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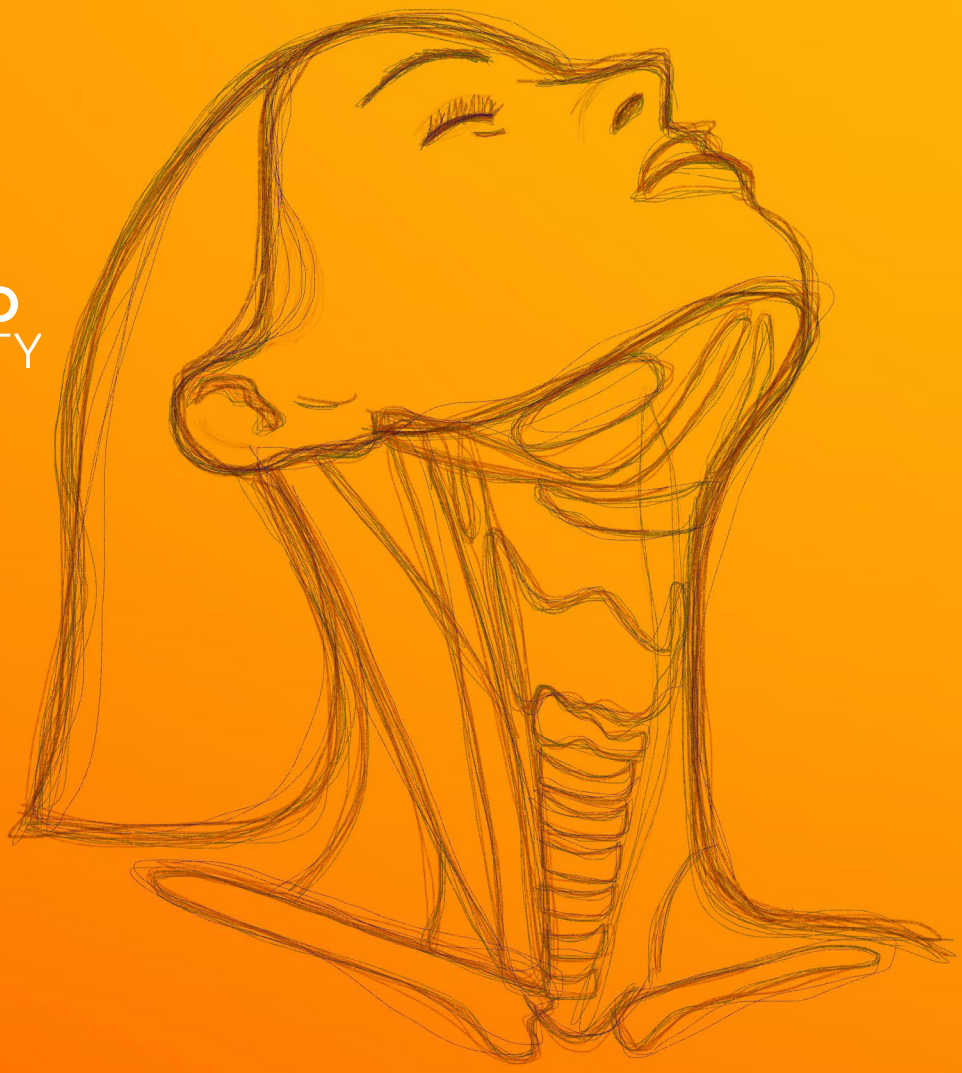

Quality of Life and Treatment-Induced Morbidity in Patients with Head and Neck Cancer

Special Emphasis on Oropharyngeal Cancer

Pihla Ranta

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1908 | MEDICA – ODONTOLOGICA | TURKU 2025

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The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

Cover image by the author

ISBN 978-952-02-0336-8 (PRINT)
ISBN 978-952-02-0337-5 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2025

Stat rosa pristina nomine, nomina nuda tenemus

The rose of old continues to exist through its name,
yet its name is all that remains to us

Bernard de Cluny

To Aleksi

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Clinical Medicine
Otorhinolaryngology – Head and Neck Surgery
PIHLA RANTA: Quality of Life and Treatment-Induced Morbidity in Patients with Head and Neck Cancer: Special Emphasis on Oropharyngeal Cancer
Doctoral Dissertation, 156 pp.
Doctoral Programme in Clinical Research
October 2025

ABSTRACT

The demographics of head and neck cancer (HNC) are evolving. The current human papillomavirus (HPV) epidemic has led to an increasing incidence of HNC among patients under the age of 45, particularly those without a history of smoking or heavy alcohol consumption. Despite advances in treatment, HNC survivors often experience treatment-induced toxicities that impair their long-term quality of life (QoL), such as dysphagia, xerostomia, and dysphonia. HPV-related HNC occurs mainly in the oropharynx. The optimal treatment modality for oropharyngeal cancer (OPC) remains unresolved. While surgical and nonsurgical treatments seem to offer comparable overall survival rates, neither has demonstrated clear superiority in terms of functional outcomes or QoL.

The aim of this thesis was to analyse treatment- and patient-related factors associated with QoL outcomes in patients with OPC. We assessed the long-term QoL of a nationwide, population-based cohort of OPC survivors diagnosed between 2000 and 2009. Additionally, we conducted a prospective multicentre study involving patients with OPC diagnosed between 2019 and 2023. Furthermore, we examined the prevalence of and risk factors for long-term side effects of radiation therapy (RT) in patients with HNC through a single-centre study. We also validated the MD Anderson Dysphagia Inventory (MDADI), a swallowing-related QoL questionnaire, in Finnish HNC patients.

We found that single-modality treatment was associated with better long-term swallowing-related QoL outcomes compared to combined treatment. Among patients with early-stage OPC, surgery alone offered superior QoL outcomes compared to chemoradiotherapy (CRT). Poor QoL was associated with smoking, heavy alcohol use, and feeding tube dependence. Age, gender, tumour subsite, and neck RT influenced susceptibility to late RT-induced toxicities in HNC patients. The Finnish MDADI proved to be a valid, reliable dysphagia questionnaire.

This thesis suggests that single-modality treatment for OPC should be pursued whenever it is oncologically safe. In early-stage OPC, surgical treatment appears to offer better QoL outcomes than CRT; however, it should only be offered to patients whose imaging findings indicate a high likelihood of cure with surgery alone.

KEYWORDS: head and neck cancer; oropharyngeal cancer; quality of life; patient-reported outcome measures; human papillomavirus

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Korva-, nenä- ja kurkkutautioppi
PIHLA RANTA: Elämänlaatu ja hoidon sivuvaikutukset pään ja kaulan syövän jälkeen
Väitöskirja, 156 s.
Turun kliininen tohtoriohjelma
Lokakuu 2025

TIIVISTELMÄ

Pään ja kaulan alueen syövän ilmaantuvuus kasvaa. Pään ja kaulan syöpä koskettaa ihmisen papilloomavirusepidemian vuoksi yhä enemmän myös alle 45-vuotiaita, joilla ei ole tupakointi- tai alkoholin riskikäyttötaustaa. Hoitojen kehittymisestä huolimatta moni pään ja kaulan syövästä selvinnyt kokee elämänlaatua alentavia hoidon sivuvaikutuksia kuten nielemisvaikeuksia, suun kuivuutta ja äänen käheyttä. Ihmisen papilloomavirukseen liittyvä pään ja kaulan syöpä ilmenee pääosin suunielussa. Suunielusyövän hoitomuoto ei ole vakiintunut – kirurgia ja kemosädehoito näyttävät tuottavan yhtä hyvän ennusteen. Kirurgialla ja kemosädehoidolla on kuitenkin omat haittavaikutusprofiilinsa ja vaikutuksensa elämänlaatuun.

Tämän väitöskirjan tavoite oli analysoida hoito- ja potilaskohtaisten tekijöiden vaikutusta elämänlaatuun suunielusyöpäpotilailla. Ensimmäisessä osatyössä analysoimme kansallisessa aineistossa suunielusyövän myöhäisvaikutukset elämänlaatuun vuosina 2000–2009 diagnosoiduilla potilailla. Lisäksi keräsimme vuosina 2019–2023 Oulussa, Tampereella ja Turussa diagnosoidut uudet suunielusyöpätapaukset prospektiiviseen elämänlaadun seurantaan. Analysoimme myös sädehoidon myöhäiset sivuvaikutukset pään ja kaulan syöpäpotilailla, jotka hoidettiin vuosina 2010–2015 Tyksissä. Validoimme nielemiskyselyn MDADI (MD Anderson Dysphagia Inventory) suomenkielisten pään ja kaulan syöpään sairastuneiden käyttöön.

Kirurgian ja (kemo)sädehoidon yhdistelmähoito tuotti suunielusyöpäpotilaille huonommat nielemistulokset kuin kirurgia tai kemosädehoito yksinään. Siksi yhdistelmähoitoa tulisi mahdollisuuksien mukaan välttää. Kun verrattiin kirurgiaa kemosädehoitoon, kirurgia näytti tuottavan paremman elämänlaadun matalan levinneisyysasteen suunielusyövässä. Tupakointi, alkoholin riskikäyttö ja riippuvuus ruokintaletkusta olivat yhteydessä huonompiin elämänlaatutuloksiin. Ikä, sukupuoli, kasvaimen sijainti ja kaulan sädehoito vaikuttivat sädehoidon myöhäisten haittojen todennäköisyyteen pään ja kaulan syöpäpotilailla. Suomenkielinen nielemiskysely (MDADI) todettiin luotettavaksi elämänlaadun mittariksi pään ja kaulan syöpään sairastuneille.

AVAINSANAT: pään ja kaulan alueen syöpä; suunielusyöpä; elämänlaatu; potilaan raportoimat hoidon tulokset; ihmisen papilloomavirus

Table of Contents

Abbreviations

AI	Artificial intelligence
CI	Confidence interval
CICI	Chemotherapy-induced cognitive impairment
CRT	Chemoradiotherapy
CT	Computed tomography
ctDNA	Circulating tumour deoxyribonucleic acid
EAT-10	Eating Assessment Tool
EBV	Epstein-Barr virus
ENE	Extranodal extension
EORTC	European Organisation for Research and Treatment of Cancer
F-EAT-10	Finnish Version of the Eating Assessment Tool
^{18}F-FDG	Fluorine-18-fluorodeoxy-D-glucose
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICC	intraclass correlation
IMRT	Intensity-modulated radiotherapy
IQR	Interquartile range
MDADI	MD Anderson Dysphagia Inventory
MRI	Magnetic resonance imaging
ND	Neck dissection
NPC	Nasopharyngeal cancer
OR	Odds ratio
OS	Overall survival
OPC	Oropharyngeal cancer
OPSCC	Oropharyngeal squamous cell carcinoma
p16	protein p16^{INK4a}
PAR	Population attributable risk
PD-1	Programmed cell death protein 1

PD-L1	Programmed death-ligand 1
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PROM	Patient-reported outcome measure
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RS	Relative survival
RT	Radiation therapy
SCC	Squamous cell carcinoma
SD	Standard deviation
SES	Socioeconomic status
Sx	Surgery
TSH	Thyroxine stimulating hormone
TNM	Tumour, Node, Metastasis
TORS	Transoral robotic surgery
UICC	Union for International Cancer Control
VMAT	Volumetric modulated arc therapy
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Ranta P, Kinnunen I, Jouhi L, Vahlberg T, Back LJJ, Halme E, Koivunen P, Autio T, Pukkila M, Irjala H. Long-term quality of life after treatment of oropharyngeal squamous cell carcinoma. *Laryngoscope*, 2021; 131: E1172–E1178.
https://doi-org.ezproxy.utu.fi/10.1002/lary.29042

II Ranta P, Kytö E, Nissi L, Kinnunen I, Vahlberg T, Minn H, Haapio E, Nelimarkka L, Irjala H. Dysphagia, hypothyroidism, and osteoradionecrosis after radiation therapy for head and neck cancer. *Laryngoscope Investigative Otolarygology*, 2021; 7(1): 108–116s
https://doi.org/10.1002/lio2.711

III Ranta P, Kinnunen I, Irjala H. Validation of the Finnish MD Anderson Dysphagia Inventory (MDADI) in patients with head and neck cancer. *Scientific Reports*, 2025, 15(1), 1–10.
https://doi.org/10.1038/s41598-025-03616-1

IV Ranta P, Irjala H, Kinnunen I, Halme E, Tiitto P, Koivunen P. Single-modality treatment is superior in quality of life outcomes in oropharyngeal cancer survivors – a prospective multicenter 1-year follow-up. *Manuscript.*

1 Introduction

Head and neck cancer (HNC) is the sixth most common malignancy worldwide, accounting for nearly 950,000 new cases every year. (Bray Bsc et al., 2024) In Finland, the annual incidence is approximately 1,000. (Finnish Cancer Registry, 2025) More than 90% of all HNCs are derived from the squamous cells that line the mucosal surfaces of the upper aerodigestive tract, and hence, are referred to as squamous cell carcinomas of the head and neck (HNSCC). (Leemans et al., 2018) The leading sites of HNC are the lip and oral cavity, larynx, nasopharynx, and oropharynx, each accounting for more than 100,000 new cases annually worldwide. (Bray Bsc et al., 2024) Additionally, HNC can arise in the hypopharynx and salivary glands, both of which still rank among the top 30 most common cancer sites globally. However, regardless of their location, cancers of the skin, thyroid, and lymphatic system are not usually classified as HNCs.

