk patients with 30–50% response and high-risk patients with >50% response received 45 Gy CRT (CRT45), and (3) patients with lesser response received standard-of-care 75 Gy CRT (CRT75). Given the significantly reduced RT/CRT doses in the experimental arms, patients underwent surgical evaluation four to six weeks post completion of RT/CRT via modified/selective ND and possible biopsy/excision of the primary as deemed appropriate by the surgeon for pathologic confirmation of response. There were 62 patients enrolled and there was a median follow- up of 29 months. There were 28 low-risk and 34 were high-risk patients. The response rate following induction chemotherapy for the whole cohort was 89%, with 71% of the patients experiencing greater than 50% tumor size reduction. In the low-risk cohort, 20/28 patients received RT50, 6/28 patients received CRT45, and 2/28 patients received CRT75. In the high-risk group, 24/34 patients received CRT45, 9/34 patients received CRT75, and one patient transferred care. The pathological complete response rate for all patients (n = 52, 19 RT50, 28 CRT45, and 5 CRT75) in whom post-treatment surgery was performed as per protocol was 90% (47/52): 92% (43/47) for patients receiving de-escalated treatment arms and 80% (4/5) for the poor responders treated with standard CRT. Two-year progression- free survival and overall

survival rates were 95% and 100% for low-risk patients, and 94% and 97% for high-risk patients, respectively. PEG-tube requirement at 12 months post- treatment were 0/28 in the low-risk group of patients and 2/34 in the high-risk patients. This trial concluded that there is a good pathological and toxicity-related result to induction chemotherapy and risk-stratification modifications of adjuvant RT or CRT.

OPTIMA-II (NCT03107182 (accessed on 1 January 2022)) is a follow-up phase II trial for HPV-positive OPSCC aiming to determine radiologic response to induction chemotherapy and additional induction nivolumab. Patients will receive induction carboplatin, nab- paclitaxel, and nivolumab. Treatment groups will be stratified based on staging and pathological features, as well as volume reduction from the induction chemotherapy. Options include TORS or radiation with or without chemotherapy. OPTIMA-II utilizes the same risk stratification regime as the OPTIMA trial, but low-risk patients with >50% response will be offered either TORS and SND as a definitive treatment if technically feasible with adjuvant radiation for adverse pathologic features, or the same 50 Gy RT as in the above study. Low- risk patients with a tumor volume response between 30 and 50% or high-risk patients with >50% reduction will receive de-intensified chemoradiation (intermediate dose of 50 Gy). Low-risk patients with <30% reduction or high-risk disease with <50% reduction or any patients with progressive disease during induction chemotherapy will undergo standard chemoradiotherapy with 70–75 Gy and concurrent cisplatin or paclitaxel, 5-fluorouracil, and hydroxyurea. Adjuvant nivolumab will be offered to all patients for 6 months post completion of definitive therapy. This study is ongoing with no results available thus far.

The CCRO-022 (NCT02048020/NCT01716195 (accessed on 1 January 2022)) phase II multicentric trial included stage III or IV HPV-associated OPSCC [72]. Patients underwent induction chemotherapy of two cycles of paclitaxel and carboplatin and further chemotherapy and IMRT regimens were determined by the response [72]. Those with no response (n = 20) were treated with 60 Gy adjuvant IMRT, while those with partial or complete response (n = 24) were treated with 54 Gy. The primary objective of the study was to estimate the two-year progression-free survival. Three (7%) of 44 patients developed local-regional failure, two of whom had received 60 Gy. One patient within the 60 Gy group developed distant metastasis and

underwent further systemic therapy and their disease remained stable at the time of publication. Overall, this study yielded survival results similar to historical controls treated with standard CRT as the two-year progression-free survival rate was 92%. There was also found to be a reduction in long-term side effects with the lower dose RT using standardized patient reported outcome measures.

9. Discussion

As evidenced by this review, the management of HPV-associated OPSCC is a topic of great interest given the favorable survival outcomes and the need to personalize the treatment and improve the patient-reported quality of life and functional outcomes. Various treatment de-escalation approaches have been suggested to achieve optimal oncologic outcomes while minimizing treatment-associated morbidity. These include surgery and risk-based adjuvant treatment de-escalation, altered regimen CRT, neoadjuvant chemotherapy with surgical consolidation, and neoadjuvant chemotherapy with risk-based RT consolidation.
Trials exploring upfront surgery and employing pathology-based de-intensification, perhaps provide improved risk stratification and patient candidacy for de-escalated adjuvant treatment regimens. The largest study was E3311, where 359 patients were enrolled, and 113 patients had adjuvant CRT due to multiple positive lymph nodes or ENE. Almost a third (31%) of the enrolled participants having had upfront surgery required adjuvant CRT, thereby, received tri-modality therapy [48]. The major advantage of this approach was within the intermediate-risk category, which included those with two to four positive lymph nodes without ENE. In this cohort of 206 patients, it was determined that there was no difference in oncological outcomes and patients were subsequently treated with 50 Gy RT instead of 60 Gy. While this de-escalation is significant for post-treatment morbidity, 50 Gy is well beyond the salivary gland tolerance for RT and may lead to significant toxic- ity [20]. However, the results from the subsequent MC1273 trial described in the manuscript suggest upfront surgery with concurrent CRT may allow major RT dose de-escalation to 30–36 Gy [44]. While these patients would nonetheless receive tri-modality therapy, the reduced-dose adjuvant RT is more likely to spare salivary gland function.

The role of pathological ENE as a prognostic factor in HPV-associated OPSCC remains somewhat controversial. Indeed, in the updated AJCC 8th edition staging manual of HPV-related OPSCC, the pathological staging of lymphadenopathy, now, only relies on the number of positive lymph nodes, with no inclusion of ENE, nodal size, or laterality. However, concern has been raised within the head and neck oncology community that ENE may, in fact, impact survival and should continue to be a prognosticator for HPV- related OPSCC. A review of the National Cancer Database (NCDB) from 2010 to 2012 included 1043 patients with HPV-related OPSCC and examined the impact of ENE. ENE- positive patients had a worse three-year overall survival as compared with patients without ENE (89.3% vs. 93.6%, $p = 0.01$) [73]. In the ENE-positive cohort from this study, those receiving adjuvant concurrent CRT versus adjuvant RT alone did not have a difference in three-year overall survival (89.6% vs. 89.3%, $p = 0.55$). Therefore, it appears the addition of chemotherapy has a limited role in patients with ENE. A similar study revealed consistent results when analyzing the NCDB from 2010 to 2014. This study included 3745 patients with primary HPV-related OPSCC and 41% of node-positive cases demonstrated ENE [74]. ENE was more commonly found in pN2 (69.4%) disease as compared with pN1 (35.5%) and four-year overall survival was 92% in the ENE-negative patients, while just 85% in the ENE-positive cases ($p < 0.001$). These results remained significant when stratifying by nodal stage. Further research using this same database and expanding the population cohort to 2015 noted that ENE-negative patients had a higher five-year survival than ENE-positive patients (92.6% vs. 84.0%) and ENE-positivity was associated with a 1.90 hazard ratio of death [75]. Another study using the NCDB determined that ENE was a negative prognostic factor in both HPV-related and unrelated OPSCC, although with a worse overall survival in HPV-negative disease [76]. The upfront surgery approach allows pathologic identification of ENE and, as such, may allow better risk-based stratification to assess patient candidacy for de-escalation adjuvant regimens. Indeed, in patients with pathologic ENE, standard treatment should be favored over de-escalation, owing to the demonstrated 4–8% increased five-year mortality even with standard doses/volumes.

Our modern definitive CRT regimens have certainly greatly evolved in recent years. Docetaxel, cisplatin, and 5-fluorouracil have been used concomitantly with good results [77]. However, the use of 5-fluorouracil has been questioned given its additional toxicity pro- file. Indeed, in a

retrospective study of patients undergoing chemotherapy for locally advanced head and neck cancer as compared with carboplatin plus 5-fluorouracil to cis- platin, tolerance was assessed by the percentage of patients completing the three cycles of chemotherapy. It was found that only 60.2% of patients receiving carboplatin with 5-fluorouracil completed three cycles, in contrast to 76.7% of patients treated with cisplatin. Therefore, head and neck oncologists have since largely abandoned routine triple agent chemotherapy [78]. There are many trials investigating CRT dose or volume de-escalation. NRG HN002 is a well-known study where positive findings have concluded that the RT dose in CRT could be lowered to 60 Gy from 70 Gy, while maintaining efficacy [54]. This study also demonstrated that the results were dependent on the concomitant chemotherapy, as the RT alone group did not meet the minimum progression-free survival 90% threshold for acceptability. While there is benefit from decreasing the RT dose by 10 Gy, it remains above the threshold of salivary gland tolerance, as previously mentioned [20]. It should be noted that this study was limited as it excluded radiographically matted lymph nodes, a common finding in OPSCC. In the Memorial Sloan Kettering approach employing functional imaging to assess hypoxia, the patients receiving significant RT dose de-escalation down to 30 Gy with concurrent cisplatin demonstrating excellent survival results [55]. Using hypoxia as a marker for radiosensitivity proved a promising avenue for individualized dose de-escalation, with a 60% RT dose reduction in 15/18 patients within the study, and no radiation-related grade III toxicities noted.

The next de-intensification approach for HPV-related OPSCC utilizes neoadjuvant chemotherapy to decrease the tumoral burden and allow definitive surgical resection with- out adjuvant RT. This approach allows radical de-escalation of the locoregional treatment to surgery only in the vast majority of patients with HPV-associated OPSCC, reserving RT for salvage treatment. The neoadjuvant chemotherapy de-escalates the surgery by decreasing gross tumoral bulk and nodal disease, allowing smaller resection just outside the pre-chemotherapy tumor margin as opposed to standard 1 cm margin, while potentially addressing distant micro-metastasis with induction systemic therapy [30]. Sparing of RT also allows complete avoidance of all minor and major salivary glands. This approach allows for saving RT for salvage, for unanticipated pathologic findings, for recurrence, and or potential future second primary cancers within the head and neck region. An important consideration with surgical management is the

heightened risk of post-operative bleeding and its associated morbidity or mortality. Nonetheless, it is felt this risk is likely smaller than upfront surgery approaches where larger resection margins are typically required.

Similar to the above protocol are the trials investigating the efficacy of neoadjuvant chemotherapy with risk-based RT dose de-escalation. However, the lowest doses of RT given to patients in trials discussed in this category were 50 Gy RT or 45 Gy with concurrent chemotherapy in the OPTIMA study [71]. These decreased doses are a great improvement and will likely improve the side effect profile, but still carry a high-risk of radiation-induced xerostomia and dysphagia [20,49,50].

Targeted therapy with the monoclonal anti-EGFR antibody cetuximab has been investigated as a potential replacement to standard cisplatin-based chemotherapy, in hopes of further decreasing toxicity. However, two phase III studies (De-ESCALaTE HPV and RTOG1016) have concordantly reported inferiority in oncologic outcomes [62,64]. Sub- sequent publications have highlighted the controversial rationale of EGFR-targeting in HPV-positive OPSCC, as the pathogenesis of these tumors was largely related to viral oncoproteins E6 and E7 rather than the altered signaling pathways these agents target [79]. Thus, authors have postulated these early trials perhaps lacked a strong preclinical basis and highlight the need for intensive experimental studies preceding large clinical trial.

10. Conclusions

HPV-associated OPSCC is an evolving field due to the younger population and the markedly improved prognosis [8]. The longer lifespan means that these patients live for many years with the sequelae of treatments, and therefore, quality of life has become a priority. Specifically, emphasis must be placed on treatment modality optimization and selection due to the effects on patents' senses, functional capabilities, and emotional expressions. These efforts to improve quality of life have been noted with great advancements in radiotherapy techniques, chemotherapy regimens, surgical approaches, and the use of personalized de-escalated combination therapies. Comparing these novel studies is difficult, and therefore, it is difficult to determine the best approach, due to a variety of reasons including differences in patient inclusion

criteria such as staging and tumor characteristics, and center-specific factors such as equipment availability and provider expertise. It may well be that more therapeutic options that are equally effective will be available to this patient population and the choice will be driven by patients' preferences for short- and long-term outlooks. In selecting the treatment, while five-years survival and outcomes are the norm for decision making, in this otherwise healthier and younger patient population, the long term sequela of treatment and outcomes over a 20–30 year outlook need be strongly considered. Improvements in our understanding of the biology of HPV-related disease have caused a shift towards more individualized approaches based on patients and tumor factors. The employment of the novel techniques discussed in this paper will hopefully maintain or improve current mortality rates, while significantly reducing the long-term morbidities in low-risk patients.

11. Table

Table 1: Overview of both published and ongoing treatment de-escalation clinical trials for human papillomavirus-associated oropharyngeal squamous cell carcinoma

Study name	NCT code	Phase	Status	Eligibility	De-escalation strategy	Outcomes
UPFRONT SURGERY AND PATHOLOGY-BASED ADJUVANT THERAPY						
ORATOR	NCT01590355	II	Complete	T1-T2, N0-2 OPSCC (7th edition)	Patients randomized to: 1. Surgical arm: TOS and ND ± adjuvant therapy (60 Gy RT or 64 Gy RT and chemotherapy) 2. RT: 70 Gy ± high dose cisplatin (carboplatin or cetuximab if unfit)	Surgery group (n=34): 16 received adjuvant RT, 8 received adjuvant CRT. RT group (n=34): 2 withdrew, 23 received concomitant CRT. RT group had a better one-year swallowing-related quality of life however not a clinically meaningful difference. ~4 year follow-up
ORATOR2	NCT03210103	II	Complete, no published results	T1-2, N0-2 potentially resectable HPV-related OPSCC (8th edition)	Patients are risk stratified by smoking history, then randomized to de-intensified 60 Gy RT ± weekly cisplatin or TOS and ND ± adjuvant 50 Gy RT	Surgery group (n=31), RT group (n=30). Recruitment closed early due to two treatment related deaths in the surgical arm. Two-year OS estimates were 89.1% in the TORS group and 100% in RT group The two-year PFS estimates were 83.5% in the TORS group and 100% in the RT group. 71% of the surgical group had grade 2-5 toxicities versus 67% of patients in the RT arm.
SURGERY AND DE-ESCALATION OF ADJUVANT RADIOTHERAPY						
MC1273	NCT01932697	II	Complete	Resectable HPV-related OPSCC, stage III or IV, ≤10PY (7th edition)	All patients underwent surgery with curative intent. Post-operatively deemed high risk if ENE, LVI, PNI, ≥2 regional LN involved, any LN >3cm, or ≥T3 primary tumor. Stratified based on ENE: 1. ENE negative: 30 Gy and docetaxel 2. ENE positive: 36 Gy and docetaxel	Group A (n=37): 1 distant recurrence Group B (n=43): (4 locoregional recurrence, and 5 distant metastases) Whole cohort, two-year DMFS, PFS and OS were 94.9%, 91.1%, and 98.7% respectively. This aggressive RT de-intensification achieved similar results as historical controls. Toxicity and adverse events were improved compared to historical controls. Pre-RT QOL scores were improved at one year follow-up.
AVOID	NCT02159703	II	Complete	Resectable pT1-2, pN1-3 HPV-related	All patients undergo TORS and ND on with >2mm margins, no PNI, no LVI.	All patients received adjuvant RT at 60-66 Gy (n=60), ENE+ received concurrent CRT (n=13).

				OPSCC (7th edition)	All patients receive adjuvant therapy to neck only (no primary site): 1. Neck involved in disease: 60-66 Gy 2. Neck uninvolved in disease: 54 Gy With concurrent chemotherapy if ENE+	Follow up of 2.4 years. Mean primary site radiation of 36.9 Gy. Recurrence: primary site (n=1), regional recurrence (n=1), distant metastases (n=2). Two-year LCR 98.3%, OS 100% at the time of analysis. Adverse events: late soft tissue necrosis in the primary site with conservative management (n=2). No long-term feeding tube dependence (n=0).
E3311	NCT01898494	II	Complete	T1-2, N1-2b HPV-related OPSCC (7th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Group A = Low risk = pT1-2, pN0-1 + negative margins: observation 2. Intermediate risk = negative margins, ≤1mm ENE, 2-4 LN involved, PNI or LVI: randomized to a. Group B - 50 Gy adjuvant RT b. Group C - 60 Gy adjuvant RT 3. Group D = High risk = positive margins, >1mm ENE, >5 LN involved: 66 Gy adjuvant RT with concurrent cisplatin	Group A (n=38), group B (n=100), group C (n=108), group D (n=131) Follow up period of 35 months. No significant difference in PFS or OS: - PFS 96.9% for arm A, 94.9% for arm B (50 Gy), 96.0% for arm C (60 Gy), and 90.7% for arm D. - OS was 100% for arm A, 99.0% for arm B, 98.1% for arm C, and 96.3% for arm D. MDADI and FACT-H&N for both intermediate risk groups were similar.
SIRS	NCT02072148	II	Complete	T1, N1-2b or T2, N0-2b HPV-related OPSCC with <20PY (7th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = pT1-2, pN0-2b, no high risk features: observe 2. Intermediate risk = pT1-2, pN0-2b, negative margins, LVI, PNI, <3 LNs, <1mm ENE: 50 Gy adjuvant RT 3. High risk = ≥3LN, positive margins, ENE+, contralateral LNs: 56 Gy adjuvant RT with concurrent cisplatin	Group A (25), Group B (15), Group C (14). Median follow up 43.9 months. PFS probability was 91.3% for group 1, 86.7% for group 2, and 93.3% for group 3. Global MDADI QOL scores improved with time and returned to baseline scores.
PATHOS	NCT02215265	II/III	Accrual	T1-3, N0-2b HPV-related OPSCC (7th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = pT1-2, no adverse features: observe	N/A