Although the incidence of tobacco- and alcohol-related HNC is declining in many countries, the global incidence of oropharyngeal cancer (OPC) is increasing. (Stein et al., 2015) This is largely attributed to the human papillomavirus (HPV) epidemic, which is responsible for up to 690,000 cancer cases annually. (Mukherjee et al., 2023) Globally, cervical cancer remains the most widespread HPV-mediated malignancy. (Mukherjee et al., 2023) However, due to widespread cervical cancer screening and the early detection of precancerous lesions, OPC has become the most common HPV-associated cancer in the United States since 2015. (Van Dyne et al., 2018) At present, HPV accounts for more than 50% of all OPC cases in many countries across North America, Europe, Asia, and Australia. (Carlander et al., 2021)

Since HPV-related OPCs tend to both affect younger individuals (Hussein et al., 2017) and have a better prognosis than HPV-negative OPCs, there is a growing emphasis on treatment strategies that result in good post-treatment quality of life (QoL). (Sedghizadeh et al., 2016) However, the optimal treatment modality for OPC remains unresolved. (Culié et al., 2021; Tsai et al., 2021) In both HPV-negative and HPV-positive OPC, primary surgical treatment and chemoradiotherapy (CRT) appear to yield similar overall survival (OS) outcomes. (Kelly et al., 2017, 2018)

Nevertheless, many OPC survivors report clinically important deteriorations in QoL especially regarding swallowing, dry mouth, chewing, speech, taste, and

appearance. (Høxbroe Michaelsen et al., 2017) Moreover, HNC survivors may experience neurocognitive impairment persisting for at least 2 years after (chemo)radiotherapy. (Iyizoba-Ebozue et al., 2024; Zer et al., 2018) When asked to identify their two most serious long-term concerns, HNC survivors most frequently cited dry mouth, difficulty swallowing, difficulty speaking, and pain in the head and neck region. (Taylor et al., 2023)

These QoL-reducing symptoms may be permanent and even worsen over time: HNC survivors have reported increasing severity of swallowing dysfunction as late as 6 years post-treatment. (Nilsen et al., 2019) Therefore, functional outcomes and QoL considerations should guide physicians and patients in choosing the best individualised treatment for HNC.

However, there is a lack of research investigating the QoL of HNC survivors, particularly long-term outcomes. In measuring QoL, validated questionnaires are essential. In this thesis, we aimed to analyse treatment-induced morbidity and patient-related factors associated with QoL outcomes in patients with HNC. Moreover, we aimed to validate the first disease-specific Finnish dysphagia questionnaire for patients with HNC to provide reliable clinical and research utility regarding swallowing-related QoL.

Artificial intelligence (AI) disclosure statement: During the preparation of this thesis, I used ChatGPT-4o for language and grammar refinement. After using this tool, I carefully reviewed, edited, and revised the text according to my own preferences.

The language of this thesis has also been reviewed by professional editor Adelaide Lönnberg (MapleMountain Editing). I take full responsibility for the final content of the thesis.

2 Review of the Literature

2.1 General considerations for head and neck cancer

2.1.1 Epidemiology

In 2022, nearly 950,000 new cases of HNC were diagnosed worldwide, while in Finland the incidence was approximately 1,000 the same year. (Finnish Cancer Registry, accessed April 2025; Bray Bsc et al., 2024) The incidence of OPC is rising rapidly, primarily due to the human papillomavirus (HPV) epidemic. (Stein et al., 2015) In many Western countries, including Finland, the majority of new OPC cases are now HPV positive. (Carlander et al., 2021; Jouhi et al., 2017) This rising trend is visible in the Finnish Cancer Registry statistics: 1,309 new cases of OPC were diagnosed between 2018 and 2022, whereas 20 years earlier, between 1998 and 2002, there were only 493 new cases. (Finnish Cancer Registry, 2025) OPC is more common in men; of 1,309 new cases reported over the last 5 years, 957 (73.1%) occurred in male patients.

2.1.2 Risk factors

2.1.2.1 Smoking and heavy alcohol consumption

Many HNC cases are attributable to the combined effects of smoking and heavy alcohol consumption. However, the respective contribution of these risk factors remains unclear. (Gormley et al., 2020) A pooled analysis of 11,221 cases and 16,168 controls suggested that the population attributable risk (PAR) for tobacco or alcohol is 72% for HNC, of which 4% was due to alcohol alone, 33% to tobacco alone, and 35% to their combined effect. (Hashibe et al., 2009) Smoking and heavy alcohol use were more important risk factors in patients with laryngeal cancer (PAR 89%), men (PAR 74%), and patients >60 years of age (PAR 73%). A more recent multivariable Mendelian randomisation analysis suggested that for oral or oropharyngeal cancer, the inverse variance weighted odds ratio (OR) was 2.6 for

smoking alone and 2.1 for alcohol consumption alone. (Gormley et al., 2020) These findings suggest that the causal effect of alcohol consumption may have been previously underestimated.

However, smoking prevalence is declining globally: in 2022, current tobacco use was estimated to be 20.9% among persons aged 15 years and older, compared to 26.4% in 2010. (WHO World health statistics report, 2023)

In Finland, both smoking prevalence and total alcohol consumption are declining. In 2022, 12% of males and 11% of females aged 20 to 64 years were current smokers, compared to 30% and 20%, respectively, in 1997 (Jääskeläinen & Kovanen, 2024) The same year, in 2022, total alcohol consumption was approximately 9 litres of 100% alcohol per person aged 15 and older, compared with nearly 12 litres in 2010, representing a 33% drop. (Finnish Institute for Health and Welfare, 2023)

2.1.2.2 Human papillomavirus and Epstein-Barr virus

Human papillomavirus (HPV) infection is considered one of the three major risk factors for HNC in addition to smoking and heavy alcohol consumption. The estimated lifetime probability of acquiring HPV among those with at least one opposite-gender partner is >80% for both women and men. (Chesson et al., 2014) HPV is most commonly transmitted through close skin-to-skin contact, usually during vaginal, anal, or oral sex. It can also be transmitted from mother to embryo, foetus, or child during pregnancy or delivery. (Milano et al., 2023) Moreover, transmission can occur via infected spermatozoa at the time of fertilisation, through breast milk, via fomites, and through autoinoculation. (Sabeena et al., 2017)

Globally, approximately 38,000 cases of HNC are attributable to HPV every year. (de Martel et al., 2017) Of all HNCs, OPC has the strongest association with HPV. To a much weaker extent, also oral cavity cancer and laryngeal cancer may be associated with HPV. (Kava et al., 2024) High-risk HPV subtypes (hrHPV) 16 and 18 are globally responsible for 85% of HPV-HNCs. Nevertheless, also HPV subtypes 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are classified as carcinogenic, and HPV68 as probably carcinogenic. (de Martel et al., 2017)

For HPV-OPC, risk factors include a history of multiple sex partners, anal sex, oral sex, and a weakened immune system. (Murray-Stewart et al., 2023) However, in the United States, HPV vaccination, first approved in 2006, has already reduced the prevalence of oral HPV 6, 11, 16, and 18 by >80% among young females. (Rosenblum et al., 2021) It remains to be seen how the implementation of vaccination programmes will affect the incidence of HNSCC. In Finland, the HPV vaccine protecting against HPV types 16 and 18 has been included in the national

vaccination programme for girls since 2013, and for boys since 2020. It is expected to reduce healthcare costs and yield significant health benefits. (Lehtinen et al., 2018)

For assessing HPV causation in HNCs, the surrogate biomarker p16 (protein $p16^{INK4a}$) is widely used (Larsen et al., 2014), see Figure 1. It is also used in the original publications of this thesis, despite its limitations. In the future, additional testing for HPV DNA or RNA may be required. (Mehanna, Taberna, et al., 2023)

Another virus with a clear association with HNCs is the Epstein-Barr virus (EBV). It is usually transmitted through bodily secretions and is best known as the cause of infectious mononucleosis. In addition, it is associated with nasopharyngeal carcinoma (NPC), several lymphoma types, and gastric adenocarcinoma, NPC representing the closest association of EBV with malignancy. (Vasudevan & Yom, 2021) However, NPC is considered a distinctive entity among HNCs because of its unique worldwide distribution and histopathological characteristics. (Stan et al., 2021) NPCs are most common in Eastern and South-Eastern Asia, Africa, and South-Central Asia. (Tsang et al., 2020)

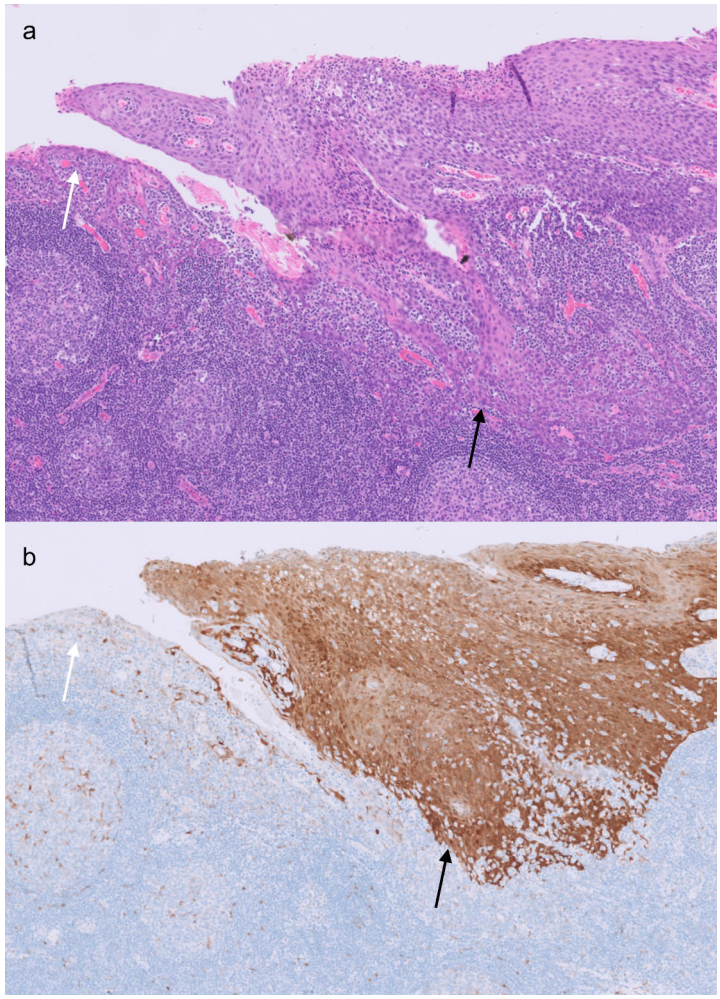

Figure 1. Histological image of oropharyngeal squamous cell carcinoma. a) Haematoxylin-eosin staining. b) Immunohistochemical staining for p16 is positive, suggesting HPV-related squamous cell carcinoma. White arrows: normal tonsil. Black arrows: tumour. From *Ranta P., Irjala H., Minn H., and Kinnunen I. Suunielusyöpä ja elämänlaatu. Duodecim. 2023;139(17):1359–1366* with permission from the copyright holders. Picture: Jutta Huvila.

2.1.2.3 Gender and age

Globally, men have a twofold to fivefold greater risk of HNC than women. (Simard et al., 2014) This difference is explained by higher rates of smoking and heavy alcohol use and by differences in sexual behaviour. (Hussein et al., 2017; Simard et al., 2014)

Moreover, the risk of developing HNC increases with age: the median age of diagnosis for most HNC sites is between 55 and 70 years. (SEER Cancer Statistics Review, 2021) An underlying mechanism to this is that the major risk factors for

HNC, smoking and heavy alcohol consumption, are cumulative and dose dependent. (Hydes et al., 2019) Furthermore, HPV infections are associated with the development of cancer only if they persist, the malignancies often occurring several decades later. (McBride, 2024)

2.1.2.4 Socioeconomic status

A pooled analysis of 23,964 cases and 31,954 controls suggested that low educational attainment is associated with an increased risk of HNC (OR 2.5, 95% confidence interval [CI] 2.02–3.09). Notably, one-third of this increased risk could not be attributed to differences in the distribution of smoking and alcohol consumption. Similar findings were observed for the estimated effect of low versus high household income. (Conway et al., 2015) These findings are consistent with previous literature on socioeconomic disparities in HNC risk. (Boing et al., 2011; Hwang et al., 2013)

Conway et al. discussed whether the causal mechanisms linking low socioeconomic status and disease operate via behavioural lifestyle factors and/or through psychosocial, material, and life-course pathways such as time preference, that is, whether one places emphasis on one's present or future wellbeing.

2.1.2.5 Other risk factors

Another major risk factor for HNC, particularly oral cavity cancer, is smokeless tobacco, including betel quid and areca nut. (Rettig & D'Souza, 2015) However, the smokeless tobacco used in Finland (Swedish snuff) has not been associated with oral cancer. (Araghi et al., 2021)

Furthermore, minor risk factors for HNC include premalignant lesions such as leukoplakia and erythroplakia, immune suppression, poor nutrition, low folate levels, poor oral hygiene, occupational exposures (including wood dust and asbestos), sun exposure, and some genetic and rare diseases. (Rettig & D'Souza, 2015)

2.1.3 Distinct characteristics of oropharyngeal cancer (OPC)

Oropharyngeal cancer (OPC) has a rapidly rising incidence, making it a hot topic in research. (C. D. L. Smith et al., 2024) OPC affects the tonsillar complex (palatine tonsils, tonsillar fossae, and tonsillar pillars), base of the tongue (posterior third), soft palate (inferior surface and uvula), and pharyngeal wall (lateral and posterior), Figures 2 and 5.

The leading explanation for the rising rates of OPC is the HPV epidemic. (Stein et al., 2015) As mentioned earlier, OPC unarguably has the strongest association

with HPV among all HNCs. Due to this association, OPC affects many non-smokers and younger patients, unlike many other HNCs. (Hussein et al., 2017) Moreover, HPV-positive HNSCCs (mostly OPCs) have a significantly better prognosis than HPV-negative HNSCCs. (Ang et al., 2010; Wang et al., 2015)

The current state of the HPV epidemic is the focus of many studies. A systematic review and meta-analysis investigating oral HPV infections in 56,600 healthy individuals across six continents demonstrated an overall prevalence of 7.7% for all types of HPV and 1.4% for high-risk HPV16. (Tam et al., 2018) Nevertheless, the lifetime risk of OPC is low, only 37 per 10,000. (D'Souza et al., 2017)

The high prevalence of oral HPV infections, combined with the rising incidence of HPV-positive OPCs, has raised discussion about screening and treatment possibilities for precancerous conditions. Nevertheless, there are currently no effective screening methods for OPC, but emerging techniques including population screening, HPV serology, and mucosal imaging are under investigation. (Timbang et al., 2019) Oral HPV screening has been discouraged because of its limited utility: most individuals with oral HPV infection, even high-risk HPV, go on to clear the infection or never progress to malignancy. (AHNS Prevention & Early Detection Committee, 2017)

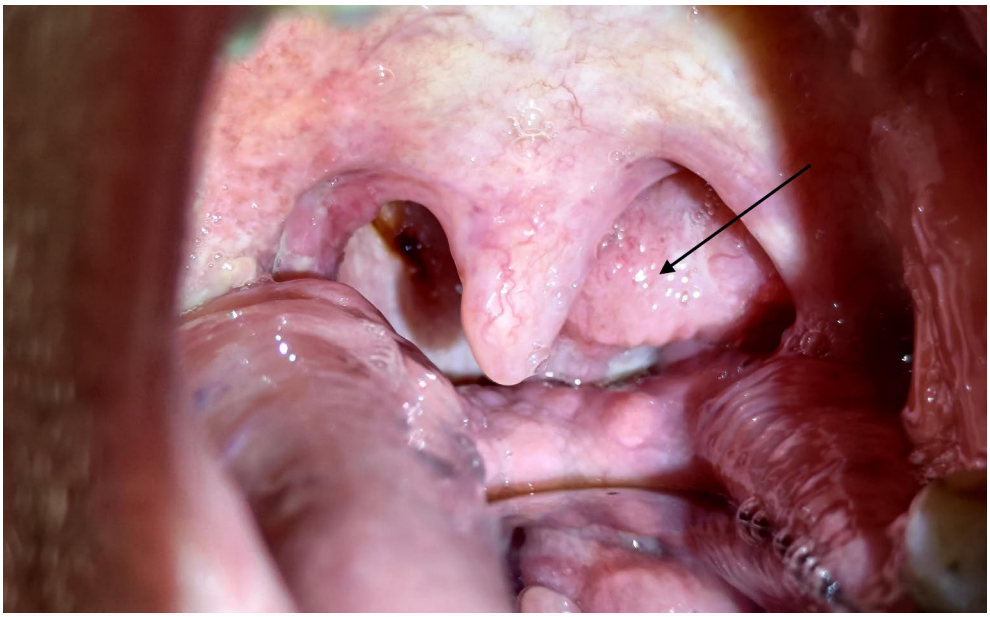

Figure 2. Oropharyngeal cancer. A tumour measuring 3.2 x 2.5 x 1.5 centimetres was found in the left tonsil (arrow) when the patient visited their local ear, nose, and throat outpatient clinic with epistaxis. A biopsy was performed under local anaesthesia. Histopathological examination suggested squamous cell carcinoma (SCC). From *Ranta P., Irjala H., Minn H., and Kinnunen I. Suunielusyöpä ja elämänlaatu. Duodecim. 2023;139(17):1359–1366* with permission from the copyright holders. Picture: Heikki Irjala.

2.1.4 Treatment modalities

For each patient, the treatment for HNC is recommended by a local tumour board. The treatment choice is guided by the tumour stage and characteristics, anatomical location, the patient's health and performance status, and the patient's personal preferences. Currently, the principal treatment options are surgery, (chemo)radiotherapy ([C]RT), or a combination of these modalities. In addition to chemotherapy, immunotherapy is an important systemic treatment modality, especially for metastatic or recurrent HNCs, possibly gaining a more important role in the future. (Fasano et al., 2022)

Most HNC patients agree with the tumour board's recommendations. (Shehan et al., 2022) Single-modality treatment is associated with better QoL outcomes compared to multimodality treatments and is thus generally pursued whenever possible. (Nordgren et al., 2008; Taylor et al., 2024)

Surgical treatment for HNC includes resection of the primary tumour and, due to the often-advanced stage at diagnosis, neck dissection of the corresponding cervical lymph node levels. In some small N0 HNCs, neck treatment is not needed and sentinel node biopsy may be a sufficient approach. (Finnish Society for Head and Neck Oncology Treatment Protocol, 2024) The surgical approach to the primary tumour may be open, endoscopic, or robotic (transoral robotic surgery, TORS). For OPSCC, TORS, as a minimally invasive treatment modality, results in better functional outcomes than open surgery, with fewer intra- and postoperative complications and no differences in positive margins or survival, making TORS the primary choice of many surgeons. (Roselló et al., 2020) However, when postoperative adjuvant therapies are required, the advantage of TORS compared to other surgical approaches or primary CRT is strongly diminished. (Guarino et al., 2024)

Radiotherapy for HNC is delivered as IMRT (intensity-modulated radiotherapy) or VMAT (volumetric modulated arc therapy). These modern methods allow the delivery of higher doses to the tumour with lower exposure to healthy tissues (Figure 3). For curative intent, RT is usually delivered as a fractionated regimen consisting of 2.0 Gy fractions given daily, 5 days a week, to a cumulative dose of 66–70 Gy. In a postoperative setting, the typical dose for a high-risk area is 60–66 Gy, whereas elective treatment for an N0 neck involves a dose of approximately 50 Gy. However, the head and neck region contains many functionally important structures, such as the parotid glands and pharyngeal constrictors, which are radiosensitive and prone to the side effects of RT. (Schindler et al., 2015)

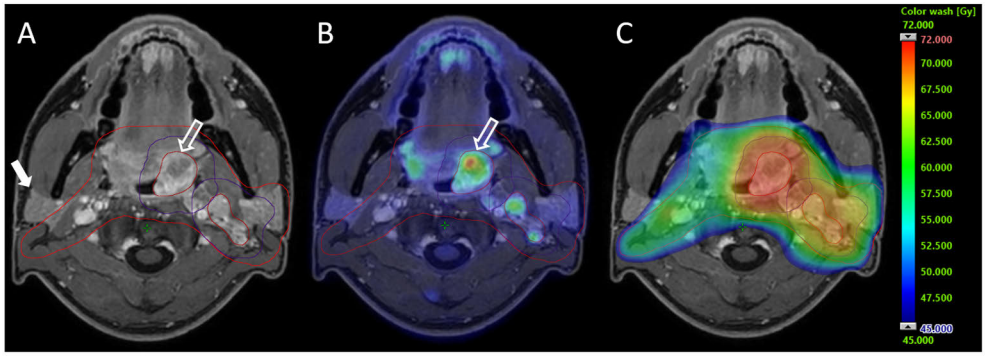

Figure 3. Radiation therapy planning for squamous cell carcinoma of the left tonsil (open arrow) with cervical lymph node metastases. The dose distribution has been modified using volumetric modulated arc therapy (VMAT) to reduce the dose received by the right parotid gland (filled arrow) and preserve salivary function. A) magnetic resonance imaging (MRI), B) hybrid imaging by positron emission tomography (PET) and MRI, C) planned target volume. From *Ranta P., Irjala H., Minn H., and Kinnunen I. Suunielusyöpä ja elämänlaatu. Duodecim. 2023;139(17):1359–1366* with permission from the copyright holders. Picture by Heikki Minn and Sami Suilamo.

2.1.4.1 Treatment selection in OPC

In OPC, the treatment guidelines for HPV+ (p16+) and HPV– (p16–) diseases differ. (Finnish Society for Head and Neck Oncology Treatment Protocol, 2024)

In HPV+OPC, the treatment recommendation for advanced tumours is usually CRT, whereas less advanced tumours can be treated with either surgery or (C)RT, both strategies resulting in similar oncological outcomes. In lateral T1–2 OPCs, surgery can be considered the optimal treatment strategy if a maximum of two regional lymph node metastases are present, if negative surgical margins are likely to be reached without significant morbidity, and if there is no sign of extranodal extension. In the base of the tongue, surgical resection should not exceed 50% of the tongue base tissue. A combination of surgery and CRT may result in better prognosis than CRT only in large T3–4N0–3 HPV+OPCs.

HPV–OPC is known to be less sensitive to radiation, and thus its treatment is either surgery or CRT regardless of the primary tumour size, with the exception of T1–2 tumours that can be treated with surgery, RT, or CRT.

In OPC, surgical treatment typically includes neck dissection of levels II–IV in HPV+ disease and levels I/II–IV/V in HPV– disease (Figure 4).

According to the current Finnish protocol, in a small (T1–2) HPV–OPC, sufficient surgical margins are >3mm. In a small (T1–2) HPV+OPC, sufficient surgical margins are ≥2mm. However, in addition to the surgical margins, the presence of extranodal extension and the size and amount of regional lymph node metastases impact the need for postoperative (C)RT.