					2. Intermediate risk = T1-3, N2a-b, PNI, LVI, 1-5mm margins: randomized to adjuvant RT of 50 Gy or 60 Gy 3. High risk = positive margins (<1mm), >1mm ENE: randomized to adjuvant 60 Gy RT or 60 Gy RT with concurrent cisplatin	
ADEPT	NCT01687413	III	Accrual	Resectable T1-4a HPV-related OPSCC, ENE positive	All patients undergo TORS and ND, nodal disease with ENE randomized to 60 Gy RT alone or with concurrent weekly cisplatin	N/A
MINT	NCT03621696	II	Complete, no published results	Stage I-III resectable HPV-related OPSCC (8^{th} edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = <T4, <cN3, no ENE, negative margins: 42 Gy adjuvant RT 2. Intermediate risk = <T4, <cN3, ENE or positive margins = 42 Gy adjuvant RT with one dose cisplatin 3. High risk = T4, cN3: 60 Gy RT with concurrent cisplatin	Preliminary results available on clinicaltrials.gov
DART-HPV (follow-up phase III randomized clinical trial to MC1273)	NCT02908477	III	Complete, no published results	Resectable T1-3, N0-3, M0 HPV-related OPSCC (7^{th} edition)	Patients are randomized to: 1. CRT with 60 Gy and cisplatin if high risk or 2. Docetaxel with 30 Gy (36 Gy if high risk)	N/A
ADAPT	NCT03875716	II	Accrual	Resectable HPV-related OPSCC, T0-2, N0-1, M0 (8^{th} edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = pT1-2, N0-1, minimum of 15 LNs examined, ≤2 LN involved, no ENE: observation 2. Intermediate risk = pT1-2, N0-2, >2 LNs involved, <15 LNs examined, positive LNs in levels Ib, IV, or V, ≤1mm ENE, contralateral LNs, close margins: reduced adjuvant RT	N/A

					3. High risk = pT1-4, N0-2 with >1mm ENE and positive margins: adjuvant RT (standard dose)	
DELPHI	NCT03396718	I	Accrual	Patients with resected primary and ND with indication for adjuvant therapy	Patients are randomized to: 1. Intermediate risk = HPV + pT3 and R0 +/- 1-2 LN involvement and no ECE: 54/59.4 Gy 2. High risk = HPV + with R1, pT4, 3+ nodes, and/or ECE: 60/66 Gy 3. Comparative group 1 (HPV -) = 60/66 Gy 4. Comparative group 2 (HPV +) = 60/66 Gy	N/A
	NCT03729518	II	Accrual	Resectable T1-3, N0-2c HPV-related OPSCC (7^{th} edition)	All patients undergo TORS and ND. If post-operative pathology demonstrates <5 involved LN, patients undergo reduced adjuvant RT to nodal areas, avoiding primary site, with or without chemotherapy	N/A
	NCT02784288	I	Active, not recruiting	Potentially resectable T1-3, N0-2c HPV-related OPSCC	All patients undergo ND and biopsy of primary site. Post-operative pathology determining treatment pathway: 1. Low risk = ≤1 LN <6cm, no ENE, no LVI, no PNI: TOS 2. Intermediate risk = >/= 2 LNs, presence of PNI/LVI, no ENE: RT 3. High risk = ENE or positive margins: concurrent CRT	N/A
ALTERED REGIMEN OF CHEMORADIOTHERAPY						
NRG-HN002	NCT02254278	II	Complete	T1-2, N1-2b or T3, N0-2b, HPV-related OPSCC (7^{th} edition) with ≤10PY	Patients are randomized to reduced dose 60 Gy IMRT with or without concomitant cisplatin	Group A = IMRT + C (n=157) and Group B = IMRT (n=149). Two-year PFS for Group A was 90.5%, and Group B was 87.6%. One-year MDADI mean scores were 85.30 and 81.76, respectively. Two-year OS rates were 96.7% and 97.3%, respectively. The IMRT-alone group did not meet acceptability criteria.

	NCT00606294 (pilot) NCT03323463	II	Complete	T1-2, N1-2c HPV-related OPSCC (7th edition)	Patients undergo pre-operative tumour resection and ^{18}F-FMISO PET for assessment of hypoxia. 1. No hypoxia = receive 30 Gy RT and cisplatin 2. Hypoxia = start CRT with repeat ^{18}F-FMISO PET in 1 week to reassess hypoxia. If no hypoxia: 30 Gy RT with cisplatin. If persistent hypoxia: 70 Gy RT with cisplatin.	18 patients included in study. 15 patients received 30 Gy and cisplatin (6 patients had no hypoxia on initial assessment, 9 patients had no hypoxia on intra-treatment assessment). 3 patients received 70 Gy and cisplatin. Two-year locoregional control, progression-free survival, and overall survival for the de-escalated cohort per protocol were 100%, 92.9%, and 92.9%, respectively
LCC1120	NCT01530997	II	Complete	T0–3, N0-N2c, M0 HPV-related OPSCC with ≤10PY (or >5 years tobacco-free if ≤30PY) (7th edition)	All patients are treated with de-escalated IMRT (60 Gy) and reduced dose of weekly concurrent cisplatin. After completion of chemoradiotherapy, patients underwent at least ND with primary site biopsy to assess pathologic response.	43/45 patients completed the study protocol. At a median 14 month from of treatment, no measurable tumor present on physical and radiologic examination in 64% of patients. The pathologic complete response rate was 86%. After a median 36-month follow-up, three-year locoregional control, distant metastasis-free survival, and overall survival rates were 100%, 100%, and 95%, respectively.
LCC1413	NCT02281955	II	Complete, results not published	T0–3, N0-N2c, M0 HPV-related OPSCC with ≤10PY (or >5 years tobacco-free if ≤30PY) (7th edition)	All patients are treated with de-escalated IMRT (60 Gy) and reduced dose of weekly concurrent cisplatin. After completion of CRT, all patients underwent PET-CT scan in place of surgery for pathologic assessment	All patients received 60 Gy IMRT (n=114), 80% of the patients staged to receive chemotherapy completed at least four cycles of cisplatin and 11% received cetuximab upfront due to contraindications to cisplatin. The post-treatment complete response on PET-CT was 93% at the primary site and 80% in the neck. All patients with residual disease at the primary site are alive and no evidence of disease. Two-year locoregional control, progression-free survival, and overall survival were as follows: 95%, 86%, and 95%, respectively.
LCCC1612	NCT03077243	II	Active, not recruiting	T0-3, N0-2c, M0 HPV-related OPSCC (7th edition), p53 mutation status	Patients are risk stratified by their p53 mutation status and smoking history: 1. Low risk = ≤10PY or >10PY without p53 mutation: 60 Gy IMRT with concurrent cisplatin 2. High risk = >10PY with p53 mutation: 70 Gy IMRT with concurrent cisplatin	N/A
	NCT01088802 (7th edition)	II	Active, not recruiting	T1-3, any N, resectable	RT dose to 63 from 70 and from 58.1 Gy to 50.75 Gy	N/A

				HPV-related OPSCC		
EVADER	NCT03822897	II	Active, not recruiting	T1-3, N0-1, M0 HPV-related OPSCC (8th edition)	Patients receive definitive RT (70 Gy) to primary site and reduced-dose elective nodal irradiation (56 Gy), with or without concurrent cisplatin	N/A
TARGETED THERAPY WITH EGFR INHIBITOR VERSUS CISPLATIN						
RTOG1016	NCT01302834	III	Complete	T1-2, N2-3 or T3-4, N0-3 HPV-related OPSCC (7th edition)	Patients receive standard-dose 70 Gy IMRT and are randomized to receive concurrent cisplatin or cetuximab	Group A cetuximab (399) and Group B cisplatin (406). Median follow-up duration of 4.5 years. Estimated five-year overall survival was 77.9% vs. 84.6%, respectively. PFS was significantly lower in the cetuximab group compared with the cisplatin group (hazard ratio 1.72)
De-ESCALaTE HPV	NCT01874171	III	Complete	T3-4, N0, T1-4, N1-3, HPV-related OPSCC with ≤10PY (7th edition)	Patients receive standard-dose 70 Gy RT and are randomized to receive concurrent cisplatin or cetuximab	Cisplatin group (n=152), cetuximab group (n=152). A significant difference in two-year overall survival of 97.5% for cisplatin versus 89.4% for cetuximab, p=0·001, and two-year recurrence rate of 6.0% for cisplatin versus 16.1% for cetuximab, p=0·0007.
TROG12.01	NCT01855451	III	Complete	Stage III (except T1-2, N1) or stage IV (except T3, N3 or M1) with ≤10PY. If >10PY, must be N0-2a (7th edition)	Patients receive standard-dose 70 Gy RT and are randomized to receive concurrent cisplatin or cetuximab	Group A cisplatin (92) and Group B cetuximab (90). There was no difference in the primary endpoint of symptom severity. The T-score was 4.35 in the cisplatin arm and 3.82 in the cetuximab arm. The three-year failure-free survival rates were 93% and 80%, respectively.
NRG HN005	NCT03952585	II	Accrual	T1-2, N1 or T3, N0-2b HPV-related OPSCC with ≤10 pack year history (8th edition)	Patients are randomized to one of three arms: 1. 70 Gy IMRT with concurrent cisplatin 2. 60 Gy IMRT with cisplatin 3. 60 Gy IMRT with cisplatin and nivolumab	N/A
NEOADJUVANT CHEMO WITH CONSOLIDATION SURGERY						
NeCTORS	NCT02760667	II	Accrual	Stage III-IV HPV-associated	All patients undergo 3 cycles of neo-adjuvant chemotherapy with cisplatin and docetaxel and transoral surgery and selective ND.	55 patients were enrolled to undergo neoadjuvant chemotherapy and surgery. 2/55 required adjuvant CRT for unresectable positive margins following TORS. 0/55

				OPSCC (7th edition)		required salvage RT for recurrence. Five-year disease free survival was 96.1% compared to 67.6% for concurrent CRT.
NEOADJUVANT CHEMOTHERAPY AND LOW DOSE RADIOTHERAPY						
E1308	NCT01084083	II	Complete	Resectable stage III or IV HPV-related OPSCC (7th edition)	All patients undergo 3 cycles of induction chemotherapy with cisplatin, paclitaxel, and cetuximab. 1. Complete clinical response: 54 Gy adjuvant RT with weekly cetuximab 2. Incomplete clinical response: 69.3 Gy adjuvant RT with weekly cetuximab	80 patients were enrolled. 70% achieved a primary-site complete clinical response to induction chemotherapy, and 51 patients continued to cetuximab with IMRT 54 Gy. After median follow-up of 35.4 months, two-year PFS and OS rates were 80% and 94%, respectively for those who had complete initial response. In the 69 Gy RT arm, there were higher rates of these same adverse events, with 47% suffering from mucositis and 29% having dysphagia.
Quarterback	NCT01706939	II	Complete	Stage III-IV HPV-related OPSCC, no distant metastases, ≤20PY (7th edition)	All patients undergo 3 cycles of induction chemotherapy with docetaxel, cisplatin, 5-fluorouracil. Patients with partial clinical response or complete clinical response were randomized (2:1) to reduced dose IMRT (56 Gy) or standard-dose IMRT (70 Gy), with weekly carboplatin	Group A Standard-dose chemoradiotherapy (8) and Group B reduced dose chemoradiation (12). Median follow up was 56 months. Three-year progression free survival was 87.5% and 83.3%, respectively. Non-inferiority of reduced CRT dosages could not be demonstrated given the limited number of enrolled participants.
Quarterback II	NCT02945631	II	Accrual	Stage III-IV, M0 HPV related OPSCC, ≤20PY, not a current smoker (7th edition)	All patients undergo 3 cycles of induction chemotherapy with docetaxel, cisplatin, 5-fluorouracil. Stratified based on response: 1. Low risk = partial or complete clinical response: 56 Gy RT with concurrent carboplatin 2. High risk = no response or progression: surgery or standard 70 Gy RT with concurrent carboplatin	N/A
OPTIMA	NCT02258659	II	Complete	T1-4, N2-3 HPV-related OPSCC (7th edition)	All patients undergo 3 cycles of induction chemotherapy with carboplatin and nab-paclitaxel. 1. Low-risk patients = ≤T3, ≤N2b, ≤10 pack-years: a. >50% clinical response: 50 Gy RT	62 patients (28 low risk/34 high risk) were enrolled. Of low-risk patients, 71% received 50 Gy radiation while 21% received 45 Gy CXRT. Of high-risk patients, 71% received 45 Gy CXRT. With a median follow-up of 29 months, two-year PFS and OS were 95% and 100% for low-risk patients and 94% and 97% for high-risk patients, respectively.

					b. 30-50% clinical response: 45 Gy and concurrent paclitaxel c. <30% clinical response: 75 Gy and concurrent paclitaxel 2. High risk = T4 or ≥N2c or > 10 pack-years: a. >50% clinical response: 45 Gy and concurrent paclitaxel b. <50% clinical response: 75 Gy and concurrent paclitaxel	
OPTIMA-II	NCT03107182	II	Active, not recruiting	T3-4 or N2-3 HPV-related OPSCC (7th edition)	All patients undergo 3 cycles of induction chemotherapy with carboplatin and nab-paclitaxel, with additional nivolumab. Risk stratification based on staging and clinical response: 1. Low-risk patients = T1-2, N2a-b a. >50% clinical response and TORS-eligible: TORS/neck dissection +/- reduced RT b. >50% clinical response and TORS-ineligible: reduced RT (50 Gy) c. 30-50% clinical response: 50 Gy RT with concurrent cisplatin d. <30% clinical response: 75 Gy and concurrent cisplatin 2. High risk = T4, bulky N2b-2c-3, >10 pack-years: a. >50% clinical response: 50 Gy RT and concurrent cisplatin b. <50% clinical response: 75 Gy and concurrent cisplatin	N/A

					All patients will be offered adjuvant nivolumab for 6-months post completion of definitive therapy.	
CCRO-022	NCT02048020/ NCT01716195	II	Complete	Stage III-IV HPV-related OPSCC (7th edition)	All patients undergo 2 cycles of induction chemotherapy with paclitaxel and carboplatin. 1. Low risk = complete clinical response or partial clinical response: 54 Gy adjuvant IMRT with concurrent paclitaxel 2. High risk = <partial clinical response: 60 Gy adjuvant IMRT with concurrent paclitaxel	44 patients were enrolled. 24 (55%) patients with complete or partial responses to induction chemotherapy received 54 Gy radiation, and 20 (45%) with less than partial responses received 60 Gy. Median follow-up was 30 months. Two-year PFS was 92%.

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13. Linking statement

This narrative review is a comprehensive summary of all de-escalation strategies ongoing or completed for HPV-related OPSCC. The large volume of trials proves that the ideal treatment regimen is still under debate. Individual patients may prioritize avoiding particular adverse events, therefore, risks and benefits, including treatment side effects must be clearly defined when discussing treatment options.

These trials mainly focus on mortality and survival statistics to determine their safety to continue. Few published QOL outcomes and those within this review utilizing patient-reported QOL measures mostly reported overall QOL scores or data on physical QOL scores. Specifically, dysphagia-related QOL has gained popularity as it is has become a focus for OPSCC post-treatment QOL presentation. However, physical QOL is just one aspect of patient QOL and lacks an accurate assessment of the patient as a whole.

The following chapter (Chapter 4, Manuscript 2), presents a scoping review exploring psychosocial QOL outcomes in patients with OPSCC.

Chapter 4: Patient-Reported Outcome Measures of Psychosocial Quality of Life in Oropharyngeal Cancer Patients: A Scoping Review (Manuscript 2)

Jennifer A. Silver[1] , Russell Schwartz[,2], Catherine F. Roy[1], Nader Sadeghi[1,2,3] and Melissa Henry[1,3,4,5]

1. Department of Otolaryngology-Head and Neck Surgery, McGill University, Montreal, Quebec, Canada
2. Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada
3. Gerald Bronfman Department of Oncology, Faculty of Medicine and Health Sciences, McGill University, Montreal, Quebec, Canada
4. Lady-Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC H3T 1E2, Canada
5. Segal Cancer Centre, Jewish General Hospital, Montreal, QC H3T 1E2, Canada

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Abstract:

Background: Oropharyngeal squamous cell carcinoma (OPSCC) patients are burdened by the effect of the disease process and treatment toxicities on organs important in everyday activities, such as breathing, speaking, eating, and drinking. There is a rise in OPSCC due to human papilloma virus (HPV)-associated OPSCC, affecting younger and healthier patients and with a better overall prognosis. Emphasis must be shared between oncologic outcomes and the effects on quality of life. While there have been efforts to study global and physical quality of life, the impact on psychosocial quality of life has not yet been specifically reviewed.
Methods: A scoping review methodology was employed to explore the emotional, social, and mental quality of life in OPSCC patients and determine the impact of HPV status or treatment modalities.
Results: Eighty-seven full-text articles were evaluated for eligibility. Fifteen articles met final inclusion criteria. The majority of the studies were conducted in the United States (n = 10) and study methodology was divided between cross- sectional (n = 6), prospective (n = 5), and retrospective studies (n = 4). Four psychosocial quality of life themes were explored: the impact on mental health and emotional wellbeing, social wellbeing and function, stress, and relationship and sexual behavior. Eighteen different patient-reported outcome measures were used, including both general head and neck oncology questionnaires and symptom- specific surveys.
Conclusion: There is a paucity of research regarding the effect of OPSCC on patients' psychosocial quality of life. Learning more about this component of quality of life can guide outreach programs and multidisciplinary involvement in improving patient care.

Keywords:

oropharyngeal cancer; human papillomavirus; psychosocial; quality of life

1. Introduction

While the number of head and neck cancer diagnoses is decreasing, the prevalence of oropharyngeal squamous cell carcinoma (OPSCC) has been increasing in North America due to human papillomavirus (HPV)-associated disease [1]. Currently, approximately 60–70% of OPSCC is associated with HPV, in contrast to traditional tobacco- and alcohol- related OPSCC [1–4]. HPV-associated OPSCC differs significantly from conventional OPSCC. Clinically, these patients are younger and healthier at baseline, with little or no tobacco exposure, and the prognosis is favorable with standard treatments [3–5]. As such, psychosocial issues related to head and neck cancer survivorship are increasingly apparent in this patient population, yet remain understudied in the scientific literature [6].

Oropharyngeal cancers originate at keystone areas for breathing, eating, and speech [7]. Patients with oropharyngeal cancer experience stress from facing their cancer diagnosis and intensive treatment regimens, with the added effects on organs essential to the activities of daily living and communication [7–10]. With improved prognosis for most OPSCC cases, goals are shared between maintaining the excellent overall survival and disease-free survival, and quality of life (QOL) [11]. Recent reviews have summarized ongoing or recently completed clinical trials attempting to de-escalate standard therapies for HPV- associated OPSCC patients to minimize or lessen treatment-related side effects [12,13].