According to the ASCO Guidelines published in 2025, a non-positive surgical margin may be sufficient in HPV-positive disease, and surgical margins narrower than 2mm are not always an indication for adjuvant RT. (Holsinger et al., 2025)

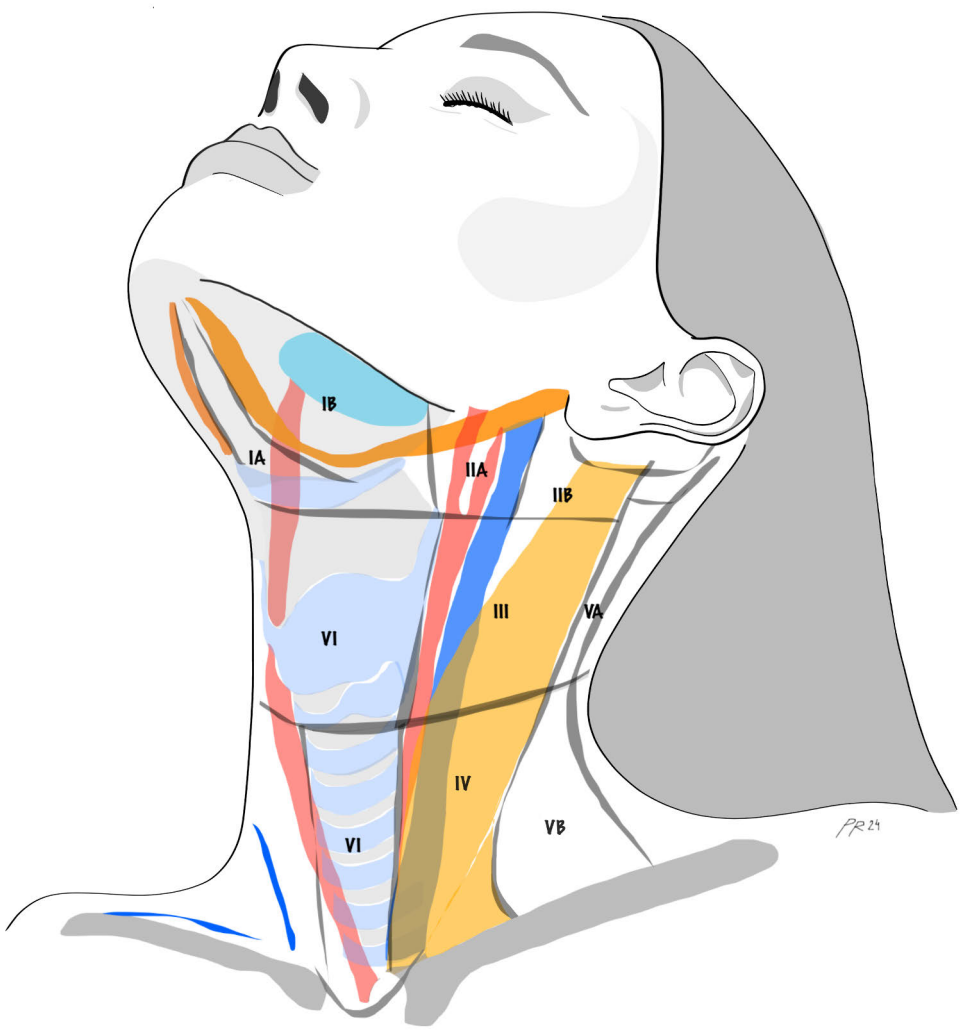

Figure 4. Main cervical lymph node levels; main regional metastatic sites in head and neck cancer. IA) submental, IB) submandibular, IIA) upper jugular anterior, IIB) upper jugular posterior, III) mid jugular, IV) lower jugular, VA) upper posterior triangle, VB) lower posterior triangle, VI) anterior cervical. Head and neck cancer at a specific anatomical site tends to spread to its corresponding cervical lymph node levels; for example, oropharyngeal cancers typically metastasise to levels II and III. Illustration by the author.

2.2 Prognosis in head and neck cancer

In Europe, 5-year survival rates for HNCs increased between 1999–2001 and 2005–2007 across nearly all sites, with the exception of laryngeal cancer. (Gatta et al., 2015) Gatta et al. also reported differences in relative survival (RS) between European countries. Five-year age-standardised RS was highest in Northern Europe, Ireland, and the United Kingdom, whereas it was low in Eastern European countries. This was attributed to differing risk factor prevalence and anatomical distributions of HNCs.

2.2.1 Prognostic factors

2.2.1.1 Tumour site

In a recent pooled analysis of 4,759 HNC patients from Western Europe, Brazil, and Japan, the 5-year OS was 51.4%. (Giraldi et al., 2017) However, the OS differed significantly among HNC sites: it was 63.9% for the larynx, 50.3% for the oral cavity, 41.1% for the oropharynx, and only 35.0% for the hypopharynx (Figure 5). When HNC-specific survival was analysed, 5-year survival rates were 57.4% for all HNC sites combined, 72.3% for the larynx, 54.6% for the oral cavity, 45.4% for the oropharynx, and 37.1% for the hypopharynx.

The prognosis for hypopharyngeal cancer is the poorest among all HNC sites, because patients with hypopharyngeal cancer often present at an advanced stage and in poor general health. Furthermore, the hypopharynx is rich in highly anastomotic regional lymph vessels, leading to early dissemination. (Gatta et al., 2015; Koo et al., 2006; Newman et al., 2015)

In Finland, for patients with OPSCC treated with curative intent, the 5-year OS was 60% (Jouhi et al., 2017), which was nearly one-half higher than what the pooled analysis by Giraldi et al. suggested. However, Giraldi et al. included all patients with histologically confirmed OPSCC without excluding those treated with palliative intent. In addition, the prognosis of OPSCC varies significantly depending on the HPV status of the tumour (Ferris & Westra, 2023), which we discuss in greater detail in Subsection 2.1.5.1.3.

In addition, subsites within HNC sites may have differing prognoses. For example, in advanced-stage OPC, tumours arising from non-tonsillar regions have been associated with worse OS. (Tsai et al., 2021)

Figure 5. Head and neck cancer sites. 1) nasal cavity and paranasal sinuses, 2) nasopharynx, 3) oral cavity and lip, 4) salivary glands (only the submandibular gland is visible), 5) oropharynx, 6) hypopharynx, 7) larynx. Illustration by the author.

2.2.1.2 TNM classification and stage

The internationally accepted standard for cancer staging is the UICC TNM (Tumour, Node, Metastasis) Classification of Malignant Tumours. (Brierley J.D. et al., 2017) The extent of HNC is classified using tumour staging (I–IV), which is determined by the primary tumour's anatomical site; size; regional metastases and their possible extranodal extension (ENE); distant metastases; and, in OPC, also the HPV classification of the tumour (Figures 1 and 6).

The major predictive factors for patient survival in HNC are the TNM classification and stage. (Gatta et al., 2015) In a population-based study involving 250,000 HNC patients, Gatta et al. reported a 5-year relative survival (RS) of 68.7% for patients diagnosed at a localised stage (tumour confined to the site of origin), and a significantly lower survival of 33.7% and 8.2% for patients with regional or distant metastases, respectively, at diagnosis.

Consistent with international findings, a recent Finnish retrospective cluster study of 1,341 HNC patients also found that advanced cancer stage is associated with poorer OS. (Heinolainen et al., 2025)

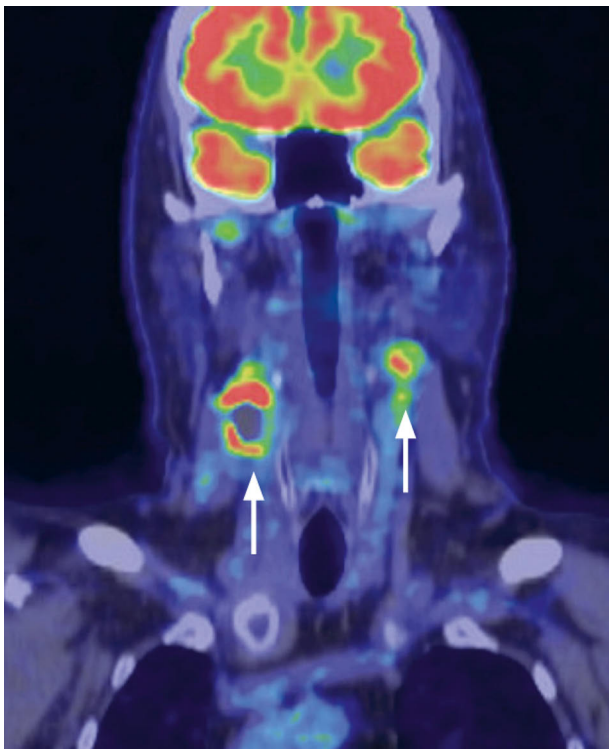

Figure 6. Positron emission tomography–computed tomography (PET-CT) scan showing bilateral regional cervical lymph node metastases (white arrows) between the submandibular glands and the sternocleidomastoid muscles. From *Ranta P., Irjala H., Minn H., and Kinnunen I. Suunielusyöpä ja elämänlaatu. Duodecim. 2023;139(17):1359–1366* with permission from the copyright holders. Picture by the author.

2.2.1.3 Human papillomavirus

In OPSCC, HPV status is the single most important determinant of prognosis. (Ferris & Westra, 2023) Three-year OS rates exceed 80% for HPV-positive OPCs but fall to around 50% for HPV-negative OPCs. (Ang et al., 2010)

The OS of patients with HPV-positive HNSCC is significantly higher even after adjusting for stage, age, gender, smoking, and alcohol consumption. (Wang et al., 2015) Furthermore, a systematic review by Wang et al. found that HPV-positive HNSCC patients had better survival outcomes than HPV-negative HNSCC patients regardless of treatment modality. In contrast, HPV-negative OPSCC patients tend to have poorer outcomes when treated with primary RT, as HPV-negative tumours are less responsive to radiation compared to HPV-positive OPSCC.

In addition to OPC, HPV-positivity is associated with better survival in hypopharyngeal cancer and laryngeal cancer. (Burbure et al., 2021; Li et al., 2018; Sahovaler et al., 2020) The most significant survival difference between HPV groups

is found in the oropharynx and hypopharynx. In contrast, in the sinonasal region, in the nasopharynx, and in the oral cavity, HPV positivity seems to have no association with improved OS. (Li et al., 2018; Sahovaler et al., 2020) According to a recent meta-analysis, in oral cavity SCC, HPV infection can even be used as a negative prognostic factor. (Christianto et al., 2022)

2.2.1.4 Patient and healthcare delays

A systematic review and meta-analysis found that a longer time interval from first symptom to referral to specialist services was associated with poorer prognosis in patients with oral cavity cancer. (Seoane et al., 2016) The authors concluded that the longer the diagnostic delay, the more advanced the disease was at diagnosis. In support of this, diagnostic and treatment-planning scans in a cohort of 648 HNC patients revealed a median tumour volume doubling time of 99 days; however, for the half of patients with the fastest growing tumours, the median doubling time was only 30 days. (Jensen et al., 2007).

In a Finnish study, the median patient, primary health care, and specialist care delays were 35, 20, and 49 days, respectively, for HNC patients. Patient delay was found to be associated with specific symptoms, whereas no significant associations were observed between delay and patient characteristics. Symptoms that correlated with longer patient delay were hoarseness and breathing difficulties, whereas a lump on the neck correlated with shorter delay. (Nieminen et al., 2018) In patients with OPSCC, the treatment modality had a significant impact on specialist care delay: patients treated primarily with surgery experienced shorter delays than patients treated with (C)RT. (Nieminen et al., 2020)

2.2.1.5 Smoking and heavy alcohol consumption

Smoking has been found to increase the risk of overall mortality in patients with OPC and oral cavity cancer, whereas heavy alcohol consumption is associated with increased overall mortality in patients with laryngeal cancer. (Conway et al., 2015)

In a Finnish cohort of 1,033 HNSCC patients, a history of heavy alcohol consumption increased the risk of mortality independently of other prognostic variables. (Denissoff et al., 2022) Moreover, Denissof et al. found that the continuation of at least moderate alcohol consumption (10–20 units per week) is associated with increased mortality risk. Furthermore, current smoking at diagnosis was associated with poorer prognosis. According to their study, quitting smoking at diagnosis did not show a clear improvement in prognosis within the studied Finnish cohort. However, evidence supports the conclusion that quitting smoking after HNC diagnosis does improve survival. (Caini et al., 2022; Sheikh et al., 2024)

2.2.1.6 Socioeconomic status and psychological distress

In a recent German study involving 20,821 HNC patients, the most socioeconomically deprived patients had the highest risk of mortality compared to the most affluent ones (hazard ratio [HR] 1.25, 95% CI 1.17–1.34). (Bedir et al., 2021) Among patients with the lowest socioeconomic status (SES), the 5-year age-adjusted relative survival was lowest (50.8%), whereas among the most affluent patients it was highest (56.7%). Most of the effect of low SES on survival was explained by a higher stage at diagnosis.

In addition, psychological distress may contribute to patient delay and thus poorer prognosis: HNC patients experiencing psychological distress have been found to present with more advanced disease. (Kugaya et al., 2000) Furthermore, a recent study found that genetic predisposition to depression and inflammation significantly predicts 3-year survival in patients with HNC; patients with a higher polygenic risk score for depression and inflammation, respectively, had a higher risk of death within 36 months. (Henry et al., 2023)

2.2.1.7 Other prognostic factors

A high comorbidity score negatively impacts the OS of HNC patients. However, comorbidities did not impact HNC-specific mortality. (Boje et al., 2013) Hence, especially in elderly patients, a multidisciplinary approach may be needed to treat both the cancer and the comorbidities. (Boje et al., 2013)

Gender also plays a role: 5-year relative survival appears to be significantly better in women than in men across all HNC sites, except for patients with laryngeal cancer. (Gatta et al., 2015) The authors considered whether this gender disparity might be attributed to women generally being more health-conscious than men, leading to shorter patient delays. In laryngeal cancer, however, the most fatal subsites, including the supraglottis, are more commonly affected in women, which may explain the lack of a survival advantage among women with this cancer.

Furthermore, both recurrences and second primary cancers reduce OS. In an international multicentre study involving 4,005 HNC patients, 1,161 (29%) patients were diagnosed with recurrent disease and 343 (8.6%) with second primary cancer during a median follow-up of 21 months. (Leoncini et al., 2018) Advanced tumour stage was associated with an increased risk of recurrence. Women were found to be at greater risk of second primary cancers, whereas men were at higher risk of cancer recurrence in the larynx specifically.

Another prognostic factor in cancer patients is physical activity, with growing evidence on its importance. A systematic review and meta-analysis involving 118,805 cancer patients found superior survival outcomes in patients with the highest levels of pre- or postdiagnosis total or recreational physical activity. (Friedenreich et

al., 2019) Some of the 136 studies included in the review also involved HNC patients. The benefits of physical activity regarding cancer prognosis have been confirmed in other large studies focusing on breast, prostate, and colorectal cancers. (Benke et al., 2018; Qiu et al., 2020; Salam et al., 2022)

2.3 Adverse effects of treatment for head and neck cancer

2.3.1 Acute side effects

Up to 50% of HNC patients treated with curative intent have poor treatment tolerance, present severe adverse effects of treatment, and may fail to complete multimodality treatment. (Bahig et al., 2015; Mascarella et al., 2022) In a prospective study involving 259 HNC patients, postoperative complications occurred in 27.7% of patients, whereas acute radiation-induced toxicity was found in 53.7%. (Bras et al., 2021)

Acute postoperative complications in HNC patients include bleeding, unplanned intubations, pulmonary embolism, failure to wean off the ventilator >48 hours after surgery, acute renal failure, cardiac arrest, acute myocardial infarction, stroke, pneumonia, deep venous thrombosis, and sepsis. (Abt et al., 2016; Holm et al., 2025; H. K. Kwon et al., 2021)

Common acute toxicities of RT for HNC are mucositis, dysphagia, dermatitis, and aspiration, which have been shown to affect 25–40%, 44–46%, 21%, and 10% of HNC patients, respectively. (Dragan et al., 2019; Muzumder et al., 2019) Moreover, xerostomia, sticky saliva, pain, decreased voice quality, and impaired chewing are common. (Naderi et al., 2021) Modern RT techniques including IMRT (intensity-modulated radiotherapy) and VMAT (volumetric modulated arc therapy) aim to spare the important functional structures of the head and neck from unnecessary radiation (Figure 3).

Acute xerostomia after RT for HNC has been associated with 16 single nucleotide polymorphisms in a genome-wide association study. (Naderi et al., 2021) Genome-related findings may eventually enable the identification of RT-sensitive patients, allowing for more individualised treatment planning.

Another factor influencing acute adverse effects of HNC treatment is possible concurrent chemotherapy. In patients who receive CRT, the incidence of acute toxicities is higher than in those receiving RT alone. (Rosenthal et al., 2014) Chemotherapy for HNC may induce anaemia, neutropenia, febrile neutropenia, thrombocytopenia, infections, nausea, vomiting, diarrhoea, mucositis, and digestive haemorrhage. (Lere-Chevaleyre et al., 2022)

In a recent systematic review and meta-analysis involving 292,560 HNC patients, frail patients were twice as likely to suffer short-term treatment-related toxicity compared to non-frail patients. The effect was most pronounced in patients treated primarily with surgery. (Mascarella, Vendra, et al., 2024) Another systematic review and meta-analysis found that patients with sarcopenia are also twice as likely to experience short-term treatment-related toxicity when undergoing curative-intent HNC treatment (n=3,187). (Mascarella, Ferdus, et al., 2024) Four independent predictors of severe acute radiation-induced toxicity have also been identified: female gender, low performance status, obesity, and more advanced stage. (Meyer et al., 2012)

2.3.2 Late side effects

Late toxicities of treatment are defined as symptoms occurring more than 3 months from the initiation of treatment. (Cox et al., 1995) Some severe late adverse effects are permanent; for example, a small percentage of HNC patients remain dependent on a feeding tube due to persistent swallowing difficulties. (Crombie et al., 2015; Mehdizadeh et al., 2020)

Long-term RT toxicities depend on the dose, volume, and site of the primary treatment and may include xerostomia, dysphagia, hypothyroidism, neck fibrosis, dental caries, skin changes, trismus, pharyngoesophageal stenosis, osteoradionecrosis, and chronic pain. (Allen-Ayodabo et al., 2019; Brook, 2020; Hamilton et al., 2019) Some persistent adverse effects are relatively common; in a median follow-up of 31 months, xerostomia, taste disorder, and dysphagia affected 42%, 23%, and 8% of HNC patients treated with IMRT. (Dragan et al., 2019) Moreover, IMRT-induced mandibular osteoradionecrosis affects up to 14% of HNC patients. (De Felice et al., 2020) Among the predictors of late RT toxicities, female gender and weight loss during treatment have been identified as independent risk factors. (Meyer et al., 2012)

Surgery for HNC has been shown to impair long-term QoL in relation to swallowing, aspiration, silent aspiration, speech, appearance, neck and shoulder mobility, and salivation. (Z. shan Huang et al., 2016; Mattioli et al., 2021; Tonsbeek et al., 2024; van Hinte et al., 2022) Major surgery combined with reconstruction leads to greater declines in health-related QoL. (Tonsbeek et al., 2024) In a 12-month follow-up study of patients after surgical treatment for HNC, frail and pre-frail patients experienced a greater decrease in global QoL compared to non-frail patients. (Thomas et al., 2021) While non-frail patients reported long-term issues with insomnia, fatigue, dry mouth, and sticky saliva, frail patients experienced a greater number of QoL-impairing symptoms.

2.3.3 Psychological and financial

Depression at an earlier time point is significantly associated with later depression in HNC patients. (Korsten et al., 2019) A systematic review by Korsten et al. found no other associations between depression diagnosis and symptoms among a wide range of sociodemographic and clinical factors including gender, age, being married, having children, higher income, higher education, smoking, alcohol consumption, higher HNC stage, treatment modality, and sleep. These findings are consistent with a previous systematic review of cancer patients in general. (Cook et al., 2018) According to another systematic review of coping styles among HNC patients, coping strategies aimed at distancing oneself from cancer were associated with increased psychological distress, (Morris et al., 2018) whereas coping behaviours aimed at actively changing or adjusting to cancer were found to be more beneficial.

In a review of 29 studies involving 362,766 HNC patients, psychological distress was reported by 54% of patients, emotional problems by 10–44%, and financial difficulties by 54%. (Mäkitie et al., 2024) In the same study, the prevalence of depression increased from 15% at diagnosis to 29% post-treatment.

Rosi-Schumacher et al. and Mäkitie et al. found that financial distress is highly prevalent among patients with HNC. Medical expenses for patients with HNC are often higher than for many other cancers. The most expensive treatment is trimodal therapy (surgery and CRT). Additionally, after HNC treatment, many patients do not return to work, leading to income loss. Patients who fail to return to work are also at greater risk of depression, anxiety, and social isolation. (Rosi-Schumacher et al., 2023)

2.4 Quality of life (QoL)

2.4.1 Definition of QoL and HRQoL

The terms QoL (quality of life) and HRQoL (health-related QoL) are often used to refer to the same concept. However, QoL is a broader concept that relates to all aspects of human life, whereas HRQoL focuses on the effects of illness and treatment. (Guyatt et al., 2007) The World Health Organization (WHO) defines QoL as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.” (WHO Programme on Mental Health, 1997)

Nevertheless, it has been noted that as the concept of HRQoL overlaps with that of QoL, the terms are confusing and hard to distinguish. (Karimi & Brazier, 2016) A recent systematic review found that in medicine and the health sciences, 94% of studies do not distinguish QoL from HRQoL. (Haraldstad et al., 2019) In this thesis, we mainly use the term QoL, even though we focus on the effects of illness and treatment.

2.4.2 Aims of the measurement of QoL

For a cancer patient, not only survival but also post-treatment QoL is a top priority. QoL assessment is necessary for evaluating treatment options, developing rehabilitative services, and patient education. In addition, QoL outcomes may predict survival (Chapter 2.6.3). Furthermore, the use of generic QoL instruments enable the calculation of quality-adjusted life years (QALYs), facilitating the comparison of different treatment strategies across many illnesses. QALYs are calculated simply by multiplying *years of life* by *health state by HRQoL score*. For example, if a person lives for half a year in perfect health, they will have 0.5 QALYs, and if they live for 1 year in "half health", they will also have 0.5 QALYs.

As many patients with a history of HNC live longer, survivorship is an increasingly important phase of the HNC treatment timeline; in the United States, approximately 3% of all cancer survivors are HNC survivors. (Miller et al., 2019; Seaman et al., 2021) The largest cancer survivor groups among males are those who have had prostate cancer, colorectal cancer, and melanoma of the skin. Among females, the majority of cancer survivors are those who have had breast cancer, uterine corpus cancer, and colorectal cancer.

2.4.3 Instruments

HNC may affect many complex and functionally important anatomic regions, impairing speech, swallowing, and breathing, and altering physical appearance. Consequently, many HNC patients experience that their cancer symptoms diminish their QoL. (Nayak et al., 2017)

In HNC patients, both general QoL aspects and disease-specific QoL outcomes are areas of research interest. Patient-reported outcome measures (PROMs) are the gold standard for measuring QoL. However, no single instrument is regarded as superior for measuring QoL in HNC patients. (Heutte et al., 2014) The following chapter briefly introduces the most relevant QoL instruments from the perspective of this thesis.

2.4.3.1 Generic

2.4.3.1.1 EORTC QLQ-C30

The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) is widely used among patients with different types of cancer. It includes a global health scale, functional scales (physical, role, emotional, cognitive, social), symptom scales (fatigue, nausea and vomiting,

pain), and symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties). (Groenvold et al., 1997)

All questions are answered using a four-level Likert scale (not at all, a little, quite a bit, very much). All scales are scored to range from 0 to 100. In the functional scales, a high score represents high QoL. In the symptom scales and items, a high score indicates more problems (low QoL). The minimal clinically important difference is considered to be 10 points (i.e., 10% of the maximum instrument score). (Ringash et al., 2007)

2.4.3.2 Dysphagia-specific

Dysphagia (swallowing difficulty) is one of the most important QoL-impairing symptoms of HNC patients before, during, and after treatment. Up to 53% of HNC patients report dysphagia before treatment, up to 70% 3 months after treatment, and up to 50% during long-term follow-up from 1 to 2 years. (Bhethanabotla et al., 2025; Denaro et al., 2013; Vermaire et al., 2022) Therefore, swallowing function is measured using numerous different PROMs, many of which have been specifically developed to assess dysphagia, including those we present here.