Most reviews assessing health-related QOL in OPSCC patients focus on xerostomia, dysphagia, mastication, and other physical complaints [9,14]. While these are important markers for assessment of post-treatment toxicity, QOL is multifactorial. The World Health Organization defines QOL as “an individual’s perception of their position in life, in the context of culture and value system in their life and in relation to their goals, expectations, standards and concerns” [15]. Our definition of QOL should extend beyond physical and functional dimensions and incorporate social and emotional factors. This is especially important in head and neck cancer patients, a population in which the prevalence of diagnosed major depressive disorders is as high as 40% [16]. Head and neck cancer patients are more likely to commit suicide when compared to the general population or to patients diagnosed with 19 other cancers [17,18]. However, the

changed demographic and better prognosis of HPV-associated OPSCC patients may lead to a different impact on psychosocial QOL.

There has not yet been a review addressing the psychosocial impact of oropharyngeal cancer on patients. Most research focuses on survival and on physical aspects of the disease, in striking contrast with patient-centered concerns. The primary objective of this review is to assess the broad psychosocial QOL in oropharyngeal cancer patients using patient- reported outcome measures (PROMs). Secondary objectives are to determine whether treatment regimens or HPV status play a role.

2. Methodology

This scoping review seeks to identify the current literature published in this field, examine how the research was conducted, and detail the key factors and gaps in knowledge. We followed the scoping review framework proposed by Arksey and O'Malley, expanded by Levac et al. [19,20]. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews was followed as a complementary guideline [21].

2.1. Identifying the Research Question

This scoping review was developed to describe the nature, number, and scope of published research articles examining the relationship of psychosocial QOL in patients with OPSCC using validated patient-reported outcome metrics.

2.2. Identifying Relevant Studies

A systematic literature search of PubMed, Embase, PsycINFO, and CINAHL was conducted of all articles published between 1946 and August 2022. Search terms included a combination of appropriate database MeSH terms, subject headings, and keywords for the concepts of oropharyngeal cancer, QOL, patient-reported outcome measures, and different emotional and mental states (Supplementary S1). The search strategy was de- veloped with the assistance of a medical librarian guided by the Joanna Briggs Institute; inclusion and exclusion criteria were determined by population type, concept, and context framework (Table 1) [22].

2.3. Study Selection

The titles and abstracts of all identified studies were screened by two independent reviewers (JS, RS), with a senior author available to resolve conflicts not agreed upon by discussion (MH). The abstract screening protocol was discussed among authors, and criteria defined using Rayyan, a software designed to allow multiple reviewers to independently select studies for inclusion or exclusion [23]. A pilot sample of 20 abstracts was completed to ensure that both reviewers had a common understanding of the inclusion and exclusion criteria (Table 1). All article abstracts were screened in increments of 100–200 articles to regularly check inter-rater reliability and ensure consistent results.

The full-text articles were screened by two reviewers (JS, RS) with more refined criteria (Table 1). Articles were included if they were studies published in peer-reviewed journals with a population of adult patients with OPSCC who are undergoing or completed treatment for their disease (surgery, chemotherapy and/or radiation therapy (RT)). The included studies reported on QOL with validated patient-reported outcome metrics, and at least one component of psychosocial QOL was a primary or secondary outcome of the paper. The reference lists of eligible studies were also reviewed to identify any further studies that had been missed in the electronic searches.

2.4. Data Extraction

From the full texts, two authors (JS and RS) extracted the following data: author(s), year of publication, study design, study location, participant characteristics, PROMs em ployed, psychosocial QOL concepts discussed, and important findings. The psychosocial theme content analysis was compiled using NVivo software and inter-rater reliability was calculated [24]. Risk of Bias was assessed using the National Institutes of Health Quality As- sessment Tool by two independent reviewers (JS and RS) [25]. Disagreements were resolved by discussion and by consulting a senior author (MH) to resolve remaining discrepancies. Prior to submission, the search was repeated and an additional two articles were included in the analysis. New articles identified since the primary search were screened and data extraction was performed by the same reviewers jointly to ensure agreement.

2.5. Collation, Summarizing and Reporting the Results

The data from the included studies were collated and included study demographics, PROMs employed, and psychosocial theme (mental health and emotional wellbeing, social contact, stress, and interpersonal relationships).

3. Results

3.1. Study Population and Demographics

The study selection process is outlined in Figure 1. The databases yielded 2630 citations (Medline: 933, Embase: 1343, PsycINFO: 308, CINAHL: 39), reduced to 1603 articles after removing duplicates. Of these, 87 full-text articles were deemed to be eligible for full-text review. There was a 96.9% inter-rater reliability between the two screening authors (JS and RS). Cohen's kappa was calculated at 0.73, representing substantial agreement [26]. Fifteen articles met eligibility criteria. Their references were screened, but no further articles met inclusion criteria. The included studies had varied study designs, cross-sectional (n = 6), prospective (n = 5), and retrospective (n = 4). The majority of the studies were conducted in the United States (n = 10), with the remainder from Australia (n = 3), and single studies from both Sweden (n = 1) and the Netherlands (n = 1). The three studies from Australia were conducted by the same research group using the same cross-sectional methodology and patient cohort. Studies were published between 2013 and 2022. Sample sizes ranged from 24 to 972 patients, with an average of 179 patients per study. The average age of participants was 59 years (range18 to 89). All studies assessed QOL post-treatment at an average of 30.9 months follow-up (range six months to six years).

3.2. Quality Assessment

Using the National Institutes of Health Quality Assessment Tool, the majority of the studies were rated as fair (n = 11), with the remainder graded as good (n = 3) and poor (n = 1).

3.3. QOL Metrics

This scoping review identified 18 different validated patient-reported outcome mea- sures (PROMs) utilized by studies, summarized in Supplementary S2. The most frequently employed were the MD Anderson Symptom Inventory for Head and Neck cancer (MDASI- HN) (n = 5) and the European Organization for Research and Treatment of Cancer Core QOL Questionnaire (EORTC QLQ-C30) (n = 5). Within the different themes, there were symptom-specific PROMs. In the mental health category, three different depression metrics were utilized: the Center for Epidemiologic Studies Depression Scale (CES-D), Patient Health Questionnaire (PHQ), and Patient-Reported Outcomes Measurement Information System-Depression 8b (PROMIS®-Depression 8b). Two different anxiety metrics were used: General Anxiety Disorder-7 (GAD-7) and the Patient-Reported Outcomes Measurement Information System-Anxiety 7a (PROMIS®-Anxiety 7a). The variability of components of stress required symptom PROMs for each specific element (i.e., Fear of Cancer Recurrence Inventory, Decision Regret Scale).

3.4. Identification of Psychosocial QOL Themes and Thematic Analysis in Oropharyngeal Cancer Patients

The eligible studies reported on four main themes within psychosocial QOL (Table 2), subdivided as follows: mental health and emotional wellbeing (n = 10), social wellbeing and function (n = 4), stress (n = 5), and relationship and sexual behavior (n = 3). The content analysis of psychosocial QOL themes conducted by both reviewers yielded a Cohen's kappa correlation coefficient of 0.77, demonstrating substantial agreement.

3.4.1. Mental Health and Emotional Wellbeing

The mental health domain comprised studies addressing impacts on depression, anxiety, mood, and emotional function.

Only one study by Kaffenberger evaluated patient mental health after different treatment modalities [27]. This retrospective cohort study compared patients with advanced oropharyngeal cancer treated with primary chemoradiotherapy (CRT) (n = 44) to those treated with surgery with adjuvant RT or CRT (n = 29) and found no significant difference in depression or anxiety scores between the two cohorts, using the PHQ-8 and GAD-7 PROMs, respectively.

The studies that evaluated mental health at different time points noted improvement in mental health scores over time. Janz's prospective cohort study exploring differences between HPV-associated OPSCC patients (n = 21) and HPV-negative oral cavity cancer patients who smoke (n = 17) found that, at 12 months, the HPV-associated OPSCC cohort had an improved depression score on the CES-D [28]. Rajeev-Kumar conducted a retrospective analysis of OPSCC patients treated with RT (n = 69) using the University of Washington QOL (UW-QOL) questionnaire and noted that anxiety and mood scores improved at 12 months compared to pre-treatment values [29].

Berg performed a cross-sectional study comparing BOT cancer patients (n = 190) to tonsillar cancer patients (n = 405) and to the general population (n = 190) [30]. This research identified better emotional function in the patients with HPV-associated OSPCC than in the HPV-negative patients on the EORTC QLQ-C30. Qualliotine's retrospective review of OPSCC patients (n = 69) noted that a lower proportion of HPV-associated OPSCC patients use anti-depressants [31]. Korsten prospectively compared HPV-positive and HPV-negative OPSCC patients and identified greater post-treatment emotional function in the former group using the EORTC QLQ-C30 and the EORTC Head and Neck Cancer module (EORTC QLQ-HN35) [32]. Lee found decreased anxiety ($p = 0.005$) but no significant difference in mood ($p = 0.288$), using the UW-QOL scale in 25 HPV-associated OPSCC patients treated with neoadjuvant chemotherapy and transoral robotic surgery (n = 25) compared to a normative cohort [33].
Several other studies did not associate worsening mental health with HPV status (Qualliotine on CES-D initial screen, Rajeev-Kumar on UW-QOL, and Shinn using both the PHQ-9 and the CES-D) [29,31,34]. Shinn performed a prospective cohort study on 130 patients with OPSCC [34]. Casswell et al. did not compare their data of their HPV-associated cohort to HPV-negative patients [27,35,36]. Casswell and McDowell studied the same 136-patient, HPV-positive OPSCC cohort treated with CRT in their cross-sectional studies, using the Patient-Reported Outcomes Measurement Information System (PROMIS®) Anxiety and Depression questionnaires [35,36,37].

3.4.2. Social Wellbeing and Function

The social wellbeing and function domain comprised studies addressing impacts on social quality of life, social contact, and social eating.

Berg did not identify any significant difference in social domain of the EORTC QLQ-C30 or in the EORTC QLQ-HN35 scores in BOT OPSCC patients who underwent different treatment modalities [30]. Kaffenberger did not identify differences in UW-QOL social scores when comparing CRT to surgery with adjuvant RT or CRT [27]. However, this study did establish that the mean dose of RT delivered to the ipsilateral parotid gland correlated with worse social scores. Dziegielewski performed a prospective cohort study exploring swallowing, speech, and QOL outcomes after transoral robotic surgery in 81 patients with OPSCC, using the Head and Neck Cancer Inventory (HNCI) [38]. The social QOL domain declined immediately after surgery, reaching a nadir at three months; however, this domain recovered and was similar to baseline results at one-year post-therapy.

Comparing HPV-positive and HPV-negative patients, Korsten identified better social functioning at baseline, which worsened to a greater extent during treatment, and recovered better and more quickly at follow-up compared to patients with an HPV-negative cancer [32]. However, mixed-model analysis did not demonstrate a significant difference between HPV-positive and negative patients on social contact and social eating domains. There was no difference in social scores in HPV-positive and HPV-negative patients in the two studies that performed this comparison (Berg, Dziegielewski) [30,38].

3.4.3. Stress

Stress was a diverse theme within this scoping review, with five studies discussing four stress-related concepts: fear of cancer recurrence [35,39], overall attitude/bother or satisfaction with function [38], decisional regret [39,40], and cancer worry [28].

Casswell employed the Fear of Cancer Recurrence Inventory and found that this fear was present in over half of the patients, with younger patients more likely to report this stress [35]. Fear of cancer recurrence was also associated with lower global QOL, higher symptom interference with

daily activities, and greater anxiety and depression scores [39]. This study used a patient perspective questionnaire, a measure developed by the researchers based on previously validated metrics.

Dziegielewski identified a significant difference in change in overall attitude in the Head and Neck Cancer Inventory (HNCI; a measure capturing patients' ratings of their function and how much they are bothered by that function) in patients who received adjuvant RT ($p = 0.003$) and those receiving adjuvant CRT ($p = 0.04$) compared to those without adjuvant treatment [38]. There was no difference in overall attitude in HPV-positive or HPV-negative patients ($p = 0.56$). The study by Janz used the Assessment of Survivor Concerns instrument to compare cancer worry in HPV+ OPSCC patients with smoking oral cavity cancer patients and found that there was no statistically significant difference in cancer worry score ($p = 0.1$) [28]. Cancer worry also decreased over time in both cohorts but was not statistically significant (HPV+ OPSCC: 21 to 16, $p = 0.11$, oral cavity: 16 to 15, $p = 0.07$).

Goepfert and Shaverdian both examined decisional regret in their cohorts using the Decision Regret Scale [39,40]. Goepfert's cross-sectional study reported an average score correlating to mild decision regret ($n = 935$, median follow-up 6 years) [40]. A total of 15.5% of the patients did exhibit moderate to strong regret, which was significantly associated with higher T classification, combination treatment (surgery and RT/CRT), smoking at diagnosis, and high MDASI-HN symptom score (associated with dysphagia symptom). Shaverdian [39] performed a single-arm cross-sectional study of HPV-associated OPSCC patients ($n = 24$) enrolled in a de-escalation clinical trial protocol (induction chemotherapy and then concurrent CRT with reduced dose RT of either 54 Gy or 60 Gy based on response). Patients were satisfied overall with their treatment, agreeing that they had made the right decision to pursue a de-escalated treatment. No patient regretted the choice or was dissatisfied with their treatment at a median follow-up of 24 months.

3.4.4. Relationship and Sexual Behavior

The relationship and sexual behavior domain comprised studies addressing impacts on sexuality and relationship quality/function.

Berg commented on sexuality in the context of a comparison of BOT cancer patients (n = 190) to patients with tonsillar carcinoma (n = 405) and to the general population (n = 190) [30]. Those treated with radiotherapy alone reported worse sexuality scores on the EORTC QLQ-HN35 than those who had surgery with adjuvant CRT (40 versus 28). Overall, BOT cancer patients and patients with HPV-negative disease reported worse sexuality scores than the general population and HPV-positive patients (36 versus 25, $p = 0.002$ and 48 versus 31, $p = 0.05$, respectively). There was no significant difference in subgroup analyses comparing subsite (BOT vs. tonsillar), gender, or disease stage.

Casswell utilized the EORTC Sexual Health Questionnaire (EORTC QLQ-SHQ-22) to assess the physical, social, and psychological aspects of sexual health [37]. This study demonstrated that an active sexual life is important to most in this cohort of HPV-associated OPSCC survivors (60%), but there was a much lower rate of recent significant sexual activity (20%). There was no difference in the rating of importance, nor in frequency of sexual activity in patients who knew their cancer was caused by HPV compared to those unaware of the viral etiology. The majority of patients reported no change (57%) or a positive change (27%) in the quality of relationships, while there was a negative impact on the sexual aspect of the relationship in 37% since their diagnosis.

Taberna's prospective research compared the effects of diagnosis and treatment on relationship and sexual behavior in HPV-positive (n = 142) and negative patients (n = 120) [41]. In both groups, they found a high satisfaction with their relationship in elements such as honesty with their partner, lack of regret, confidence in the future of the partnership, and having an overall happy relationship, using the Dyadic Adjustment Scale. There was a significant decrease in frequency of sexual activity at 6-month follow-up for both cohorts ($p < 0.01$).

3.5. Association of Psychosocial QOL and Treatment Modality

Berg reported no difference in depression, anxiety, or social quality of life scores when comparing OPSCC patients treated with primary CRT versus surgery with adjuvant RT/CRT [30]. Kaffenberger showed that patients receiving higher doses of RT to the ipsilateral parotid

gland experienced higher anxiety levels and worse social function [27]. Goepfert's study sub-analyzed decision regret based on treatment modality and found that receiving combined treatments (primary CRT or surgery and adjuvant RT/CRT) was an independent predictor of decisional regret [40]. Dziegielewski demonstrated significant differences in overall attitude in patients who received adjuvant RT ($p = 0.003$) and adjuvant CRT ($p = 0.04$) compared to those without adjuvant therapy [38].

3.6. Association of Psychosocial QOL and HPV Status

A summary of all HPV-related results is included in Table 3. Six studies did not have a non-HPV-associated OPSCC comparator group [27,33,35,36,37,39].

Six studies reported specific mental health and emotional wellbeing-related results for HPV-associated OPSCC patients. Berg and Korsten noted better emotional functioning in the HPV-positive cohort and Janz described a significant decrease in depression scores in the HPV-positive OPSCC cohort, without a significant decrease in the oral cavity cancer patients [28,30,33]. In the studies by Qualliotine, Rajeev-Kumar, and Shinn, no significant differences in mental health scores between HPV-positive versus HPV-negative cohorts were identified [29,31,34]. In the aforementioned studies, Qualliotine focused specifically on the mental health components of depression, Rajeev-Kumar on mood and anxiety, and Shinn on depression [29,31,34].

Berg reported better social functioning in the BOT OPSCC patients who were HPV-positive, using the EORTC QLQ-C30, while Dziegielewski did not find any difference in social function or social attitude between HPV-positive and negative cohorts, using the Head and Neck Cancer Inventory (HNCI) [30,38]. Korsten found that the HPV-positive cohort had worse social functioning during the treatment but recovered faster and to a greater degree in follow-up [32].

Dziegielewski found no difference in overall attitude based on HPV status, and Goepfert did not identify any difference in decisional regret in HPV-associated or non-associated patients [38,40]. There was a non-significant decrease of cancer worry at 12-month follow up for both the HPV-positive OPSCC patients and the oral cavity cancer patients described by Janz [28].

Taberna conducted the sole study describing the effect of HPV on relationship, finding no difference at baseline, but higher distress, though not significant, in the HPV-positive patients [41].

4. Discussion

This scoping review aimed to understand the landscape of published literature on the psychosocial QOL in oropharyngeal cancer patients and determine whether treatment regimens or HPV status play a role. Despite the rise in OPSCC globally and the current efforts to de-escalate treatments to allow for better QOL outcomes with long-term survival, this review identified a lack of observational research in this field.