2.4.3.2.1 EAT-10

The Eating Assessment Tool (EAT-10) is a rapid and easily scored dysphagia instrument including 10 items rated on a 5-point Likert scale from no difficulty (0) to severe difficulty (4). A sum score of >2 points is considered suggestive of dysphagia. The items assess weight loss, ability to go out for meals, swallowing liquids, swallowing solids, swallowing pills, painful swallowing, pleasure of eating, food sticking in the throat, coughing when eating, and stressful swallowing. The questionnaire is not HNC-specific; it was validated in patients with dysphagia of various aetiologies (functional, related to oesophageal cancer or HNC, neurological, oesophageal, and age-related). (Belafsky et al., 2008) The tool was recently validated in Finland and named F-EAT-10, the Finnish version of the Eating Assessment Tool. (Järvenpää et al., 2021)

2.4.3.2.2 MDADI

The MD Anderson Dysphagia Inventory includes 20 items and is an HNC-specific dysphagia-specific questionnaire (A. Y. Chen et al., 2001) All items are rated on a 5-point Likert scale from strongly agree to strongly disagree. Thereafter, six domains are calculated: total (20 questions), global (1 question), composite (19 questions), emotional (6 questions), functional (5 questions), and physical (8 questions). Higher

scores indicate better dysphagia-related QoL. In an individual's within-subject MDADI scores, a change of 20 points is interpreted as clinically meaningful. (Lu et al., 2012) Between groups of HNC patients, a 10-point difference in composite MDADI scores is interpreted as clinically meaningful. (Hutcheson et al., 2016)

The MDADI was developed in the United States and has since been validated in many languages and cultural contexts across Europe, Asia, and South America. (Schindler et al., no date; Speyer et al., 2011; Carlsson et al., 2012; Guedes et al., 2013; Kwon et al., 2013; Hajdú et al., 2017; Matsuda et al., 2018; Montes-Jovellar et al., 2019; Lechien et al., 2020; Yee et al., 2020; Fakhriani et al., 2021; Alsubaie et al., 2022; Waghmare et al., 2023) In this thesis, the MDADI is validated for use in Finland.

2.4.3.2.3 MiniDADI

A recent preliminary study suggested that the 20-item MDADI may be feasibly abbreviated to a 5-item version, "MiniDADI". (Lin et al., 2022) The aim of shortening the questionnaire was to enhance its utility in routine clinical practice. After performing exploratory factor analysis on a cohort of surgical and non-surgical HNC patients spanning a diverse group of HNC sites, stages, and treatment modalities, Lin et al. suggested five questions that reliably represent the most commonly reported HNC-specific dysphagia symptoms.

These top five questions are as follows: *I feel excluded because of my eating habits* (functional domain), *Other people are irritated by my eating problem* (emotional domain), *I have low self-esteem because of my swallowing problem* (emotional domain), *My swallowing problems limit my social and personal life* (functional domain), and *People ask me, "Why can't you eat that?"* (physical domain).

To our knowledge, the MiniDADI is not currently used in research and is not in clinical use in Finland.

2.4.3.3 HNC specific

HNCs affect QoL in ways that are distinct from many other types of cancer. The most common HNC specific patient-reported outcome measure QoL instruments are the EORTC QLQ-H&N35 (Bjordal et al., 1999), the University of Washington QOL questionnaire (UWQOL) (Hassan & Weymuller, 1993), the FACT-HN (List et al., 1996), and the University of Michigan Head and Neck QOL questionnaire (HNQOL) (Terrell et al., 1997). Other less used but well tested instruments include the MD Anderson Symptom Inventory Head and Neck questionnaire (MDASI-HN)

(Rosenthal et al., 2007) and the Head and Neck Cancer Inventory (HNCI) (Funk et al., 2003). (Ojo et al., 2012)

2.4.3.3.1 EORTC QLQ-H&N35

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N35) was developed to be used in conjunction with the EORTC QLQ-C30 to assess HRQoL of HNC patients before, during, and after treatment with RT, surgery, and/or chemotherapy. (Bjordal et al., 1999b)

The EORTC QLQ-H&N35 includes 35 questions and, within them, seven multi-item scales (pain, swallowing, sensory problems, speech problems, trouble with social eating, trouble with social contact, reduced sexuality) and 11 single-item scales (teeth, opening mouth, dry mouth, sticky saliva, coughing, feeling ill, painkiller use, nutritional supplements, feeding tube use, weight loss, weight gain). High scores indicate more problems (poorer QoL).

2.4.3.3.2 EORTC QLQ-HN43

A validation study of a revised EORTC QLQ-H&N35 was published in 2019. (Singer et al., 2019) The updated instrument is called the EORTC QLQ-HN43. The revision was justified by evolving HNC treatments, including induction chemotherapy, therapeutic vaccines, various targeted agents, immune checkpoint inhibitors, and concomitant cisplatin- or anti-epidermal growth factor receptor antibody-based chemoradiation.

The new EORTC QLQ-HN43 includes 43 questions and, within them, 12 multi-item scales (anxiety, body image, dry mouth and sticky saliva, pain in the mouth, sensory problems, shoulder problems, skin problems, social eating, speech, swallowing, sexuality, problems with teeth) and seven single-item scales (coughing, neurological problems, opening mouth, social contact, swelling in the neck, weight loss, problems with wound healing). Of these items, new domains are addressed such as anxiety, body image, shoulder problems, skin problems, neurological problems, swelling in the neck, and problems with wound healing. Nevertheless, for the purposes of this thesis, the older EORTC QLQ-H&N35 version is used.

2.4.3.4 Properties of HRQoL Instruments

The COSMIN (Consensus-based Standards for the Selection of Health Measurement Instruments) guidelines require PROMs to demonstrate established psychometric properties before they can be used in research and clinical settings. (Mokkink et al.,

2010) The important psychometric domains are reliability, validity, responsiveness, and interpretability. Feasibility is another important characteristic of a measurement that is often assessed in validation studies.

However, a recent review found that among 39 PROMs used for HNC patients, only one demonstrated sufficient content validity and internal structure according to COSMIN guidelines. (Manduchi et al., 2024) This was the SOAL (Swallowing Outcome after Laryngectomy), developed in 2012. (Govender et al., 2012) This could be because many of the PROMs used for HNC patients were developed prior to publication of the COSMIN standards.

2.4.3.4.1 Reliability

Reliability is defined as the degree to which a measurement is free from *measurement error*, the systematic and random error of a patient's score that is not attributed to true changes. (Mokkink et al., 2010) To elaborate further, it is the extent to which scores for patients have not changed across repeated measurements.

For example, *internal consistency* can be measured using different sets of items from the same health-related patient-reported outcomes. Moreover, *test-retest reliability* is measured by the answers from the same respondents on different occasions (intrarater) or by different raters on the same occasion (interrater).

2.4.3.4.2 Validity

Validity is defined as the degree to which a health-related patient-reported outcome instrument measures the construct(s) it purports to measure. (Mokkink et al., 2010) It can be divided into content validity, construct validity, and criterion validity.

Content validity is the degree to which the content of an HR-PRO instrument is an adequate reflection of the construct to be measured. For good content validity, the COSMIN group has published 10 criteria that assess relevance, comprehensiveness, and comprehensibility. (Manduchi et al., 2024) For example, these include questions such as whether the response options are appropriate (relevance), whether the included items are relevant for the target population (relevance), whether all key concepts are included (comprehensiveness), and whether the instructions are understood by the population (comprehensibility).

Construct validity is the degree to which the scores of an HR-PRO instrument are consistent with hypotheses. For example, it can be demonstrated through relationships to scores from other instruments or differences between relevant groups. If a questionnaire is developed to measure overall health, its construct validity is not good if it only succeeds in measuring one aspect of health such as chronic pain. Construct validity is sometimes divided into convergent validity

(correlation with other measures that are expected to correlate) and discriminant validity (non-correlation with other measures that are not expected to correlate).

Criterion validity is the degree to which the scores of an HR-PRO instrument are an adequate reflection of a "gold standard". It describes the extent to which the instrument behaves as expected.

2.4.3.4.3 Responsiveness

Responsiveness is defined as the ability of an HR-PRO instrument to detect change over time. (Mokkink et al., 2010) It is sometimes also called *sensitivity to change* or *longitudinal validity*, but these terms are no longer recommended by the COSMIN group.

2.4.3.4.4 Interpretability

Interpretability is the degree to which one can assign qualitative meaning (clinical or commonly understood connotations) to an instrument's quantitative scores or change in scores. (Mokkink et al., 2010) It is considered an important characteristic of a measurement instrument, even though it is not technically a measurement property.

2.4.3.4.5 Feasibility

In this context, feasibility describes how easy an instrument is to fill in. To evaluate the feasibility of a questionnaire, the following factors can be assessed: response rate, percentage of questions left unanswered, participant satisfaction, questionnaire completion time, or the number of times each patient requested help from the investigators. (Park, 2013)

2.4.3.5 Comparison of different QoL measures in head and neck cancer

A recent systematic review assessing the validity of PROMs in head and neck oncology concluded that while many instruments exist, very few have adequately incorporated patient input in the development process. (A. I. Mendez et al., 2022) Moreover, as previously mentioned, not many HNC-related PROMs demonstrate sufficient content validity and internal structure according to current guidelines. (Manduchi et al., 2024)

Thus, in the review by Mendez et al., only three studies met the inclusion criteria: the Xerostomia Questionnaire (XQ) (Eisbruch et al., 2001), Swallow Outcomes After Laryngectomy (SOAL) (Govender et al., 2012b), and Edmonton-33 (E-33) (A. Mendez et al., 2020). Nevertheless, these instruments are not among those most

commonly used in HNC research. (Ojo et al., 2012) Mendez et al. emphasised the need for PROMs specifically targeting speech and chewing function that incorporate patient input in the development process, as such instruments are currently lacking. This is an important issue, because speech and chewing are two of the four functional outcomes that HNC patients consider the most significant (in addition to swallowing and dry mouth) regardless of the tumour subsite and progression of the disease. (Metcalfe et al., 2014)

Patient preferences regarding commonly used HNC-specific QoL questionnaires have recently been investigated. (Mehanna, Carter, et al., 2023a) Of 558 participants, 82% found QoL questionnaires useful when communicating with their clinician, and 55% supported the routine use of questionnaires during follow-up. Of the four QoL questionnaires used, men and individuals over 70 years of age preferred a shorter questionnaire (e.g., UW-QOL (Hassan & Weymuller, 1993)), whereas women preferred the FACT-HN (List et al., 1996), and younger patients favoured the EORTC QLQ-H&N35. Most participants preferred structured, disease-specific instruments, whereas a simple patient-generated unstructured list was the least preferred. QoL questionnaires may not be one-size-fits-all, and different subgroups of HNC patients may benefit the most from different instruments, regardless of their cancer site.

2.4.4 QoL and survival

Among HNC patients, QoL domains have been shown to predict survival. A study involving 540 HNC patients enrolled in a randomised trial found that both the baseline physical functioning score (EORTC QLQ-C30) and changes in the EORTC QLQ-C30 physical functioning score were independent predictors of OS. (Meyer et al., 2009)

Moreover, another study involving 495 HNC patients found that the Short Form-36 physical component score, along with the pain, eating, and speech domains of the Head and Neck QoL scale, were associated with survival. (Karvonen-Gutierrez et al., 2008) Consistent with these findings, self-reported pain levels among HNC patients were associated with survival outcomes. (Scharpf et al., 2009) This underscores the value of routine QoL assessment in clinical practice.

3 Aims

This doctoral thesis focuses on quality of life and treatment-induced morbidity in patients with HNC. The specific aims of this thesis are:

1. To compare QoL outcomes after single-modality treatment versus combined treatment in patients with OPC.
2. To compare QoL outcomes after surgical treatment versus CRT in patients with early-stage OPC.
3. To establish patient-related factors associated with QoL outcomes in OPC.
4. To assess the prevalence of, and risk factors for, long-term side effects of RT for HNC.
5. To translate and adapt the swallowing-related QoL questionnaire MDADI into Finnish and validate it among patients with HNC.

4 Materials and Methods

4.1 Patients and source of data

4.1.1 Study I

Study I was a nationwide, population-based retrospective study analysing QoL outcomes in OPSCC patients 10 years after treatment. The study included all surviving patients in Finland who had been diagnosed with OPSCC and treated with curative intent over a 10-year period between January 1, 2000 and December 31, 2009. In October 2018, a list of eligible survivors was obtained from the Digital and Population Data Services Agency. Participants were recruited by mail and phone between October 2018 and February 2019.

Within the study period, the total number of patients treated with curative intent was 595. At the beginning of our study, there were 263 survivors (44.2% of all curatively treated patients). Of these survivors, 164 agreed to participate (62.4%). The median follow-up time from OPSCC diagnosis was 11.8 years (range 8.6–18.5 years).

All participants completed the QoL questionnaires assessing their long-term QoL results. Moreover, relevant patient characteristics were collected from the original dataset used in a previous survival outcome publication by our coauthors (Jouhi et al., 2017).

4.1.2 Study II

Study II was a single-centre retrospective chart analysis of persistent dysphagia, hypothyroidism, and osteoradionecrosis after RT for HNC. It included all HNC patients treated with RT at Turku University Hospital over a 6-year period between 2010 and 2015. From the same patient cohort, a recurrence analysis and detailed description of RT techniques and concomitant chemotherapy has previously been published by our coauthors. (Nissi et al., 2021) IMRT with standard fractionation was applied in each case.

In September 2020, a list of dates of death for the patient cohort was obtained from the Digital and Population Data Services Agency. All patients who had

survived for more than a year were included. The participant characteristics (age, gender, smoking history, alcohol consumption, primary tumour site, HPV status, stage, treatment modality, and chemotherapy details) and possible persisting radiation-induced toxicities were collected retrospectively from patient charts and from the original dataset previously assembled by Nissi et al. (Nissi et al., 2021)

Due to the retrospective nature of the study, the adverse effects collected were predefined and limited to three toxicities that were both clinically meaningful and relatively reliably recorded in patient charts: dysphagia, hypothyroidism, and osteoradionecrosis. All patients had been questioned about dysphagia during regular follow-up visits. Dysphagia symptoms were recorded at each visit in free text format by clinicians. Possible hypothyroidism was identified through laboratory tests ordered by clinicians at various timepoints during routine follow-up visits. Moreover, all patients were routinely screened for osteoradionecrosis by otorhinolaryngologists and dentists, with diagnosis often confirmed by radiological imaging.

4.1.3 Study III

Study III was a validation study of the Finnish version of the MDADI, a QoL questionnaire related to dysphagia. A total of 64 dysphagic HNC patients and 30 age- and gender-matched non-dysphagic controls, with no history of HNC or RT to the head and neck, participated in the study. All participants were native Finnish speakers. The dysphagic HNC patient group is described in Figure 7.

All participants with HNC were recruited by phone. The matched controls were non-hospitalised and were recruited from the local community through a mail-out/mail-back procedure. All participants completed both the Finnish MDADI questionnaire and the previously validated general dysphagia questionnaire, the Finnish version of the Eating Assessment Tool (F-EAT-10). Additionally, the dysphagic participants were asked to complete the MDADI a second time 1 week after the first initial assessment. They were also asked to provide written feedback on the MDADI. No reminders were sent regarding returning the questionnaires.

The general patient characteristics of the HNC group (age, gender, education, marital status, alcohol consumption, smoking, pack-years, comorbidities, regular medication) were collected retrospectively from patient charts. The control group was asked to provide the same information on a separate structured form. Moreover, regarding the dysphagic group, the HNC characteristics (time from diagnosis to study entry, dryness of mouth, feeding tubes, weight loss since diagnosis, treatment modality, cancer subsite, tumour TNM classification and stage, HPV status) were collected from patient files.

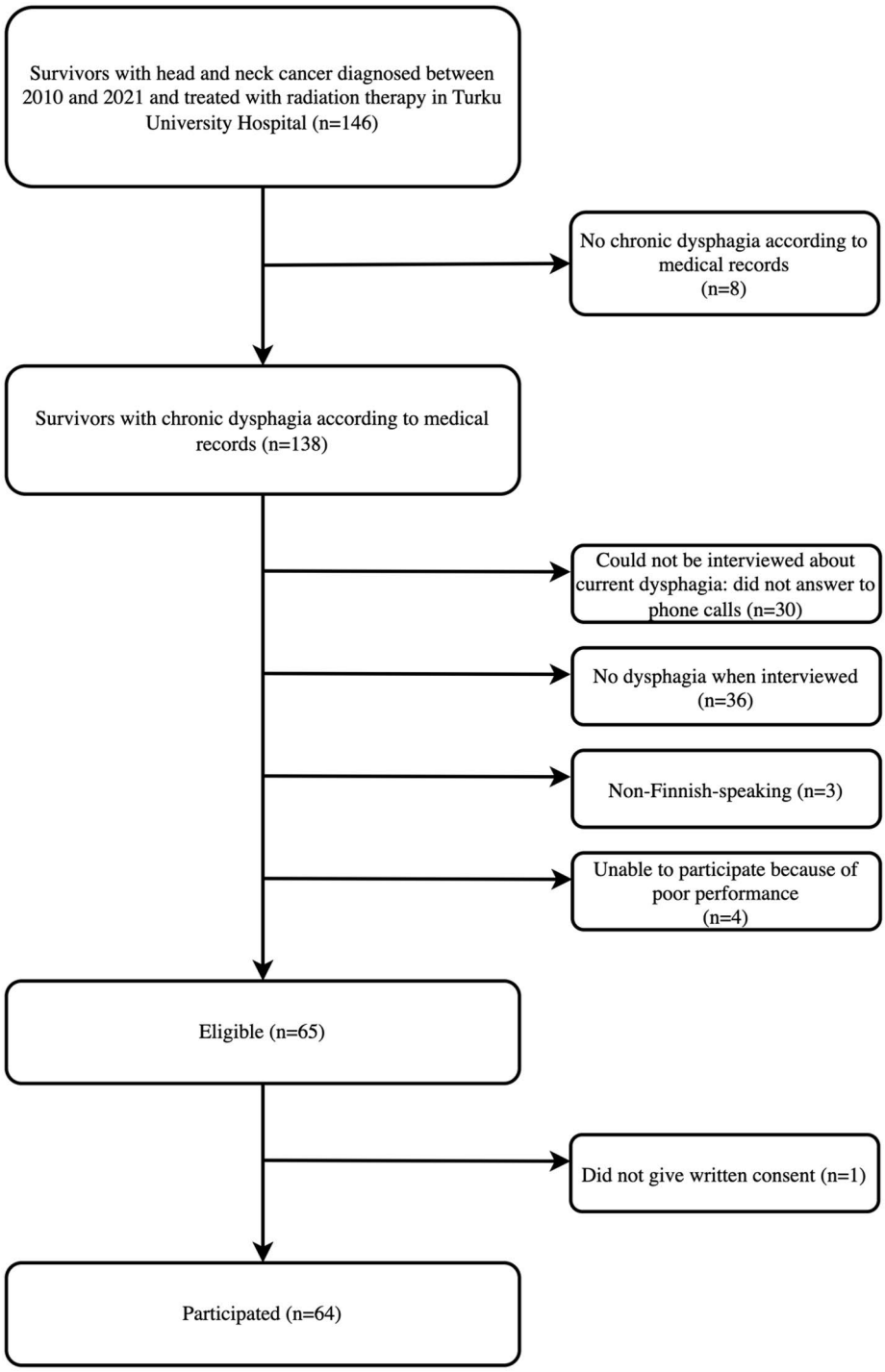

Figure 7. Flow chart of recruitment of dysphagic patients with head and neck cancer to Study III. From original publication III with permission from the copyright holders.

4.1.4 Study IV

Study IV was a multicentre, prospective cohort study of QoL during the first year after OPC diagnosis. It included patients with OPC enrolled during a 4-year period between January 2019 and February 2023 at three of the five tertiary care HNC centres in Finland: Oulu, Turku, and Tampere University Hospitals. The inclusion criteria were specified as follows: biopsy-verified OPC, curative treatment intent, and no history of HNC or RT to the head and neck. The participants provided informed written consent.

The following data were collected pretreatment: age, gender, weight, comorbidity score, smoking, alcohol use, performance status, tumour classification, stage, primary tumour location, size, depth of invasion, and HPV status. Treatment-related data included information on treatment modalities, bi- or unilateral neck treatment, feeding tubes, weight changes, tracheostomies, treatment adverse effects, recurrences, and treatment of recurrences.

QoL was measured once pretreatment, and twice post-treatment at 6 and 12 months after the OPC diagnosis.

4.2 Single-modality and combined treatment (Studies I and IV)

In Study I, the single-modality treatment group included patients treated with surgery, definitive (C)RT, or definitive CRT combined with neck dissection. The combined-treatment group included patients treated with a combination of surgery to the primary tumour and (C)RT.

In Study IV, the single-modality treatment group included patients treated with surgery alone, definitive CRT, or definitive RT. The combined-treatment group had the same definition as that used in Study I.

4.3 HPV status (Studies I–IV)

The HPV status of the tumours was determined by the widely used surrogate biomarker, p16 (protein $p16^{INK4a}$) immunohistochemistry. If more than 70% of the tumour cells were strongly immunopositive, the tumour was regarded as p16-positive and classified as HPV-positive.

4.4 Heavy alcohol consumption (Studies I–IV)

Heavy alcohol consumption was defined as ≥16 drinks per week for women and ≥24 drinks per week for men in line with the Finnish national guidelines for high-risk alcohol use published in 2015 (Alkoholiongelmat Käypä hoito -suositus, 2018).

Moreover, alcohol consumption was considered heavy if there was a mention of heavy alcohol use or alcohol use disorder in the participant's patient files.

4.5 Smoking (Studies I–IV)

The criteria used to classify smoking history varied across Studies I–IV.

In Studies I and IV, participants were divided into three groups according to their smoking history: never smokers, current smokers, and previous smokers (cessation before the OPC diagnosis).

In Study II, smoking history groups were defined as follows: never smoker, early quitter (cessation 1 year or earlier before the diagnosis of HNC), recent quitter (cessation less than 1 year before the diagnosis of HNC), and current smoker.

In Study III, participants were also divided into never smokers, early quitters, recent quitters, and current smokers. However, the definitions of early quitter and recent quitter were different than in Study II; in Study III, early quitters had quit smoking 6 months or earlier before the diagnosis of HNC, whereas recent quitters had quit smoking less than 6 months before the diagnosis of HNC.

4.6 Quality-of-life questionnaires (Studies I, III, and IV)

The same set of three widely used QoL instruments (European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire [EORTC QLQ-C30 version 3.0], its Head & Neck Cancer Module [EORTC QLQ-H&N35], and the MD Anderson Dysphagia Inventory [MDADI]) were used in Studies I and IV.

The EORTC QLQ-C30 is a general instrument developed to measure QoL in patients with all cancer types. The EORTC QLQ-H&N35 and the MDADI are HNC-specific, the former assessing a wide range of symptoms related to HNC, and the latter analysing dysphagia symptoms and their effect on QoL.

In Study III, we revised the previously used preliminary unofficial translation of the Finnish MDADI according to a formal forward-backward translation method. Thereafter, we assessed its criterion and construct validity against the previously validated general non-disease-specific dysphagia instrument F-EAT-10 (the Finnish version of the Eating Assessment Tool).

The characteristics of these questionnaires are discussed in more detail in the Review of the Literature in Chapter 2.4.3.

4.7 Hypothyroidism and osteoradionecrosis (Study II)

Hypothyroidism was defined as plasma thyroid-stimulating hormone (TSH) concentration above the normal reference range and thyroxine concentration below the normal reference range.

Osteoradionecrosis was defined as mucosal breakdown in the gingiva, or failure of healing in irradiated areas, resulting in bone exposure and necrosis of the overlying bone. The diagnosis was clinical; however, radiological imaging was often used for confirmation and evaluation of the extent of bone involvement.

4.8 Imaging and interpretation (Study IV)

The imaging modalities used in the follow-up of OPC patients were positron emission tomography–computed tomography (PET-CT) and positron emission tomography–magnetic resonance imaging (PET-MRI). PET-CT was used at Oulu and Tampere University Hospitals, while PET-MRI was employed at Turku University Hospital. The PET scans were reviewed by local nuclear medicine physicians.

A positive PET scan was defined as exhibiting higher ^{18}F-FDG (fluorodeoxyglucose) uptake compared to the surrounding background, with no similar activity on the contralateral side, or as showing increased activity at any location incompatible with normal physiological distribution. Similarly, a negative scan showed no abnormally increased ^{18}F-FDG uptake at any site.

4.9 Translation of the MDADI into Finnish (Study III)

For the translation of the MDADI into Finnish, the formal forward-backward translation method introduced by Wild et al. (2005) was employed. First, the authors produced two independent forward translations of the MDADI from English to Finnish. These were then synthesised into a single forward translation, which was then translated back into English by a native English-speaking professional translator. Thereafter, an independent speech therapist, an independent nutrition therapist and two independent otolaryngologists evaluated the original and the back-translation. Upon comparison of these questionnaires, no critical differences were identified.

4.10 Statistical analysis (Studies I–IV)

IBM SPSS Statistics versions 25–29 (IBM, Armonk, NY) were used in the statistical analyses. *p* values of <.05 were considered statistically significant. Normality of distributions was assessed graphically using histograms. (Studies I–IV)

Crosstabs, the $\chi 2$ test, and Fisher's exact test were used to assess whether patient groups were different in terms of risk factors or tumour characteristics (Studies I and IV). Crosstabs, the $\chi 2$ test, and Fisher's exact test also were used to assess differences in RT toxicity between patients grouped by risk factor profile, tumour classification, or treatment (Study II). To assess group similarity regarding age, a one-way analysis of variance (Study I and Study II) or independent samples T test (Study IV) was applied.