The main mental health and emotional wellbeing theme findings are heterogeneous within the ten different studies. Interestingly, Janz, Berg, Qualliotine, and Korsten's research all identified better mental health and emotional scores in patients with HPV-associated disease when compared to non-HPV-associated head and neck cancers (oropharyngeal or oral cavity) [28,30,31,32]. In contrast, Rajeev-Kumar and Shinn did not find an association with HPV status and mental health scores [29,34].

Within the social wellbeing and function domain, there were significant positive findings. Kaffenberger identified worse social scores in patients with higher RT doses to their ipsilateral parotid gland, and Dziegielewski found that post-operative social scores reached a low at three months but returned to baseline after one year [27,38]. Korsten noted that HPV-positive patients had better social functioning at baseline, worsened during treatment, but recovered to a greater level [32]. It is unclear why HPV-associated OPSCC patients have a greater toxicity burden from treatment, yet recover more quickly and better than HPV-negative patients; however, this is consistent with other research [42,43].

The stress category that emerged from the thematic analysis comprises four diverse concepts. These different feelings were identified in select subgroups within each study: younger patients

and those with lower global QOL, higher symptom interference scores, and worse mental health scores had greater levels of fear of cancer recurrence [35,39]. A worse overall attitude/anxiety with function was found in patients receiving adjuvant therapy [38]. Greater decisional regret was reported in patients with higher T classification, those receiving combination treatment, smokers, and those with more dysphagia-related symptoms [39,40]. There was no difference in cancer worry scores between the groups compared (HPV-associated OPSCC patients vs. oral cavity cancer patients) [28].

The three studies focusing on relationship and sexual behavior employed three different PROMs, creating a challenge in comparison. Interestingly, none of the studies identified significant differences in their scores based on HPV status [30,37,41]. However, Taberna did learn that 28% of patients felt guilty about exposing their partner to HPV. A secondary objective was to identify the impact of different treatment modalities on psychosocial QOL; however, only three studies addressed this topic. Kaffenberger compared advanced stage OPSCC patients treated for curative intent with CRT (non-surgical cohort) to surgery and adjuvant RT or CRT (surgical cohort) [27]. Social scores from the UW-QOL questionnaire and depression and anxiety-specific PROM screening did not demonstrate differences between the two treatments. Of note, patients who received higher doses of RT to the ipsilateral parotid gland experienced higher anxiety levels and worse social function. Goepfert's study demonstrated a significant relationship between decisional regret scores and multimodality therapy [40]. While the cohort undergoing surgery and adjuvant therapy had the highest level of decisional regret, this represented few patients within the study and thus must be interpreted with caution (n = 17, 1.8% of study population). Shaverdian's patients were enrolled in the CCRO-22 clinical trial and treated with neoadjuvant chemotherapy and de-escalated CRT based on individual response, reporting excellent decision regret outcomes [39]. The lack of a control group nonetheless limits analysis of psychosocial impact based on treatment modality.

With the rise in HPV-associated OPSCC, it is important to search for significant differences within the HPV-positive and HPV-negative cohorts. Higher emotional and social functioning and significant improvement in depression over time were found in the HPV-positive patients [28,30,32]. No significant differences were found in multiple other studies, and, specifically, no

association of HPV status with any HNCI QOL domains [38], mood scores [29,31,34], decisional regret [40], or levels of relationship distress [41].

Within the thematic analysis, multiple PROMs were used for an individual symptom. It is clear that there is no standardized, uniform mental health survey specific for head and neck oncology patients, given that the ten studies within this review used eight different PROMs reporting on mental health or emotional well-being. The heterogeneity of PROMs utilized poses a difficulty in comparing outcomes. A recent study comparing different depression and anxiety PROMs in head and neck cancer patients found the prevalence of moderate and severe symptoms differed between surveys within the same patient cohort (using the Edmonton Symptom Assessment Scale, PHQ-9 and GAD-7) [44]. A meta-analysis performed by Krebber found that 8–24% of oncology patients suffered from depression, but these values were variable based on cancer type, treatment phase, and the screening instrument used to measure depression [45]. Similarly, one of the studies included in this review reported a significant association of depression and overall survival in multivariable modelling using the PHQ-9, while there was no significant risk for mortality using the CES-D [34]. While PROMs are valuable, establishing standard, agreed-upon metrics tailored to the head and neck patient population will be an important future goal to create comparable research outcomes and to decrease survey fatigue [46].

Many completed or ongoing clinical trials are attempting to change the standard treatments for HPV-positive OPSCC and reduce the treatment-related secondary effects [4,12,13]. Patients can be offered a plethora of potential treatments. This era of patient-centered decision making may open the door for further distress due to a shift of responsibility to the patient and the possibility of decision regret [47]. Windon performed a qualitative analysis of treatment decision-making in OPSCC patients who were offered surgery or RT as primary curative intent treatments [48]. Challenges in decision making included the difficulty of incorporating the perceived recommendation of the physician, personal desire for tumor excision, fear of specific secondary effects of treatment, and individual values.

In this scoping review, decision regret was measured in an HPV-positive OPSCC cohort enrolled in a de-escalation clinical trial [39]. At 16 to 30 months post-treatment, patients logged excellent

scores on the Decision Regret Scale. In general, late RT-related adverse events, commonly xerostomia and dysphagia, are often the main drivers in post-treatment negative QOL [49,50,51,52]. The goal of lowered RT doses is shared in other trials to minimize these secondary effects [53,54,55]. While Shaverdian's results are positive, it is important to note that this was a small population (n = 24) and a median two-year follow-up may not have provided adequate time to capture the late post-radiation adverse effects. Goepfert assessed a large OPSCC cohort (n = 935) at a median of six years post-treatment, noting mild levels of decisional regret on average [40]. Higher levels of decision regret were associated with higher T staging, multimodal treatment, smoking at diagnosis, and high MDASI-HN symptom score. Decision regret is not yet well studied in OPSCC, despite current efforts to change the standard-of-care treatment, and this is a potential outcome to consider in future research.

There are several limitations to note within this scoping review. While an extensive search of four large databases with diverse target audiences was performed, additional databases may have yielded further results. Grey literature was not explored and published abstracts were not included. This was decided because the lack of full available data would not allow for analysis. Finally, the heterogeneity of themes and patient-reported outcome measures limited the ability to compare studies and draw conclusions.

5. Conclusions

This review has reported the current status of emotional, social, and psychological QOL in OPSCC survivors. With the rise of HPV-related OPSCC and characteristically younger, healthier patients with improved prognostication, treatment-related morbidity and associated psychosocial impact is now a key area of discussion amongst advocacy groups and oncology professionals alike. Specifically, decisional regret within the category of stress and the impact on relationships and sexuality have been recognized as unique avenues for future research, given the many ongoing clinical trials and the association of OPSCC with HPV, respectively. Few studies have explored these concepts, and no review has focused on these outcomes thus far. This scoping review identified a need to establish a uniform head and neck oncology-specific QOL metric to more consistently assess psychosocial burden within these patients

6. Tables

Table 1. Inclusion and exclusion criteria:.

Abstract criteria		
Study characteristics	**Inclusion criteria**	**Exclusion criteria**
Participants (population)	- Adults, aged 18+ - Oropharyngeal squamous cell carcinoma diagnosis	- Other cancers (head and neck carcinomas or otherwise, if oropharyngeal squamous cell carcinoma is not specified for)
Study design (concept)	- Observational studies with a psychosocial focus	- Secondary research - Published guidelines - Cost-effectiveness studies
Outcome measures (context)	- Validated patient reported outcome measures with specific mention to psychosocial quality of life	- Quality of life not reported in the abstract - Qualitative research without validated metrics
Other (publication)	- Published in a peer-reviewed journal - English language	- Dissertations/thesis - Study protocols - Conference proceedings - Non-English language
Full-text criteria (additional criteria)		
Study design	- HPV status testing performed	
Outcome measures	- Psychosocial quality of life is an outcome of the study	- Psychosocial quality of life is not a focus of the study

Table 2: Thematic analysis of psychosocial quality of life measures in oropharyngeal cancer patients

Primary author, Year	Study design	Country	Participant characteristics	Comparator	HPV /P16 status of participants	Cancer stage	Treatment	Time period	PROM	Summary of results
Mental health and emotional wellbeing										
Berg, 2021[30]	Cross-sectional	Sweden	190 patients with BOT cancer, aged 33-84 (median 63), 137 male, 53 female	Patients with tonsillar cancer, general population	Positive: 131 Negative: 20 Missing: 39	Stage I-II: 27 Stage III-IV: 162 Missing: 1 (AJCC 7th edition)	RT: 56 CRT: 85 Surgery +/- RT: 34 Surgery + CRT: 14 No adequate treatment: 1	15 months post-treatment	EORTC QLQ-C30, EORTC QLQ-H&N35	Emotional function is higher in general population and in males, worse in HPV negative patients, same in tonsil cancer patients.
Casswell, 2021[35]	Cross-sectional	Australia	136 patients with HPV-associated oropharyngeal cancer, aged 42-87 (median 61), 114 male, 22 female	N/A	Positive: 136/136	Stage I: 74 Stage II: 22 Stage III: 40 (AJCC 8th edition)	RT: 16 CRT: 120 Salvage surgery: 1	Mean 2.8 years post-treatment (range 1-5.5 years)	EORTC QLQ-C30, MDASI-HN, PROMIS, Fear of Cancer Recurrence Inventory	Moderate levels of anxiety and depression were reported in 11% and 4% of patients, respectively. Severe levels of anxiety and depression were both reported in 1% of patients, respectively. PROMIS anxiety and depression scores were significantly associated with fear of cancer recurrence scores.
Janz, 2019[28]	Prospective	USA	21 patients with HPV-associated oropharyngeal cancer, aged 49-76 (mean 58.2), 19 male, 2 female	17 patients with oral cavity cancer who smoke aged 32-76 (mean 55), 9 male, 8 female	Oropharynx cohort - Positive: 21/21 Oral cavity cohort – Positive 0/17	Stage IV (oropharynx): 16 Stage IV (oral cavity): 11 (AJCC 7th edition)	Surgery: 13 RT: 16 Chemotx: 17 **Combination therapies:** Surgery + RT:2 CRT: 5 Surgery + CRT: 9 Other: 3	12 month follow-up	Cancer worry "Assessment of Survivor Concerns" instrument, CES-D, Cancer Behavior Inventory	At baseline: there was no difference in depression score between HPV positive OPSCC patients and smoking oral cavity patients (p=0.041) At 12-months: depression decreased over time for the HPV positive cohort (p=0.03)
Kaffenberger, 2021[27]	Retrospective	USA	44 patients with advanced oropharyngeal cancer treated with curative intent treated with primary CRT, with a mean age of 57.6, 37 male, 7 female	29 patients with advanced oropharyngeal cancer treated with curative intent treated with surgery and adjuvant RT/CRT, with a mean age of 56.7, 25 male, 4 female	Positive: 66/73 Negative: 3/73 Unknown: 4/73	Stage III: 10 Stage IVa: 62 Stage IVb: 1 (AJCC 7th edition)	CRT: 44 Surgery + RT: 9 Surgery + CRT: 20	Median follow-up post treatment 29.7 months (range 6.1-133 months)	UW-QOL, PHQ-8, GAD-7, NDI, EAT-10	On PHQ-8: no significant difference in depression scores between groups (p=0.71) On GAD-7: no significant difference in anxiety scores between groups (p-0.77), mean dose of RT delivered to the ipsilateral parotid correlated to more anxiety symptoms.
Korsten, 2021[32]	Prospective	Netherlands	78 patients with HPV-associated	120 patients with HPV-	Positive: 78/270	Stage I: 37 Stage II: 57	RT: 99 Surgery: 4	24 months	EORTC QLQ-C30,	Emotional functioning mean scores were equal at baseline, 6

			oropharyngeal cancer, mean age 59.9, 59 male, 19 female	negative oropharyngeal cancer, mean age 59.9, 120 male, 72 female		Stage III: 59 Stave IV: 103 (AJCC 7th edition)	Combination: 89		EORTC QLQ-H&N35	weeks and 3 months after treatment between HPV-positive and negative cohorts (p=0.039). Scores improved more in HPV-positive patients at 6, 12, and 24 months compared HPV-negative patients.
Lee, 2022[33]	Cross-sectional	USA	25 patients with HPV-associated oropharyngeal cancer, aged 41-80 (median 58), 23 male, 2 female	N/A	Positive: 25/25	Stage II: 1 Stage III: 2 Stage IVa: 21 Stage IVb: 1 (AJCC 7th edition	All received neoadjuvant chemotherapy and transoral robotic surgery	Mean 4.3 years (2.0-7.6 years)	UW-QOL	Patients treated with this protocol reported less anxiety compared to the normative cohort, demonstrating near-normal recovery in long-term outcomes (p=0.005). There was no significant difference in mood scores of trial participants compared to controls (p=0.288).
McDowell, 2021[36]	Cross-sectional	Australia	136 patients with HPV-associated oropharyngeal cancer, aged 42-87 (median 61), 114 male, 22 female	N/A	Positive: 136/136	Stage I: 74 Stage II: 22 Stage III: 40 (AJCC 8th edition)	RT: 16 CRT: 120 Salvage surgery: 1	Mean 2.8 years post-treatment (range 1-5.5 years)	EORTC QLQ-C30, MDASI-HN, PROMIS, Fear of Cancer Recurrence Inventory	Anxiety (t-score 53.5 v 44.1, *d* = 0.80), and depression (t-score 42.8 vs. 51.3, *d* = 0.84) scores were significantly worse in the low functioning subgroup. PROMIS anxiety score: normal/low: 88.9%, moderate: 9.6%, severe: 1.5^ PROMIS depression score: normal/low: 95.6%, moderate: 3.7%, severe: 0.7%. Increasing age is associated with worse anxiety scores (-0.2/year increase, p=0.034)
Qualliotine, 2017[31]	Retrospective	USA	65 patients with oropharyngeal cancer between October 2011 and September 2014 who had completed the depression screening questionnaire prior to treatment, aged 44-88 (median 59.9), 55 male, 10 female	N/A	Positive: 50 Negative 15	Stage I or II: 4 Stage III or IV: 61 (AJCC 7th edition)	N/A	N/A	CES-D	A lower proportion of HPV-associated OPSCC patients than HPV-negative patients reported using antidepressants (8% vs. 27%, p = 0.05). 44.9% of the patients screened positive for depression. No association of depression score and HPV status.
Rajeev-Kumar, 2019[29]	Retrospective	USA	69 patients treated with curative intent RT between 2013 and 2016 with up to 3 year	N/A	Positive: 43 Negative: 26	Stage I: 4 Stage II: 7 Stage III: 12 Stage IVa: 41 Stage IVb: 4	Pre-RT surgery: 37 RT: 69 Induction chemotx: 16	12 months post-RT	UW-QOL	Of the 51 patients with active alcohol use, 11.8% had a severe mood score and 33.3% had a severe anxiety score before starting RT. After 12 months, 88%

			follow-up, with a mean age of 58.3, 51 male, 18 female			(AJCC 7th edition)	Concurrent CRT 38			of those patients returned to baseline or better mood (only 52% response). At consultation, anxiety was worse than mood score. At 12 months, anxiety remained mildly worse than mood but both were better than pre-treatment. Multivariate regression: no association between worse emotional status and patient/disease characteristics at 12 months, PEG placement, surgery versus CRT, HPV infection. Longer duration of treatment is more likely to be associated with worse mood (>50 days of treatment). Physical symptom worsening is associated with worse anxiety (taste scores, saliva scores) and with worse mood (swallow scores).
Shinn, 2016[34]	Prospective	USA	130 patients diagnosed with new diagnosis of oropharyngeal cancer between March 2005 and June 2007 treated with RT, aged 28.4-78.5 (mean 56.8), 94 male and 108 male, 22 female	N/A	Positive: 15/22 Negative 7/22 *Only 22 patients tested	Stage I or II: 10 Stage III or IV: 119 Missing: 1 (AJCC 7th edition)	RT: 130 Neoadjuvant chemotx: 47 Concurrent CRT: 51	Median of 4.9 years (range of 0.1-6 years)	PHQ-9, CES-D	19 patients (15%) screened positive for depression at baseline. In the univariate analysis of the PHQ-9, depression's association with survival was borderline (p=0.061) but significant in the multivariate analysis (p=0.022). Dichotomized, PHQ-9 positive depression was associated with overall survival (p=0.022). As a multivariate model, for every increased unit of the PHQ-9, the risk for reduced survival increased by a factor of 10%. Depression was associated with disease recurrence in univariate (p=0.028) and multivariate analysis (p=0..025). For every increased unit of the PHQ-9, the risk for recurrence increased by a factor of 10%. No association of HPV status and depression
Social wellbeing and function										

Berg, 2021[30]	Cross-sectional	Sweden	190 patients with BOT cancer, aged 33-84 (median 63), 137 male, 53 female	Patients with tonsillar cancer, general population	Positive: 131 Negative: 20 Missing: 39	Stage I-II: 27 Stage III-IV: 162 Missing: 1 (AJCC 7th edition)	RT: 56 CRT: 85 Surgery +/- RT: 34 Surgery + CRT: 14 No adequate treatment: 1	15 months post-treatment	EORTC QLQ-C30, EORTC QLQ-H&N35	Compared to the general population, BOT patients have worse social function (p<0.001), social eating (p<0.001), social contact (p<0.001). No difference in social domains in BOT patients who are stage I-II versus III-IV, males versus females, HPV+ versus HPV-, different treatment modalities or adjuvant treatment regimens. Patients with BOT cancer had worse social eating scores than patients with tonsil cancer (p=0.001).
Dziegielewski, 2013[38]	Prospective	USA	81 patients with oropharyngeal cancer treated with transoral robotic surgery	N/A	HPV positive: 51 HPV negative: 20 p16 positive: 60 p16 negative: 11 Missing: 10	Stage I: 7 Stage III: 9 Stage IV: 63 Missing: 2 (AJCC 7th edition	Surgery: 81 Adjuvant RT: 69 Adjuvant CRT: 49	12 month post-operatively	HNCI	All health related quality of life scores declined at 3 weeks post=operatively including social scores, which continued to drop but reached the nadir at 3 months. Social scores recovered and were indifferent from baseline (p>0.05) at 12 months. No difference of social function (p=0.81) or social attitude (p=0.57) when in HPV+ or HPV- patients.
Kaffenberger, 2021[27]	Retrospective	USA	44 patients with advanced oropharyngeal cancer treated with curative intent treated with primary CRT, with a mean age of 57.6, 37 male, 7 female	29 patients with advanced oropharyngeal cancer treated with curative intent treated with surgery and adjuvant RT/CRT, with a mean age of 56.7, 25 male, 4 female	Positive: 66/73 Negative: 3/73 Unknown: 4/73	Stage III: 10 Stage IVa: 62 Stage IVb: 1 (AJCC 7th edition)	CRT: 44 Surgery + RT: 9 Surgery + CRT: 20	Median follow-up post treatment 29.7 months (range 6.1-133 months)	UW-QOL, PHQ-8, GAD-7, NDI, EAT-10	The mean dose delivered to the ipsilateral parotid gland was correlated with worse scores on the social aspects of the UWQOL No difference in social score based on treatment modality.
Korsten, 2021[32]	Prospective	Canada	78 patients with HPV-associated oropharyngeal cancer, mean age 59.9, 59 male, 19 female	120 patients with HPV-negative oropharyngeal cancer, mean age 59.9, 120 male, 72 female	78/270	Stage I: 37 Stage II: 57 Stage III: 59 Stave IV: 103 (AJCC 7th edition)	RT: 99 Surgery: 4 Combination: 89	24 months	EORTC QLQ-C30, EORTC QLQ-H&N35	For HPV-associated patients, social functioning was better before treatment, worsened more during treatment, and recovered better and faster at follow-up compared to patients with an HPV-negative cancer (p=0.033). On mixed model analysis, social contact and social eating did not demonstrate a significant

										difference between HPV-positive and negative patients.
Stress										
Casswell, 2021[35]	Cross-sectional	Australia	136 patients with HPV-associated oropharyngeal cancer, aged 42-87 (median 61), 114 male, 22 female	N/A	Positive: 136/136	Stage I: 74 Stage II: 22 Stage III: 40 (AJCC 8th edition)	RT: 16 CRT: 120 Salvage surgery: 1	Mean 2.8 years post-treatment (range 1-5.5 years)	EORTC QLQ-C30, MDASI-HN, PROMIS, Fear of Cancer Recurrence Inventory	Clinically significant fear of cancer recurrence was reported in 53% of patients (72/135). Younger patients were more likely to report high fear of cancer recurrence (-0.9/5 years; p=0.031). Those with higher fear of cancer recurrence also had lower global QOL (-0.8/10 unit increase; p=0.012), had higher symptom interference with daily activities (0.8/unit increase; p=0.17) (MDASI-HN), and greater anxiety (0.4/unit; p<0.001) and depression scores (0.3/unit; p<0.001) (PROMIS).
Dziegielewski, 2013[38]	Prospective	USA	81 patients with oropharyngeal cancer treated with transoral robotic surgery	N/A	HPV positive: 51 HPV negative: 20 p16 positive: 60 p16 negative: 11 Missing: 10	Stage I: 7 Stage III: 9 Stage IV: 63 Missing: 2 (AJCC 7th edition	Surgery: 81 Adjuvant RT: 69 Adjuvant CRT: 49	12 month post-operatively	HNCI	There was a significant change of overall attitude from baseline, but small clinically important difference and a good recovery at 12 months. No difference of overall attitude in HPV+ or HPV- patients (p=0.56). Significant differences in overall attitude in patients who received adjuvant RT (p=0.003) and those receiving adjuvant CRT (p= 0.04).
Goepfert, 2017[40]	Cross-sectional	USA	935 patients diagnosed with oropharyngeal cancer between January 2000 and December 2014, aged 32-84 (median 56), 791 male, 144 female	N/A	Positive: 456 Negative: 59 Unknown: 420		RT alone: 276 CRT: 628 Surgery alone: 8 Surgery + CRT: 17 RT + salvage surgery: 6	1.5-15.6 years (median 6)	Decision regret scale, MDASI-HN	Patients reported a low level of decisional regret: mean score of 12.7/100 = “mild” 38.6% had no regret, 45.8% had “mild” regret, 15.5% of cohort had ”mod-strong” regret Regret significantly associated with higher T classification, combination treatment (surgery + RT/CRT), smoking at diagnosis, high MDASI-HN symptom score (associated with dysphagia symptom).
Janz, 2019[28]	Prospective	USA	21 patients with HPV-associated oropharyngeal cancer, aged 49-76 (mean 58.2), 19 male, 2 female	17 patients with oral cavity cancer who smoke aged 32-76 (mean 55), 9 male, 8 female	Oropharynx cohort - Positive: 21/21 Oral cavity cohort – Positive 0/17	Stage IV (oropharynx): 16 Stage IV (oral cavity): 11 (AJCC 7th edition)	Surgery: 13 RT: 16 Chemotx: 17 **Combination therapiess:** Surgery + RT:2 CRT: 5	12 month follow-up	Assessment of Survivor Concerns instrument, CES-D, Cancer	At baseline, the HPV+ OPSCC patients had a mean cancer worry score of 2.8 and the oral cavity cohort had a score of 3.25 (p=0.1) At baseline, the HPV+ OPSCC patients had a self-efficacy score

							Surgery + CRT: 9 Other: 3		Behavior Inventory	of 97.8 and the oral cavity cohort had a scope of 96.3 (p=0.79) Cancer worry decreased over time but was not statistically significant (2.8 to 2.4, p=0.11)
Shaverdian, 2019[39]	Retrospective	USA	24 consecutive patients enrolled in the CCRO-22 phase II clinical trial for locally advanced HPV-positive oropharyngeal cancer between March 2014 to March 2015, aged 49-83 (median 62), 21 male, 3 female.	N/A	Positive: 24	Stage III/IV: 24 (AJCC 7th edition)	Induction chemotherapy: 24 CRT: 24 (15 = 54 Gy, 10 = 60 Gy)	24 months (range of 16-30 months)	Decision Regret Scale, Chicago Priorities Scale	83% were "totally satisfied" with their treatment and its result. 17% said that they were "somewhat satisfied." None had any level of dissatisfaction with the treatment. 92% "strongly agree" that their decision to proceed with de-escalated therapy was the "right decision," 8% "agree." 92% strongly disagreeing to the statement "I regret the choice I made," none "agree" or "strongly agree." 75% "strongly agree" with the statement "I would go for the same choice if I had to do it again," 21% "agree" and the remaining 1 patient selected "neither agree nor disagree." 92% "strongly agree" hat their decision to receive de-escalated therapy was a "wise one," with the remaining 8% patients selecting "agree." The fear of disease recurrence was greater than expected in 42%, as expected in 33% and less than originally expected in 25%.
Relationship and sexual behavior										
Berg, 2021[30]	Cross-sectional	Sweden	190 patients with BOT cancer, aged 33-84 (median 63), 137 male, 53 female	Patients with tonsillar cancer, general population	Positive: 131 Negative: 20 Missing: 39	Stage I-II: 27 Stage III-IV: 162 Missing: 1 (AJCC 7th edition)	RT: 56 CRT: 85 Surgery +/- RT: 34 Surgery + CRT: 14 No adequate treatment: 1	15 months post-treatment	EORTC QLQ-C30, EORTC QLQ-H&N35	BOT cancer patients treated with radiotherapy alone reported worse sexuality scores than those treated with surgery and adjuvant CRT (40 versus 28). BOT cancer patients have worse (but not statistically significant) sexuality than the general population (p=0.002), from tonsillar cancer patients (p=0.16), comparing genders (p=0.27), nor tumor stage (p=0.44). HPV-negative patients report worse sexuality than HPV-positive patients (p=0.05)

Casswell, 2021[37]	Cross-sectional	Australia	136 patients with HPV-associated oropharyngeal cancer, aged 42-87 (median 61), 114 male, 22 female	N/A	Positive: 136/136	Stage I: 74 Stage II: 22 Stage III: 40 (AJCC 8th edition)	RT: 16 CRT: 120 Salvage surgery: 1	Mean 2.8 years post-treatment (range 1-5.5 years)	EORTC QLQ-C30, EORTC QLQ-SH22, MDASI-HN, PROMIS, Fear of Cancer Recurrence Inventory	An active sex life was considered important to the majority of survivors (60%) Only 20% of patients reported "quite a bit"/"very much" sexual activity in the 4 weeks prior Among those that reported high importance of an active sex life, 72% reported "little to no sexual activity" No difference in importance of sexual activity or recent sexual activity in patients who reported knowing if their cancer was caused by HPV Patients aware of the HPV association did not report negative changes more frequently in their general relationship (20% versus 7%), nor in their sexual relationship (39% versus 39%).
Taberna, 2017[41]	Prospective	USA	172 patients with oropharyngeal cancer who self-reported that they were in a partnered relationship, aged 18-89, 125 male, 17 female (HPV+ cohort demographics)	90 patients with oral cavity cancer 81 partners of patients with oropharyngeal cancer	Positive: 142 Negative: 30	HPV+ cohort: Stage I: 5 Stage II: 7 Stage III: 43 Stage IV: 78 (AJCC 7th edition)	HPV+ cohort; Surgery: 45 CRT: 89 RT: 7 Chemo 1 Unknown 1	6-month follow up	Dyadic Adjustment Scale	Few patients or partners reported distressed relationships at baseline or at 6-months, with no significant difference when analyzed by HPV-status. Patients reported high relationship satisfaction; confided in their partner almost always (>85%), rarely/never regretted the relationship (~95%), and had high confidence in the latter (>75%). Strong majorities also described their relationships as happy/very happy (>90%). Demonstrations of affection: >65% agreed with their partner about sexual relations. The majority reported no issues in the relationship with regards to being too tired for sex (>65%) or not showing love (>80%). Very few patients reported relationship distress (T-score </= 40) in any subscale. 38% of HPV-positive patients reported that their relationship with their partner had not changed. When a change was perceived, it was generally positive, namely

			feeling supported by their partner (92%) and that their relationship had become stronger (69%). Approximately 25% of patients either blamed themselves for their cancer diagnosis (26%) or felt guilty about exposing their partner to HPV (28%).

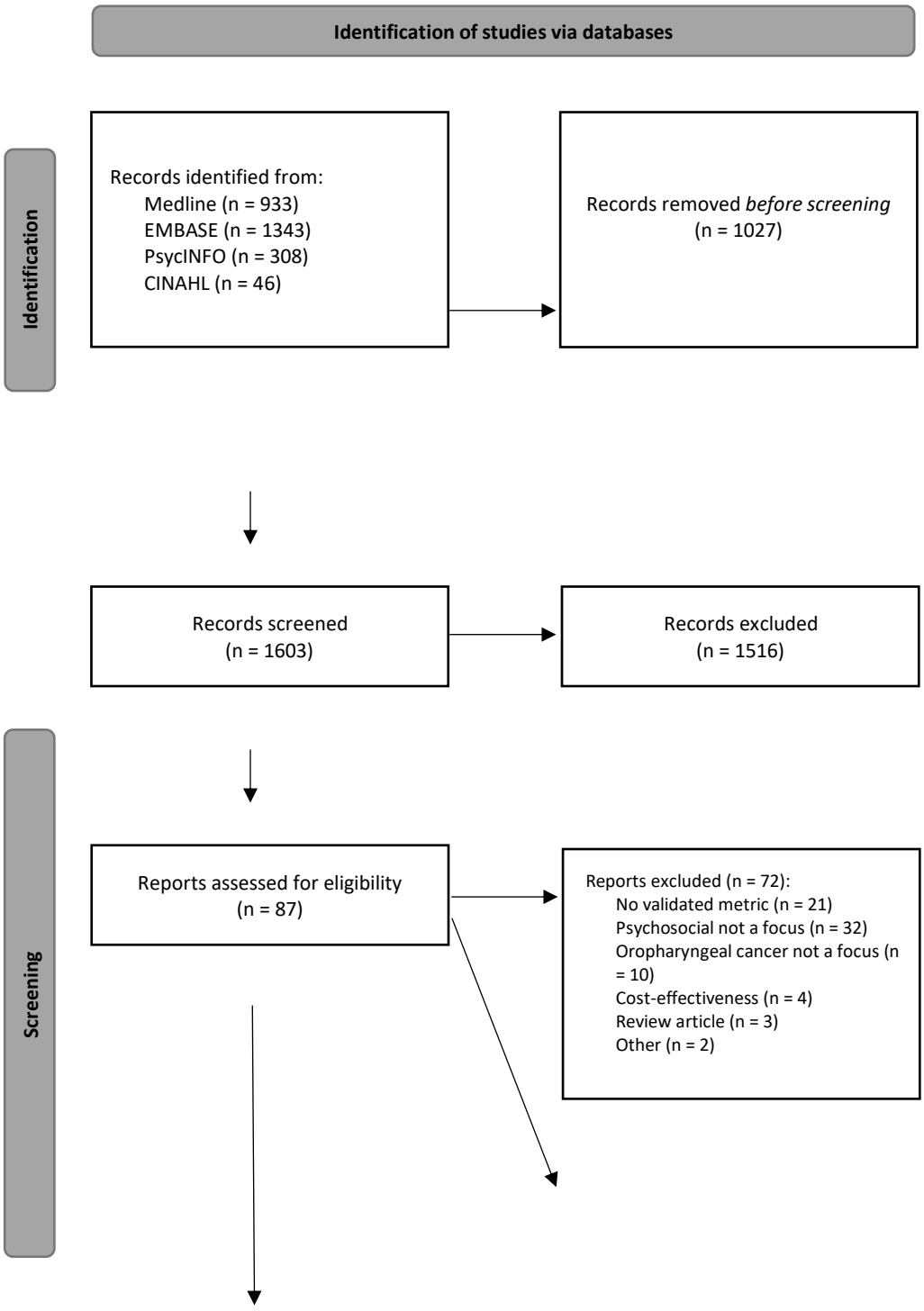
Table 3: Summary of results comparing HPV-positive and HPV-negative cohorts. Bolded = significant results.

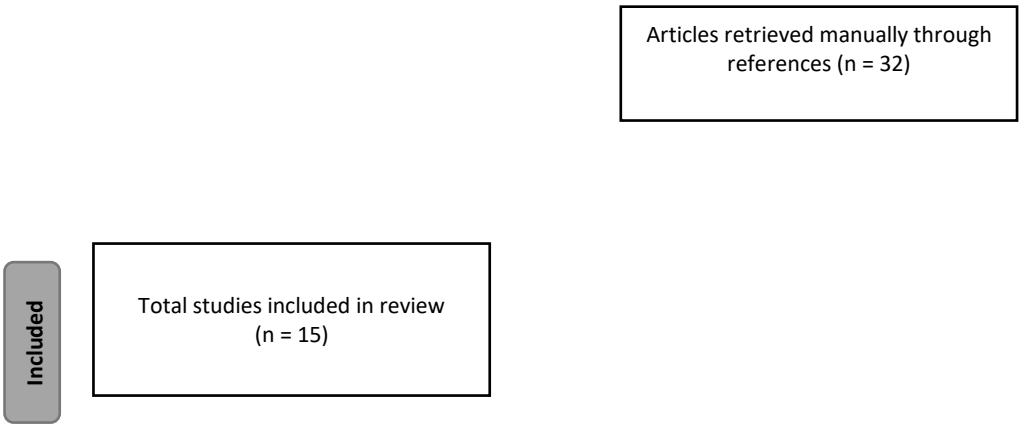
Study	HPV-related results
	Mental health and emotional wellbeing
Berg, 2021[30]	**HPV-positive BOT cancer patients had better emotional functioning (p=0.004) than the HPV-negative cohort on EORTCQLQ-C30** (Primary text, Table 5)
Janz, 2019[28]	At baseline, HPV-positive OPSCC cohort had a non-significant difference in mean depression score compared to smoking oral cavity patients (12 versus 14, p=0.41). **Depression decreased significantly over time for the HPV-positive OPSCC patients (12 to 9.9, p=0.03) and non-significantly in the oral cavity patients (14 to 9.73, p=0.1) from baseline to 12 months.**
Korsten, 2021[32]	**Emotional functioning was significantly different between HPV-positive and negative patients: average scores were equal at baseline and in close follow-up (6 weeks and 3 months), but scores improved more in HPV-positive patients (p=0.039).**
Qualliotine, 2017[31]	There was no significant association noted between depression and HPV status (p>0.1) (Primary text: Figure 1).
Rajeev-Kumar, 2019[29]	There is no statistically significant relationship between anxiety or mood and human papillomavirus infection status (p=0.089 for anxiety; p=0.731 for mood).
Shinn, 2016[34]	There was no significant difference in depression scores between HPV-positive and HPV-negative patients.
	Social wellbeing and function
Berg, 2021[30]	**HPV-positive BOT cancer patients had better social functioning (p=0.01) than the HPV-negative cohort on EORTCQLQ-C30** (Primary text, Table 5)
Dziegielewski, 2013[38]	HPV status did not correlate with any quality of life domain (i.e. social function, social attitude, overall attitude) in the HNCI (p>0.5 for all domains, Primary text: Table 5)
Korsten, 2021[32]	**Social functioning recovered faster and to a better degree in HPV-positive patients (p=0.033)** (Primary text: Figure 2).
	Stress
Goepfert, 2017[40]	There was no significant difference in MDASI-HN symptom scores (p=0.27) or proportional decisional regret (p=0.37) based on HPV status (Primary text: Table 3)
Janz, 2019[28]	At baseline, HPV-positive OPSCC cohort had a non-significant difference in mean cancer worry compared to smoking oral cavity patients (2.8 versus 3.25, p = 0.1). Cancer worry decreased non-significantly over time in both the HPV-positive OPSCC patients (2.8 to 2.4, p=0.11) and the oral cavity patients (3.2 to 2.7, p=0.07). (Primary text: Table 2)
	Relationship and sexual behavior
Taberna, 2017[41]	At baseline, there was no statistically significant differences in levels of relationship distress between HPV-positive and HPV-negative patients.

	At 6 months follow up, a non-significant trend was noted of higher distress in the affection expression subscale of the DAS for HPV-positive patients compared to HPV-negative. 38% of HPV-positive patients reported that their relationship with their partner had stayed the same, and those who reported a change felt it was positive. 70% of partners reported favorable changes in their relationship since diagnosis. **A higher proportion of partners reported more stress in their relationship since the cancer diagnosis than the patients (39% versus 14%, p<0.01).** Approximately a quarter of patients blamed themselves for their cancer diagnosis or felt guilty about exposing their partner to HPV. 14% of partners felt guilty for possibly exposing their partner to HPV or were concerned that the HPV infection may have been a result of an extramarital relationship (their or their partner's). **There was a significant decline in sexual behavior frequency in both HPV-positive and HPV-negative cohorts** (Primary text: Figure 2, p<0.01).
	No comparison
Casswell, 2021[35]	N/A
Casswell, 2021[37]	N/A
Kaffenberger, 2021[27]	N/A
Lee, 2022[33]	N/A
McDowell, 2021[36]	N/A
Shaverdian, 2019[39]	N/A

7. Figures

Figure 1: PRISMA diagram of included studies.




Articles retrieved manually through references (n = 32)
Included
Total studies included in review (n = 15)

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9. Linking statement

This scoping review identified a gap in the literature as few studies overall have explored the psychosocial QOL outcomes in OPSCC patients. This finding encouraged the reflection that comprehensive QOL data should include multiple perspectives when assessing patient outcomes.

Thoughts lead to action and our research group began collecting a psychosocial QOL metric identified in this scoping review in a cohort of patients within our institution. At the McGill University teaching hospitals, OPSCC patients who meet criteria are offered standard of care chemoradiation treatment *or* enrollment in a surgery-based clinical trial.

Within the clinical trial, patient-reported QOL scales are regularly collected. These include general and head and neck oncology-specific QOL patient-reported outcome measures. However, from this scoping review, we have selected the Decision Regret Scale as an added metric to assess stress in our cohort of patients who made a choice regarding their treatment regimen.

The following chapter (Chapter 5, Manuscript 3), presents patient-reported long term QOL and functional outcomes in HPV-associated OPSCC patients undergoing neoadjuvant chemotherapy and transoral robotic surgery with neck dissection as definitive treatment.

Chapter 5: Quality of Life After Neoadjuvant Chemotherapy and Transoral Robotic Surgery for Oropharynx Cancer (Manuscript 3)

Jennifer A. Silver MD[1], Nathaniel Bouganim MD[2] , Keith Richardson MD[1], Melissa Henry PhD[1,2,3,4] , Marco A. Mascarella MD[1,6], José Ramirez-GarciaLuna MD[5], Nahid Golabi MSc[1], Alex M. Mlynarek MD[6], Anthony Zeitouni MD[1], Michael P Hier MD[6], Derin Caglar MD[7], Khashayar Esfahani MD[2], Nader Sadeghi MD[1,2,4]

1. Department of Otolaryngology – Head and Neck Surgery, McGill University Health Centre
2. Department of Oncology, McGill University Health Centre
3. Lady Davis Research Institute, McGill University
4. Research Institute of McGill University Health Centre
5. Division of Experimental Surgery, McGill University
6. Department of Otolaryngology – Head and Neck Surgery, Jewish General Hospital. McGill University
7. Department of Pathology, McGill University Health Centre

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Abstract:

Importance

Efforts are underway to deintensified treatment protocols for patients with human papillomavirus virus−associated oropharyngeal squamous cell carcinoma (HPV-OPSCC) to achieve similar excellent oncologic outcomes while reducing treatment-related adverse effects. Transoral robotic surgery (TORS) as primary treatment often requires adjuvant therapy due to the high incidence of nodal metastasis. Treatment with neoadjuvant chemotherapy followed by TORS and neck dissection (NECTORS), reserving radiation therapy for salvage, yields excellent oncologic outcomes.

Objective

To assess patient-reported quality of life (QOL) and functional outcomes among patients with HPV-OPSCC who undergo NECTORS.

Design, settings, and participants

This was a multicenter prospective cohort study of patients with HPV-OPSCC treated with the NECTORS protocol in 2017 to 2022. Consecutive patients with stage III or IVa HPV-OPSCC treated with NECTORS in 2017 to 2022 who had completed the primary QOL questionnaire at baseline and at least once during the 24-month follow-up period were included. Ninety-four patients were eligible, and 67 were included in the analyses.

Outcome measures

QOL questionnaires at baseline, and at month 1, 3, 6, 12, 18, and 24 posttreatment. Global score on the 30-item European Organization for Research and Treatment of Cancer Core quality of life questionnaire (EORTC-QLQ-C30) was the primary outcome; the head and neck extension module (EORTC-QLQ-HN35); the MD Anderson Dysphagia Inventory for dysphagia-related QOL; and the Decision Regret Scale were also used. Paired t tests assessed change between the baseline and 12- or 24-month patient-reported outcomes.

Results

Among the study population of 67 patients (median [range] age, 63 [58-67] years; 54 [80.6%] male) with HPV-OPSCC, the most frequent cancer subsites were palatine tonsil (41 [61%]) and base of tongue (26 [39%]); none required adjuvant RT. Global QOL at 24 months improved compared with baseline (mean difference, 9.49; 95% CI, 2.45 to 16.53). All EORTC-QLQ-C30

functional scores returned to baseline or improved within 3 to 6 months posttreatment and remained stable at 24 months. EORTC-QLQ-HN35 symptom scale scores improved or were stable at 24 months. The MD Anderson Dysphagia Inventory scores demonstrated no significant difference between baseline and month 12 for global scores (mean difference, −5.00; 95% CI, −20.91 to 10.91) and composite scores (mean difference, −7.66; 95% CI, −23.29 to 7.97). Median (range) score on the Decision Regret Scale was 5 of 100 (0-30), representing mild overall regret.

Conclusion and relevance

The findings of this multicenter cohort study indicate that use of the NECTORS protocol is associated with excellent QOL outcomes. QOL measures returned to baseline levels or were better than baseline, which represents positive outcomes for patients with HPV-OPSCC who undergo this treatment regimen.

Keywords:

oropharyngeal squamous cell carcinoma, human papillomavirus, de-escalation, transoral robotic surgery, neoadjuvant chemotherapy, quality of life

Introduction

There is an increasing incidence of human papillomavirus-associated oropharyngeal squamous cell carcinoma (HPV-OPSCC)[1,2]. Patients with this form of OPSCC have a better prognosis than those with conventional OPSCC treated with standard therapies[3,4,5]. Clinical presentation differs between these 2 groups given that patients with HPV-OPSCC patients tend to be younger and healthier, and most (60-70%) have positive nodal disease at time of diagnosis[2,6-9].

Standard management algorithms for newly diagnosed HPV-OPSCC cases opt for definitive concurrent chemoradiotherapy (CRT) or surgical resection with adjuvant radiation (RT) or CRT depending on pathologic risk stratification; therefore 90% or more of these patients are treated with RT[10,11]. Transoral robotic surgery (TORS) is currently practiced in the management of early OPSCC, often requiring adjuvant RT given the high nodal burden associated with this disease[10,12]. When considering locoregional effects of overall treatment, TORS with adjuvant treatment is not a de-escalation. RT to the oropharynx and neck has been associated substantial long-term and cumulative morbidity, including xerostomia, dental loss and poor oral health, dysphagia, possible gastrostomy tube dependency, airway and/or upper esophageal stenosis[5,13-15]. Considering that patients with HPV-OPSCC are young and have a good prognosis, they may live for many years with post-treatment toxic effects.

Many clinical trials evaluate deintensification strategies to maintain the positive oncological outcomes while minimizing adverse treatment effects on patients' quality of life (QOL). In 2016, a new paradigm for the treatment of HPV-OPSCC was shown to be feasible by Sadeghi et al[15]: neoadjuvant chemotherapy followed by definitive transoral surgery and selective neck dissection (NECTORS), reserving RT for salvage. This protocol has yielded excellent oncologic outcomes[16-18]. We hypothesized that NECTORS preserves patient-reported QOL outcomes. In the current study, we report on 2-year follow-up longitudinal QOL outcomes in patients receiving the NECTORS protocol as definitive treatment.

Methodology

Ethics approval for the study was obtained from the McGill University Health Centre research ethics board (MP-37-2018-3443, MP-37-2019-4659). Written informed consent was obtained from each participant before registration and treatment. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

This prospective cohort study was conducted between January 2017 to August 2022 at the McGill University Health Centre and the Jewish General Hospital (Montreal, Canada). Eligible patients had completed the NECTORS trial treatment protocol until August 2022 and were reported as having completed longitudinal QOL questionnaires[14,16]. As described in previous publications[16-18], eligible patients were 18 to 80 years of age and diagnosed with stage III or IVa (per American Joint Committee on Cancer's *Cancer Staging Manual*, 7th Edition[19]) treatment naïve HPV-OPSCC. Patients had no evidence of distant metastases, 5 or fewer nodal metastases on radiology findings without gross extracapsular extension (ECE; minimal radiological ECE is not excluded), Eastern Cooperative Oncology Group performance status less than 2, and no previous malignancy in the past 5 years.

The included patients completed QOL questionnaires at designated time points: baseline (ie, pre-treatment) and at 1, 3, 6, 12, 18, and 24 months posttreatment. Questionnaires were sent, collected, and managed using REDCap electronic data capture tools hosted at McGill University[20,21] or completed in-person during clinic visits. Patients who were included in this QOL analysis completed the primary QOL questionnaire at pre-treatment and 1 or more questionnaires during the 24 months posttreatment.

Adverse events were recorded and graded as per the *Common Terminology Criteria for Adverse Events* Version 5.0 (US National Cancer Institute guidelines)[22]. Chemotherapy-related kidney dysfunction and myelosuppression were monitored with regular laboratory testing. Kidney injury of grade 3 or higher was recorded as follows: grade 3, acute kidney injury requiring hospitalization or creatinine level 3 to 6 times the upper limit of normal; grade 4, life-threatening consequences or dialysis indicated or more than 6 times the upper limit of normal creatinine; and grade 5, death. Neutropenia of grade 3 or higher was recorded as follows: grade 3, absolute neutrophil count from 500 to 1000 μL (to calculate $\times 10^9$/L, multiply by 0.001) or grade 4, less

than 500 μL. Thrombocytopenia of grade 3 or higher was recorded as follows: grade 3, platelet count from 25 to 50 × 10^3/μL (to calculate 10^9/L, multiply by 1) and grade 4, less than 25 × 10^3/μL. Patients underwent pre- and posttreatment audiometry assessments to monitor ototoxicity, which was defined as hearing impairment on a 1, 2, 3, 4, 6, and 8 kHz audiogram or tinnitus in at least 1 ear. Four grades of ototoxicity were defined as follows: grade 1, average threshold shift of 15 to 25 dB at 2 contiguous test frequencies; grade 2, average threshold shift of greater than 25 dB at 2 contiguous test frequencies; grade 3, average thresh- old shift of greater than 25 dB at 3 contiguous test frequencies or if therapeutic intervention indicated; and grade 4, decrease in hearing to profound bilateral loss or nonserviceable hearing. Tinnitus was defined with 3 grades as follows: grade 1, mild symptoms with no intervention indicated; grade 2, moderate symptoms that limit instrumental activities of daily living; and grade 3, severe symptoms that limit self-care activities of daily living.

At pretreatment, all participants were presented to a multidisciplinary tumor board for therapeutic recommendations; they met with a head and neck radiation oncologist and a medical oncologist, and if eligible, were offered both standard of care (RT or CRT) and the NECTORS regimen. Standard nonoperative management consisted of 66 to 70 Gy of intensity-modulated RT to the primary site and to the involved lymph nodes or high-risk level lymph nodes, with or without concurrent high-dose cisplatin (100 mg/m^2 every 3 weeks)[11]. Patients enrolled in NECTORS had baseline margins tattooed if the tumor extended beyond of tonsillar subunit or ipsilateral base of tongue. The neoadjuvant chemotherapy regimen in NECTORS consisted of 3 cycles of docetaxel (75 mg/m^2) and cisplatin(75mg/m^2) as described previously[14-16]. Laterality of neck dissection was guided by radiologic distribution of nodal disease and/or location of primary tumor. Primary base of tongue tumors or primary tonsil tumors with more than a 1-cm extension into the soft palate or the base of tongue underwent bilateral neck dissection independent of radiologic findings. Intraoperative elective tracheostomy was performed and kept for 14 days as per the policy for patients undergoing TORS at 1 participating institution (Jewish General Hospital). Post-operative pathology results were discussed with the tumor board to determine the need for adjuvant RT.

Patients who completed both pretreatment and 24-month QOL questionnaires were included in the paired analysis. Of the 94 patients who were treated with the NECTORS protocol from January 2017 to August 2022, 67 patients met all the inclusion criteria (insufficient QOL forms, n = 27).

The global score on the 30-item European Organisation for Research and Treatment of Cancer Core quality of life questionnaire (EORTC-QLQ-C30 was the primary outcome. The remaining EORTC QLQ-C30 domain and symptom scores, as well as other QOL metrics were used, including the Head and Neck extension module (EORTC-QLQ-HN35) measuring head and neck cancer-related symptoms, and the MD Anderson Dysphagia Inventory (MDADI) to measure dysphagia-related QOL[23-36]. Higher domain scores represent better QOL, while higher symptom scores represent worse QOL. A cross-sectional assessment of psychosocial stress was undertaken using the Decision Regret Scale (DRS), a score of distress due to a health care decision. Thresholds of regret scores are coded as none, 0; mild 1 to 25; moderate to strong, greater than 25[27,28]. All measures have been previously used, and have good psychometric properties when administered to patients with head and neck cancer[26,27,29].

Demographic data collected included age, sex, medical history, relationship status, occupation, and postal code. Race and ethnicity data were not collected or included in the analyses. Age and medical history determined the Charlson Comorbidity Index. Occupation was classified into high-, medium-, and low-level skills as per the International Standard Classification of Occupations (ISCO)[30]. Postal codes were used as an area-based proxy for socioeconomic status, measured by the Deprivation Index[31] that was created from the 2016 Canadian census data, divided into material and social deprivation indices where geographical units report a quintile score. Quintile 1 is the most privileged or least deprived, and quintile 5 is the least privileged or most deprived.

Statistical Analysis

Descriptive statistics described the study population; proportions were calculated for categorical variables and means (SD) for continuous variables. Data were presented with 95% CIs. Paired *t* tests were used to assess change in baseline and 2-year patient-reported outcome scores and

Analysis of Variance was used for DRS analysis. Bivariable analysis of the primary outcome and demographic variables was performed. Statistical significance was set at $P < .05$. Statistical analysis was performed using R, version 3.4.1 (The R Foundation for Statistical Computing).

Results

Demographic and Objective Data:

The study population of 67 patients had a median (SD) age of 63 (58-67) years, with 54 (80.6%) male and 13 (19.4%) female individuals. Baseline characteristics are shown in Table 1. 43 patients were treated within the NECTORS trial, and 24 patients were treated with the same protocol outside of the trial. All 67 patients received neoadjuvant chemotherapy followed by TORS and neck dissection. Two patients (2.9%) did not complete the third cycle of chemotherapy due to a hypersensitivity reaction (n = 1) and recurrent panic attacks (n = 1); both had major partial response observed on imaging results after cycle 2 and on postoperative pathology. No patient received adjuvant RT or CRT. Median (IQR) follow-up was 44 months (28-57) months. Three patients (4.5%) had regional recurrence; 2 were treated with salvage CRT and the third was enrolled in the BNT113-01 trial (NCT04534205) to receive pembrolizumab. Two patients who completed salvage CRT have no evidence of further recurrence or progression at the 36-month follow-up. Primary tumor site was palatine tonsil or tonsillar fossa in 41 patients (61.2%) and base of tongue in 26 patients (38.8%). The clinical tumor (T) staging within the cohort was T1, 26 patients (38.8%); T2, 30 patients (44.8%); T3, 10 patients (14.9%); and T4a, 1 patient (1.5%). The clinical nodal (N) staging was N0, 2 patients (3.0%); N1, 16 patients (23. 9%); N2a, 15 patients (22.4%); N2b, 30 patients (44.8%); and N2c, 4 patients (6.0%). A similar distribution of patients required unilateral neck dissection (36 [53.7%]) and bilateral (31 [46.3%]) neck dissection. Clear margins for the primary tumor site were achieved in all patients. There were 30 patients (44.8%) who were former smokers; 6 (9.0%) who were current smokers; and the median (IQR) pack-years in these 2 groups was 24.5 (10-35) packs. The median Charlson Comorbidity Index was 4. Patients' occupations were stratified by skill level: 32 (47.8%) had highly skilled occupations; 22 (32.8%), medium skill; 4 (6.0%), low skill; and 9 (13.4%), unemployed or unknown occupation. The Deprivation Index scores showed that only

13 patients (19.0%) lived in areas representing the 2 most socioeconomically privileged quintiles, and 25 (37.3%) lived in areas of the top two material privileged quintiles.

A bivariable analysis compared EORTC global score with age, sex, relationship status, urban location, occupation skill level, deprivation index, smoking pack-years, Charlson index, tumour site, and T and N stages. Only sex correlated with EORTC values, where male patients had higher EORTC baseline global QOL values than females (estimate 13.84; 95% CI, 2.91, 24.77).

A nasogastric feeding tube was placed for all patients for postoperative nutritional support in hospital for a mean (SD) of 7.8 (6.4) days. No patients required a percutaneous gastrostomy tube during treatment or follow-up. Six patients had elective tracheostomy per an institutional policy for patients undergoing TORS (Jewish General Hospital). One patient had a temporary tracheostomy for 14 days after managing a postoperative tonsillar bleed. All patients were decannulated.

Grade 3 or higher adverse events are summarized with complete data in eTable 1 in Supplement 1. Chemotherapy-related adverse events included diarrhea (n=1), a hypersensitivity reaction (n=1), and ototoxicity (described in the next section). There was no evidence of chemotherapy-related grade 3 kidney injury or myelosuppression. Surgery-related adverse events included intraoperative hypotension delaying surgery (n = 1), keloid scar (n = 1), chyle leak (n = 2), and post-operative bleeding (n = 4).

Fifty-two patients (77.6%) completed both pre-treatment and postchemotherapy audiometry. Thirty-four patients (65.4%) recorded no change in hearing. Five patients (9.6%) had mild hearing changes that did not reach ototoxicity thresholds . Eight patients (15.4%) had grade 1 ototoxic effects in at least one ear, and 5 patients (9.6%) had grade 3 ototoxicity in at least one ear.

Quality of life outcomes:
Findings of the EORTC QLQ-C30

The EORTC QLQ-C30 functional scores at baseline through 24 months are shown in Figure 1 and Table 2. The EORTC QLQ- C30 global score improved from baseline to 24 months (mean difference, 9.49; 95% CI, 2.45 to 16.53). Emotional functioning and social functioning improved at 24 months compared with baseline (mean difference, 11.11; 95% CI, 4.61 to 17.61; and 7.41; 95% CI, 2.28 to 12.53, respectively). Physical, role, and cognitive functioning returned to pretreatment values (mean difference, −0.37 [95% CI, −1.89 to 1.15], 6.02 [95% CI, −0.88 to 12.91], and 1.39 [−6.16 to 8.94], respectively).

The EORTC QLQ-C30 symptom scores at baseline to 24 months are available in Table 2. Several EORTC-QLQ C30 symptom scores improved from baseline to 24 months, including appetite (mean difference, −8.11; 95% CI, 0.51 to 15.70), fatigue (mean difference, −12.01; 95% CI, −20.58 to −3.44), financial implications (mean difference, −7.21; 95% CI, −14.20 to -0.21), pain (mean difference, −9.01; 95% CI, −16.60 to −1.42), and sleep (mean difference, −19.82; 95% CI, −29.78 to −9.86). The other EORTC QLQ-C30 symptom scales returned to baseline in 3 to 6 months posttreatment and remained stable at 24 months (ie, constipation, diarrhea, dyspnea, and nausea/ vomiting). No other EORTC QLQ-C30 symptom scores declined from baseline at 24 months.

Findings of the EORTC QLQ-HN35

The symptom scores from the EORTC QLQ-HN35 are shown in Figure 2 and eTable 2 in Supplement 1. EORTC-QLQ-HN35 symptom scales improved at 24 months, including coughing (mean difference, −11.11; 95% CI, −11.74 to −3.48), pain (mean difference, −10.61; 95% CI, −17.23 to −3.99), painkiller use (mean difference, −24.24; 95% CI, −46.01 to −2.47), and sexuality (mean difference, −15.15; 95% CI, −25.43 to −4.88). Patients experienced weight loss during treatment that remained stable at 1 month posttreatment to 24 months (mean difference, −15.15; 95% CI, −28.06 to −2.24). The remaining EORTC-QLQ- HN35 symptom scales returned to baseline at 3 to 6 months posttreatment and were stable at 24 months, including dry mouth, feeling ill, nutritional supplementation, mouth opening, senses, speech, social contact, social eating, and weight gain. No other EORTC QLQ-HN35 symptoms declined from baseline to the 24-month reassessment.

Findings of the MDADI

MDADI scores from baseline to 1 year, including subscales, are shown in Table 3. All MDADI scores returned to baseline at month 12. Global and composite scores (mean difference 6.15, 95% CI [-4.18,16.49] and mean difference 2.73, 95% CI [-1.62, 7.09]) returned to baseline.

Findings of the Decision Regret Scale

The median (range) DRS score was 5 (0-30) of 100, representing mild regret overall. Decision regret scores are plotted in eFigure in Supplement 1.

Discussion

This study identified preservation of longitudinal patient- reported QOL outcomes in patients with HPV-OPSCC treated with the NECTORS protocol. Utilization of several QOL metrics provided a multidimensional assessment of the positive results of this treatment regimen.

Description and benefits of NECTORS:

NECTORS is based on systemic escalation with neoadjuvant chemotherapy and loco-regional de-escalation with minimally invasive surgery[16-18]. Advantages include treating micrometastases, down-staging the primary tumor to allow close margins on surgical resection and reserving postoperative adjuvant RT or CRT for salvage. Margins were defined as positive or negative; negative and close margins are adequate[18]. Research on adequate margin distance in HPV-OPSCC cancers has shown that close margins (ie, >1mm to ≤5mm) have similar disease-free and overall survival rates than those with margins greater than 5mm[32,33]. In a prior report from our research group[18], patients treated with NECTORS with negative margins (n = 52) have been free of disease on follow-up, 2 patients with positive margins developed distant metastases to the lungs (n = 1) and local recurrence and death (n = 1). That study cohort of patients treated with this same NECTORS protocol demonstrated pathologic complete response in the primary site in (72%) and neck (56%)[18]. Given this response, consolidation surgery and neck dissection are performed as definitive treatment, with more than 95% of patients avoiding adjuvant or salvage radiation. This is a de-escalation of locoregional treatment, unlike the up-front TORS approach, which requires adjuvant RT in 89% of patients[10]. Recently, Samaniego et al[34] demonstrated that

neoadjuvant chemotherapy induces HPV-specific T-cell immunity. This is likely contributing to the success of neoadjuvant chemotherapy approach prior to TORS, in addition to the direct cytotoxic effect of chemotherapy on the tumor. We are currently studying our study cohort to corroborate this finding. This protocol's neoadjuvant chemotherapy regimen delivers a lower cisplatin dose than standard concurrent CRT, limiting chemotherapy's secondary effects.

This cohort demonstrated a locoregional recurrence rate of 3 in 67 patients, and the 2 patients who completed salvage therapy have been free of disease for 36 months. Previous cohorts treated with the NECTORS protocol demonstrated a recurrence rate of approximately 4%, and those who experienced recurrence had high survival rates with salvage therapy[16-18]. This survival rate is in contrast to patients with OPSCC who were treated with up-front CRT, which historically has had a risk of recurrence of approximately 10 to 15%[35-39]. Most recurrences in patients with HPV-OPSCC are distant metastatic disease (54 of 81 patients [67%]) and 5-year survival rates in these patients are extremely low, with 98% mortality[34]. Currently, the patients included in this prospective cohort are in good health, with no evidence of disease; 1 patient currently receiving salvage pembrolizumab. The data on this cohort must still mature to document survival and recurrence data.

Benefits for QOL

Traditional open surgery approaches can produce disfigurement, dysphagia, aspiration, and speech difficulties that are minimized with the TORS approach[35,36]. Chemotherapy toxic effects include neutropenia, anemia, thrombocytopenia, ototoxicity, and others[42]. Grade 3 ototoxic effects were demonstrated in less than 10% of patients. A systematic review[43] reports a wide range of ototoxic effect rates in patients with head and neck cancer who receive concurrent CRT, (17-88%). Patients with head and neck cancer treated with high-dose cisplatin (100mg/m^2 every three weeks) are more likely to experience hearing loss than those receiving weekly 40mg/m^2 low-dose cisplatin (68% versus 24%; $P < .01$)[44]. Those receiving high-dose cisplatin have ototoxic effects after a median (range) cumulative dose of 197.2mg/m^2 (39.5-511.5mg/m^2)[44]. Patients treated with NECTORS may have lower rates of ototoxic effects because the protocol uses a lower dose of neoadjuvant cisplatin (75mg/m^2) every 3 weeks for 3 cycles, with a

cumulative dose of 225mg/m^2. Moreover, the NECTORS protocol does not treat with up-front RT, avoiding exposure of the cochlea to RT.

RT-related secondary effects of treatment are well represented in the EORTC QLQ-HN35[14,45]. In our group treated with NECTORS, all domains returned to baseline levels within 3 to 6 months posttreatment. The primary goal of oncologic treatment is still eradication of disease, and this has been previously demonstrated using NECTORS paradigm[16-18]. However, in the present study, longitudinal patient-reported outcome measures collected through the EORTC QLQ-C30, EORTC QLQ-HN35, and MDADI questionnaires demonstrate recovery to baseline scores as well. The NECTORS treatment protocol maintains QOL after the initial expected decrease in subjective scores during and immediately after treatment.

The Decision Regret Scale assessed remorse regarding a treatment decision to offer a better understanding of the psychological distress of being diagnosed and treated for cancer and opting for a nonstandard of care protocol. A cross-sectional study by Goepfert et al[27] assessed decisional regret in patients previously treated for oropharyngeal cancer. Among 628 patients treated with CRT, decisional regret was expressed by 13.5%-within the mild range, but higher than among the NECTORS cohort. Patients who undergo CRT have low levels of regret on this assessment, but RT side effects are progressive, and the regret level should be reassessed at a later time point. In contrast, in the NECTORS cohort, the adverse effects profile is unlikely to progress because of the absence of adjuvant RT, and the cross-sectional assessment of the patients who underwent NECTORS is indicative of long-term sentiments.

Comparison With Previous Trials:

There are limitations in the ability to compare clinical trials due to the variety of QOL patient-reported outcome metrics, measurements at different time points, and adverse effect pro- files of treatment modalities. However, an important trial has been reviewed and compared with the NECTORS protocol.

The ECOG-ACRIN 3311 trial[10] enrolled patients with stage III and IVa[19] HPV-OPSCC, who received up-front TORS and neck dissection, and were treated with risk-based adjuvant therapy

postoperatively to evaluate the oncologic effectiveness of adjuvant 50 Gy vs 60 Gy RT. Patients without worrisome features were observed (group A) and patients with poor pathological features were treated with adjuvant CRT with 66 Gy and weekly cisplatin (group D). The intermediate groups were randomized to 50 Gy (group B) or 60 Gy (group C) of adjuvant RT. This TORS-first approach required adjuvant treatment in 89% of patients despite excluding patients with matted lymph nodes, bilateral lymphadenopathy, and/or T3 stage disease. At 1-year posttreatment, patients in group A had a similar trajectory of MDADI composite scores as our study's cohort, demonstrating a slight increase from baseline (89.1 to 94.7). The 90% of patients in groups B, C, and D who required adjuvant RT/CRT did not return to pretreatment values by 1 year and remained 9 to 15 points below their baseline. Therefore, NECTORS' neoadjuvant chemotherapy downstages the tumor, and surgery consolidates the treatment without adjuvant RT, which has been shown to be associated with QOL outcomes similar to those of group A in the ECOG ACRIN 3311 study, ie, without any adjuvant therapy after TORS.

Limitations

This study had some limitations worth noting. The MDADI instrument was introduced late in the study, which explains why there were fewer of these completed and no 24-month findings. There was no local CRT group with adequate available data to provide a comparison; however, this cohort was directly compared with their pretreatment values. Baseline QOL values are skewed because patients complete these questionnaires after a cancer diagnosis. However, this limitation is present in many, if not all, studies and gives insight into an explanation for why select posttreatment scores can exceed baseline values. Although surgical trials have a selection bias toward including healthy patients fit for surgery, this cohort had minimal exclusion criteria, including those with matted and/or large lymphadenopathy, minimal ECE on preoperative imaging, smokers of any smoking pack-year his- tory, and T3 and N2c stages.

Conclusions

The findings of this multicenter cohort study indicate that neo- adjuvant chemotherapy followed by TORS and neck dissection, while reserving RT for salvage, may be an approach that preserves QOL in all domains for patients with stage III and IVa HPV-OPSCC. Hence,

NECTORS treatment protocol is an effective therapeutic option for HPV-OPSCC with the neoadjuvant chemotherapy allowing definitive TORS and neck dissection and avoiding adjuvant RT or CRT and associated toxic effects of RT. This is a new paradigm in management of HPV-OPSCC.

Table 1: Baseline Demographic and Treatment Characteristics of Study Patients (N = 67)

Characteristic	Patients, No. (%)
Age, median [IQR], y	63 [58-67]
Sex:	
Female	13 (19.4)
Male	54 (80.6)
Primary tumor site:	
Tonsil or tonsillar fossa	41 (61.2)
Base of tongue	26 (38.8)
Clinical T stage[a]	
T1	26 (38.8)
T2	30 (44.8)
T3	10 (14.9)
T4a	1 (1.5)
Clinical N stage[a]	
N0	2 (3.0)
N1	16 (23.9)
N2a	15 (22.4)
N2b	30 (44.8)
N2c	4 (6.0)
Overall AJCC stage (AJCC 7th edition)	
II	1 (1.5)
III	22 (32.8)
IVa	44 (65.7)
Laterality of neck dissection	
Unilateral	36 (53.7)
Bilateral	31 (46.3)
Feeding tube mean (SD), d	7.8 (6.4)
Smoker	
Never	31 (46.2)
Ex-smoker	30 (44.8)
Current	6 (9.0)
Pack-years (for currently/formerly smoking), median (IQR)	24.5 (10-35)
Charlson Comorbidity Index, median (range)	4 (2-6)
Occupation skill level[b]	
High	32 (47.8)
Medium	22 (32.8)
Low	4 (6.0)
Unknown / no occupation	9 (13.4)
Social deprivation index quintile	
1	4 (6.0)
2	9 (13.4)
3	14 (20.9)
4	15 (22.4)
5	23 (34.3)
Unknown	2 (3.0)
Material deprivation index quintile	
1	16 (23.9)
2	9 (13.4)
3	18 (26.9)
4	12 (17.9)
5	10 (14.9)
Unknown	2 (3.0)

[a]Cancer stages defined by the American Joint Committee on Cancer[19].

[b]Skill levels defined per the International Standard Classification of Occupations[30].

[c]Material and social deprivation indices defined by the census bureau of Canada, with quintile 1 indicating the most privileged/least deprived and quintile 5, the least privileged/most deprived.

Table 2. Quality of Life Ratings Among Patients Treated With NECTORS, by Function

	Baseline (SD) [n]	1 month (SD) [n]	3 months (SD) [n]	6 months (SD) [n]	12 months (SD) [n]	18 months (SD) [n]	24 months (SD) [n]	Mean difference (baseline to 24 months)	95% CI
Functional Scales									
Global score	77.6 (20.6) [67]	75.4 (19.0) [42]	74.7 (20.8) [60]	79.7 (19.4) [58]	83.0 (17.3) [53]	84.7 (15.3) [44]	86.6 (11.7) [38]	9.49	[2.45, 16.53]
Emotional functioning	77.0 (21.8) [67]	86.2 (16.4) [41]	83.1 (19.0) [60]	84.2 (18.7) [59]	84.4 (19.4) [54]	88.3 (16.3) [44]	87.2 (18.4) [39]	11.11	[4.61, 17.61]
Social functioning	89.3 (18.3) [67]	80.9 (24.9) [41]	85.3 (22.4) [60]	91.8 (16.2) [59]	94.8 (16.8) [54]	93.2 (19.1) [44]	95.7 (13.1) [39]	7.41	[2.28, 12.53]
Physical Functioning	94.7 (11.3) [67]	87.6 (14.9) [41]	89.2 (13.5) [60]	91.8 (12.2) [59]	94.4 (8.4) [54]	92.8 (12.7) [44]	94.9 (9.9) [39]	-0.37	[-1.89, 1.15]
Role functioning	88.3 (22.1) [67]	66.3 (29.7) [41]	80.3 (25.9) [60]	86.7 (20.7) [59]	89.2 (20.3) [54]	90.9 (19.2) [44]	91.5 (16.6) [39]	6.02	[-0.88, 12.91]
Cognitive functioning	87.6 (18.4) [67]	91.5 (15.4) [41]	86.7 (19.6) [60]	87.8 (18.6) [59]	90.1 (17.9) [54]	92.4 (15.9) [44]	87.2 (16.9) [39]	1.39	[-6.16, 8.94]
Symptom Scales									
Appetite	11.6 (19.8) [66]	10.3 (21.8) [39]	16.7 (23.4) [60]	8.62 (16.0) [58]	8.18 (22.6) [53]	8.51 (21.4) [47]	5.13 (12.2) [39]	-8.11	[0.51, 15.70]
Constipation	8.08 (18.5) [66]	5.83 (14.9) [40]	5.56 (12.5) [60]	6.90 (16.2) [58]	7.55 (14.1) [53]	4.26 (11.2) [47]	7.69 (14.2) [39]	-2.70e-10	[-6.41, 6.41]
Diarrhea	6.06 (15.4) [66]	9.17 (21.3) [40]	5.56 (17.5) [60]	8.05 (16.9) [58]	5.03 (17.8) [53]	4.26 (13.2) [47]	4.27 (13.6) [39]	-0.90	[-5.79, 3.99]
Dyspnea	8.59 (19.7) [66]	16.7 (20.0) [40]	14.4 (22.4) [60]	12.6 (19.6) [58]	7.55 (15.5) [53]	9.4 (17.0) [47]	9.4 (17.0) [39]	2.70e-10	[-6.93, 6.93]
Fatigue	22.4 (22.4) [66]	31.9 (26.4) [40]	27.2 (25.7) [60]	21.6 (20.9) [58]	15.5 (18.1) [53]	16.8 (22.1) [47]	13.7 (18.8) [39]	-12.01	[-20.58, -3.44]
Financial impact	11.1 (24.5) [65]	12.5 (20.9) [40]	13.3 (23.1) [60]	11.5 (21.2) [58]	11.9 (25.4) [53]	11.3 (23.3) [47]	7.69 (16.2) [39]	-7.21	[-14.20, -0.21]
Nausea/Vomiting	3.54 (9.92) [66]	3.33 (12.1) [40]	1.94 (5.4) [60]	2.01 (6.3) [58]	2.83 (7.83) [53]	2.84 (7.22) [47]	2.99 (7.52) [39]	-3.15	[-7.66, 1.35]
Pain	15.4 (22.1) [66]	25.0 (26.1) [40]	19.7 (24.1) [60]	16.1 (20.0) [58]	10.7 (13.9) [53]	10.6 (19.5) [47]	8.12 (15.7) [39]	-9.01	[-16.60, -1.42]
Sleep	26.8 (31.1) [66]	33.3 (31.1) [40]	23.3 (27.0) [60]	23.6 (25.0) [58]	22.0 (24.4) [53]	12.8 (22.6) [47]	8.55 (16.6) [39]	-19.82	[-29.78, -9.86]

(EORTC-QLQ-C30) and Symptoms (EORTC QLQ-HNS35) Scores, Over Time

Table 3: Dysphagia-Associated Quality of Life Ratings on the MDADI Among Patients Treated with NECTORS, by Global and Subscale Scores

	Baseline (SD) [n]	1 month (SD) [n]	3 months (SD) [n]	6 months (SD) [n]	12 months (SD) [n]	Mean difference* (baseline to 12 months)	95% CI
Global	93.3 (19.2) [27]	82.9 (24.8) [28]	88.1 (22.4) [27]	90.4 (22.8) [23]	92.7 (20.7) [30]	6.15	[-4.18, 16.49]
Emotional	90.9 (10.8) [27]	88.2 (12.7) [29]	87.3 (14.2) [27]	89.3 (15.1) [23]	93.5 (8.9) [27]	1.49	[-3.80, 6.77]
Functional	92.2 (11.7) [27]	91.4 (10.1) [29]	92.0 (16) [27]	91.0 (16.2) [23]	96.4 (9.2) [24]	5.15	[-0.75, 11.05]
Physical	93.2 (11.6) [27]	82.7 (13.8) [29]	85.0 (23.6) [27]	86.3 (20.7) [23]	94.4 (11.6) [27]	2.12	[-5.20, 9.44]
Composite	92.2 (9.5) [27]	86.8 (9.81) [29]	87.6 (17.6) [27]	88.5 (16.7) [23]	94.7 (8.8) [27]	2.73	[-1.62, 7.09]

Figure 1. Quality of Life Ratings on the 30-item European Organization for Research and Treatment of Cancer Core's Quality of Life Questionnaire From Patients Treated With Neoadjuvant Chemotherapy Followed by Transoral Robotic Surgery and Neck Dissection, by Function Score

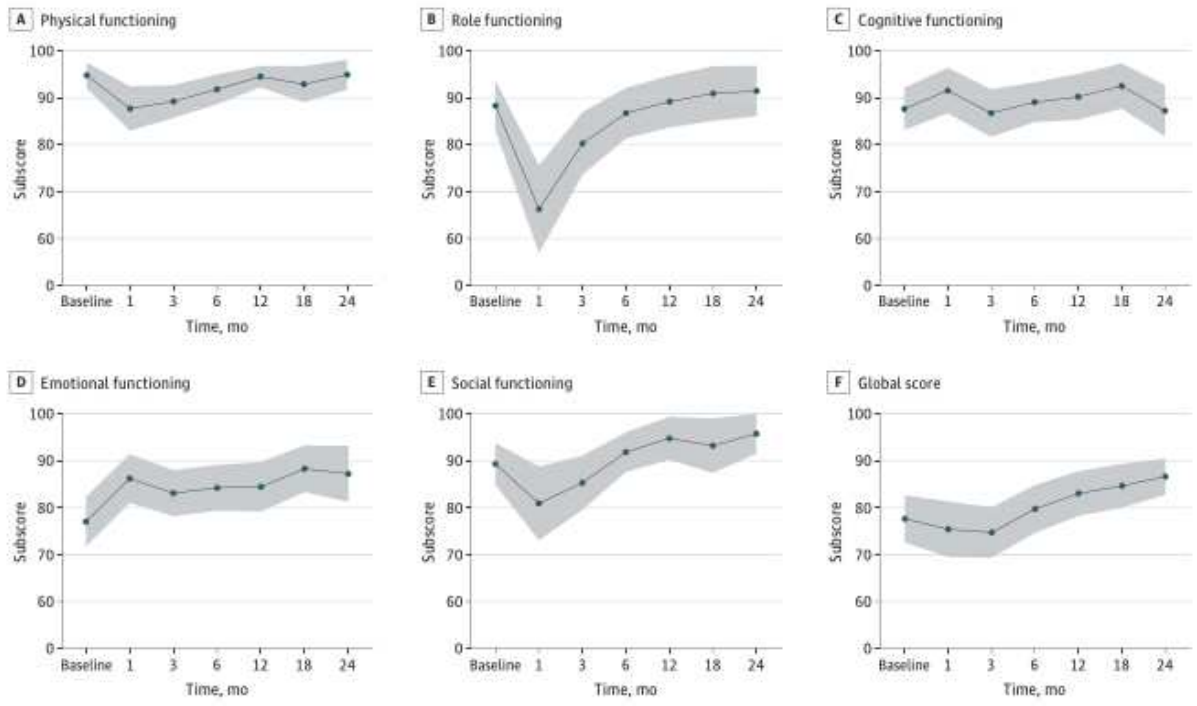
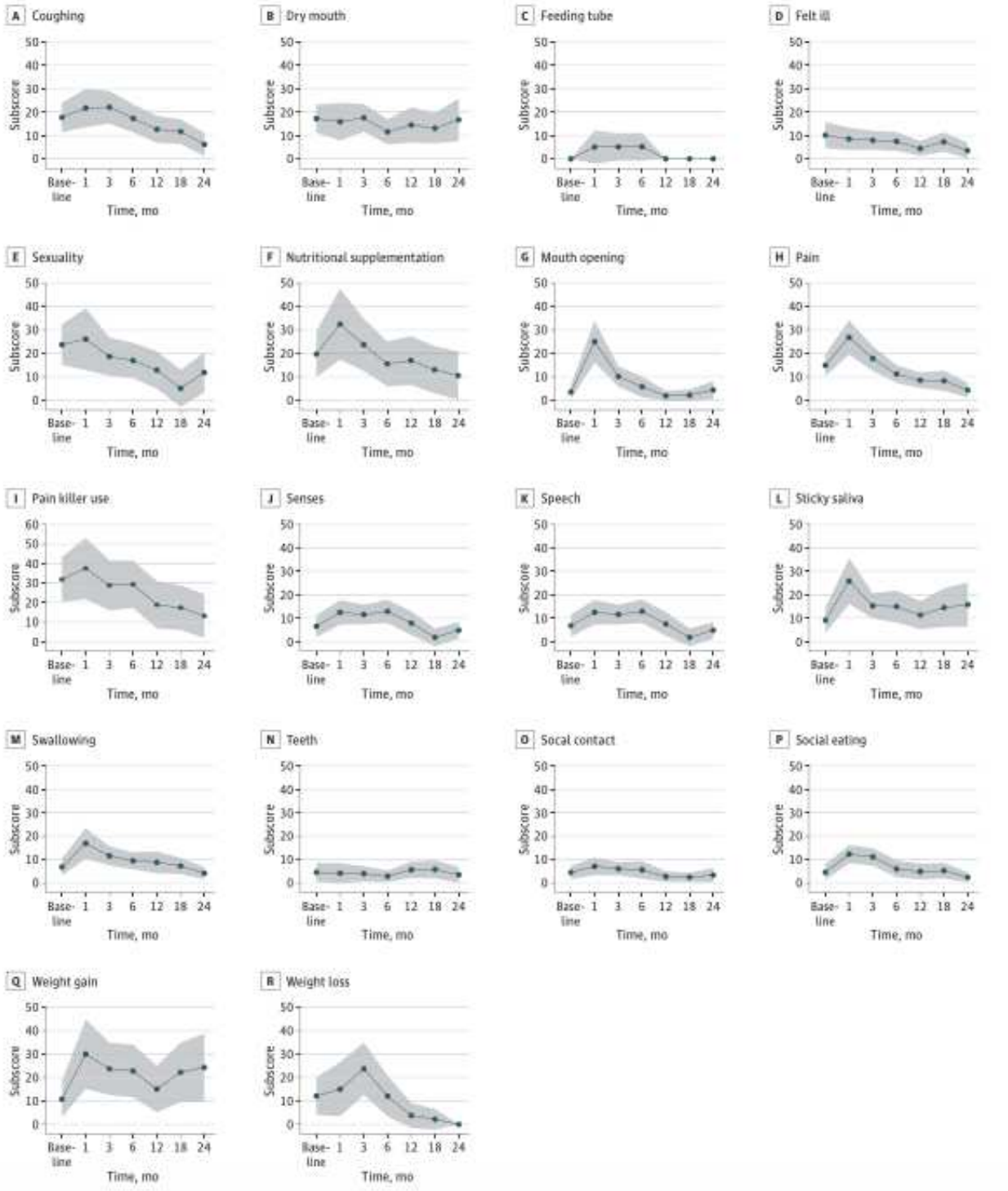


Figure 2. Quality of Life Ratings per the Head and Neck Extension Module of the European Organization for Research and Treatment of Cancer Core's Quality of Life Questionnaire From Patients Treated With Neoadjuvant Chemotherapy Followed by Transoral Robotic Surgery and Neck Dissection, by Symptom Scores


A Coughing
B Dry mouth
C Feeding tube
D Felt ill
E Sexuality
F Nutritional supplementation
G Mouth opening
H Pain
I Pain killer use
J Senses
K Speech
L Sticky saliva
M Swallowing
N Teeth
O Socal contact
P Social eating
Q Weight gain
R Weight loss
Subscore
Time, mo
Base-line
1
3
6
12
18
24

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Chapter 6: Overall Discussion and Conclusions

Discussion of thesis:

Previous standard treatment regimens for oropharyngeal cancers are effective yet overtreat HPV-related OPSCC. The classic CRT dosages create significant secondary effects that continue to worsen as time passes. New technology has allowed for minimally invasive surgery in the oropharynx limiting the acute pain and suffering associated with surgery, eliminating large disfiguring and lasting scars, and decreasing post-treatment dysphagia. The multitude of clinical trials currently available or previously conducted demonstrate the ongoing efforts to identify a treatment that balances oncologic cure and toxicity profiles. While the ideal approach is yet to be determined, it is known that each treatment protocol has individual risks and benefits based on the treatment modalities and doses.

The first manuscript reviewed the literature on de-escalation strategies for HPV-associated OPSCC patients to provide a comprehensive summary or reference. It is both exciting and overwhelming that there are many proposed treatment de-escalation strategies to optimize patient management. This clearly demonstrates that there is yet to be a consensus on the ideal de-intensification regimen. The primary outcome for these trials are oncologic efficacy. However, when patient-reported outcomes are incorporated, the focus is on global QOL scores or physical QOL outcomes (i.e. dysphagia, speech outcomes, neck/shoulder pain).

The second manuscript, the scoping review, searched the literature for reports of psychosocial QOL within HPV-associated OPSCC patients. The goal was to understand a different dimension of these patients and attempt to better understand this cohort's individual characteristics. The scoping review highlighted a gap in research about psychosocial QOL outcomes, urging a multidimensional assessment of patients enrolled in clinical trials.

This lead to the third manuscript, a comprehensive and multi-factorial assessment of HPV-associated OPSCC patients within our institution who are treated within a de-intensification clinical trial. Patients with stage III/IV treatment naïve HPV-associated OPSCC who meet

criteria are offered standard of care chemoradiation treatment *or* enrollment in a surgery-based clinical trial, NECTORS. This manuscript reports on long-term QOL and functional outcomes, including a psychosocial-specific metric, in HPV-associated OPSCC patients. From this research, it is clear that the NECTORS paradigm considers and provides excellent oncologic efficacy and maintenance of multidimensional quality of life.

Review of NECTORS:

NECTORS is not a typical de-escalation strategy. Instead, this paradigm aims to minimize the use of adjuvant RT, the modality known to cause significant morbidity. The NECTORS protocol is based on systemic escalation with neoadjuvant chemotherapy and loco-regional de-escalation with minimally invasive transoral robotic surgery and selective neck dissection[14-16]. This regimen has several advantages including treatment of micro-metastases, down-staging the primary tumor to allow close margins on surgical resection, and reserving post-operative adjuvant RT or CRT for salvage.

The NECTORS regimen QOL analysis demonstrated that there is the expected initial and immediate post-treatment decrease in QOL scores. However, these all recover by 3-6 months, and for some parameters, there is even an improvement from baseline. For the primary outcome, patient-reported outcomes were followed longitudinally for up to 24 months. While data collection is ongoing and some patients have data from beyond this time point, 24 months was chosen to demonstrate post-treatment recovery and stability. For the MDADI results, change in baseline and 12-month scores were presented as this patient-reported outcome measure was implemented later on and there were few patients with paired baseline and 24-month data.

NECTORS avoids RT in over 95% of patients, a treatment modality whose adverse effects worsen over time. Treating with neoadjuvant chemotherapy and surgical resection, avoiding RT, provides the confidence that two-year post-treatment QOL scores accurately represent long-term results. As can be seen from our data and figures, the QOL outcomes at 6 months were stable at 24 months.

The first presentation in approximately 60-70% of patients is identification of a neck mass and they are otherwise asymptomatic - without deficits and with no to minimal pain or dysphagia[58,59]. While the primary goal is eradication of disease, emphasis is placed on maintaining the functional activities and avoiding lasting side effects. The longitudinal patient reported outcome measures in this study (EORTC QLQ-C30, EORTC QLQ-HN35, and MDADI) recover to baseline scores. The NECTORS treatment paradigm has proven to maintain quality of life after the initial decrease in subjective scores that is expected immediately after the treatment.

This research is built upon the understanding that this protocol has oncologic efficacy from previous publications. By reporting on the excellent QOL outcomes, NECTORS has positive outcomes in both oncologic and QOL domains. This thesis, these publications, and recent presentations in national and international forums are working towards recognition and dissemination of the NECTORS protocol to a wider stage. Future research on this cohort continues, aiming to directly compare NECTORS patients to those receiving CRT as well as exploration of the basic science behind the protocol by assessing the role of neoadjuvant chemotherapy on HPV-specific T-cell immunity.

Discussion of study design and statistical analysis:

While this was primarily a QOL analysis, we did include the oncologic data of this cohort. The QOL data was assessed at 24-months to maximize the number of patients included in the paired analysis, however, the survival data was exhibit a long-term longitudinal outcome while still maximizing available patient data. To note, the median follow-up for oncologic outcomes reported was 44-months. The statistical analysis utilized the paired data, and was therefore limited to those with data at both baseline and 24-months. However, all patient data is included in the graphs, and fall within the confidence intervals, and therefore follow the trend noted with the analysis. To note, data was not imputed for outcomes as is current standards in the field

When designing this study and statistical analysis, the goal was to determine the long-term effects of this treatment modality. As mentioned in the study limitations, our institution lacked QOL data from a comparator group treated with CRT. Therefore, a paired analysis of the

NECTORS cohort from baseline to 24-months was performed (or 12-months for the MDADI data). An attempt was initially made to compare the NECTORS population to a historical control. However, published baseline status of global QOL and swallowing-related QOL was different from the baseline NECTORS patients, likely representing a demographically different population (different age, gender, smoking exposure, cancer stage, etc)[60]. Given the patients were treated with chemotherapy and surgery, sparing the radiation therapy that would given progressive and cumulative side effects, 24-months is felt to represent long-term QOL assessment. However, data is continuing to be collected and will be reviewed again when it matures further.

The analyses of EORTC QLQ-C30 were paired t-tests of patients with both baseline and 2-year data. A time-based analysis demonstrating the exact time point the QOL item returned to baseline was not specifically performed. However, the accompanying graphs and tables visually correspond to all available patient data and their results are within the 95% confidence interval of the paired analysis.

Future directions

There are several areas for future study when considering patients being treated with the NECTORS protocol. Firstly, a study with longer follow-up for survival/oncologic outcomes and subjective patient-reported outcome measure data will likely continue to add strength to advocate for this paradigm. The third manuscript was not originally designed to identify the exact timepoint of return to baseline as its goal was to evaluate long-term outcomes. Therefore, a future study may investigate the exact trajectory, for example, i.e. specifically at 6, 12 and 24-month time points to determine when the QOL has significantly improved, as well as identify both risk factors and protective factors.

As well, obtaining adequate patient-reported outcome data for a matched cohort undergoing standard of care CRT will allow for a head-to-head comparison. While our institution is working towards better data collection for patients undergoing CRT, one may consider patients at outside institutions if their patients can be adequately matched to the NECTORS cohort.

As mentioned, we are currently lacking a study comparing the NECTORS cohort to standard of care to determine whether there is a selection bias regarding patients enrolled in NECTORS. Specifically, a study currently in its data collection phase is investigating whether the NECTORS protocol is treating patients that would conventionally be deemed unfavorable for upfront TORS. At this time, as per the TNM staging, there is no definite criteria to identify favorable or unfavorable surgical resection patients (outside of extreme known contraindications) and so the NECTORS protocol has defined its own inclusion criteria. This study is comparing the NECTORS cohort to CRT patients treated at our institution before the NECTORS trial was available. Other de-escalation trials are being critiqued that they are able to publish better outcomes as they are enrolling and treating a more favourable subset of patients. However, the hypothesis tested in this study is that NECTORS aims to broaden the patients eligible for surgery, redefining previously unfavorable surgical candidate as favorable.

Further research is currently underway to determine if further de-escalation is possible. When considering patients with HPV-related OPSCC currently being treated on the NECTORS protocol, this may involve de-escalation of the extent of surgery. When patients are enrolled in NECTORS, they undergo neoadjuvant chemotherapy followed by TORS surgical resection of the primary tumor and neck dissection of the lymph node basin - both involved and “at-risk” neck levels. The “at-risk” nodal basin is defined as the contralateral neck for non-lateralized primary tumors, or level IV in cases that were cN0 pre-operatively. The current hypothesis being considered is whether the neck dissection component of the NECTORS protocol can be personalized and de-escalated to the involved nodal basin only, thereby avoiding the “at-risk” levels.

Chapter 7: Contribution to Original Knowledge

This Master's thesis reports on and contributes to the new landscape of research on patients with HPV-associated OPSCC. A literature review identified that the standard of care treatment regimen for these patients is not yet defined since it is now known that their diagnosis yields a better prognosis than non-HPV-related OPSCC. A scoping review has identified a paucity of research in the field of psychosocial QOL, leading to the conclusion that there is a research gap of inclusion of different QOL domains. The longitudinal QOL outcomes research on patients receiving the NECTORS protocol has demonstrated the effectiveness in the novel treatment paradigm to maintain QOL in multiple scales and scores.

Patients treated with neoadjuvant chemotherapy followed by transoral robotic surgery and neck dissection had excellent oncologic effectiveness, described in previous publications. Inclusion of multiple PROMs that prove QOL is maintained from a multi-dimensional perspective is the original aspect of this research.

Chapter 8: List of Tables and Figures

Chapter 9: List of Abbreviations

- Oropharyngeal Squamous Cell Carcinoma – OPSCC
- Human papillomavirus – HPV
- Transoral robotic surgery – TORS
- Neck dissection – ND
- Chemoradiation – CRT
- Radiation Therapy – RT
- Quality of life – QOL
- American Joint Committee on Cancer – AJCC
- Patient-reported outcome measures – PROMs
- Neoadjuvant chemotherapy followed by TORS and neck dissection – NECTORS

Chapter 10: References

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