QoL outcome distributions and weight loss between patient groups were compared using the Mann-Whitney U test and the Kruskal-Wallis test. For pairwise comparisons, the Bonferroni correction was used (Studies I, III, and IV). Additionally, the Mann-Whitney U test and the Kruskal-Wallis test were used to assess differences in radiation dose or fraction between groups stratified by RT toxicity (Study II).

To analyse the correlation between QoL at diagnosis and at follow-up, the Spearman correlation coefficient was used (Study IV). Additionally, Spearman correlation was used in Study III to analyse correlations between the MDADI and F-EAT-10 scores. A correlation coefficient of <0.3 was considered a weak correlation, 0.3–0.7 a moderate correlation, and >0.7 a strong correlation.

In Study III, internal consistency reliability was tested with Cronbach's α coefficient; test-retest reliability was analysed using intraclass correlation (ICC) coefficients by longitudinally comparing questionnaire responses at the time of enrolment and 7 days later, and known-group validity was calculated between the dysphagic group and the non-dysphagic control group. Floor and ceiling effects were considered present if more than 15% of respondents achieved the extreme summary score.

Linear regression was used to test the trend in median TSH levels between time points in Study II.

In the MDADI, a subscale score was calculated only if the participant had answered at least 70% of the subscale questions (Studies I and IV).

In Study I, the length of follow-up was calculated from the last day of treatment to the long-term QoL surveys. In contrast, in Study IV, the length of follow-up was calculated from diagnosis to the follow-up timepoints.

4.11 Ethical considerations (Studies I–IV)

All studies were designed and performed in agreement with the Declaration of Helsinki.

Study I was approved by the Institutional Research Ethics Board of Turku University Hospital (record number: 29/1802/2018).

For Study II, no new review by an Ethics Committee was needed, since the study was fully retrospective in nature and included no intervention; however, it was approved by the local Clinical Research Centre (record number: T06/049/20). Moreover, the original study which collected the dataset used in Study II was approved by the Ethics Committee of the Hospital District of Southwest Finland. The use of biological data such as p16 status was authorised through permissions granted by the National Supervisory Authority for Welfare and Health (Licence No. V47408/4017 and V47856/2018) and Auria Biobank (Licence No. AB17-8403). (Nissi et al., 2021)

For Study III, the Institutional Research Ethics Board of Turku University Hospital reviewed the study plan (record number: 26/1801/2022) and determined that, since the study did not involve an intervention, the Medical Research Act Law did not apply. Consequently, no ethical approval was required, and the study was allowed to proceed without further ethical review.

Study IV was approved by the Institutional Research Ethics Board of Oulu University Hospital (record number: 29/1802/2018).

5 Results

5.1 Study I: Long-term QoL after treatment of OPSCC

5.1.1 Single-modality treatment compared to combined treatment

In the long-term follow-up (median 11.8 years, range 8.6–18.5 years) in Study I, the single-modality group (n=75) reported better QoL outcomes than the combined-treatment group (n=89). The superiority of single-modality treatment was statistically significant in regard to pain and appetite loss (EORTC QLQ-C30), pain and opening mouth (EORTC QLQ-H&N35), and four swallowing-related MDADI scales: composite score and the emotional, functional, and physical domains, Figures 8–9.

The single-modality and combined-treatment groups in Study I were comparable in terms of gender, age, cancer stage, p16 status, heavy alcohol use, and smoking.

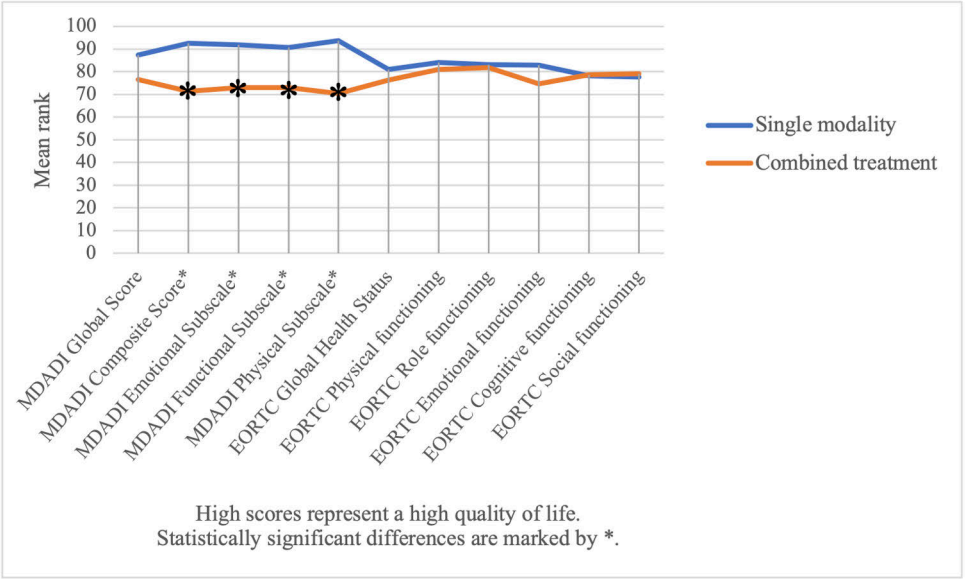

Figure 8. MD Anderson Dysphagia Inventory (MDADI) swallowing-related quality-of-life outcomes and the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) functional scales. From original publication I with permission from the copyright holders.

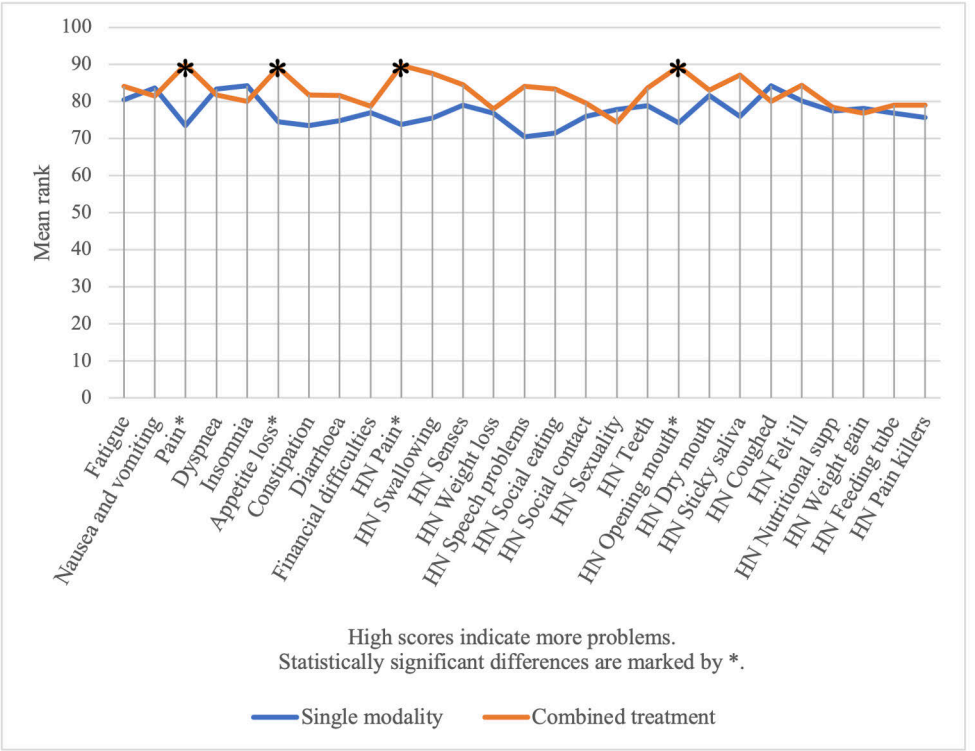

Figure 9. European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and its Head and Neck module (EORTC QLQ-H&N35) symptom scales. From original publication I with permission from the copyright holders.

5.1.2 Treatment impact

The QoL outcomes of different treatment modalities were compared between all the groups that were sufficient in size for analysis: the CRT±neck dissection (ND) group (n=68), the surgery+RT group (n=33), and the surgery+CRT group (n=50).

CRT±ND resulted in better QoL outcomes than surgery+(C)RT in the nine domains presented in Figure 10 (out of 38 analysed domains). In pairwise comparisons, CRT±ND resulted in better QoL outcomes than surgery+RT in pain, speech, opening mouth, and three swallowing-related outcomes measured by MDADI: composite score, and emotional and physical domains (marked with a line in Figure 10). In pairwise comparisons between surgery+RT and surgery+CRT, no significant differences were found.

The three treatment modality groups mentioned were comparable regarding p16 status, gender, smoking, alcohol consumption, and age. Nevertheless, two of the groups were unequally balanced across tumour stages: in the surgery+CRT group, the cancer stage was higher than in the surgery+RT group (p=0.024).

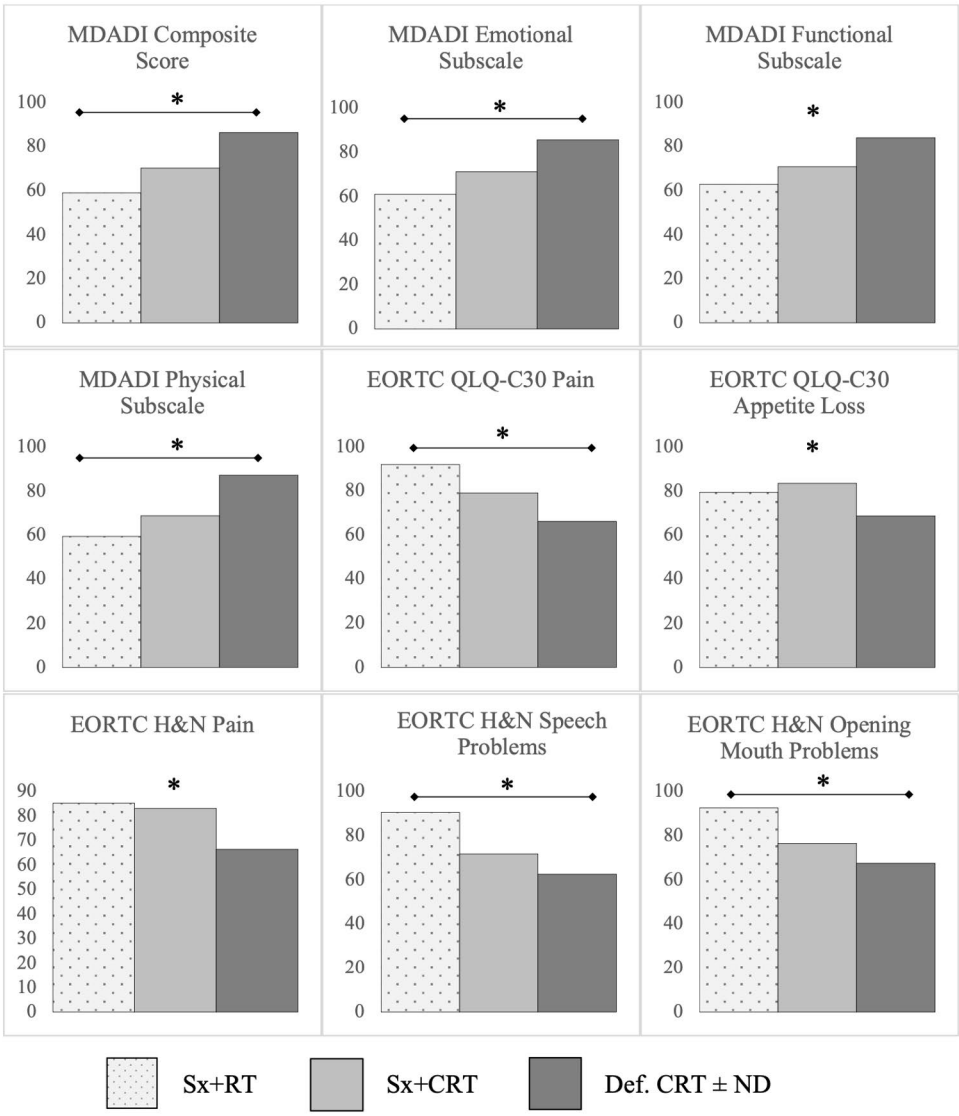

Figure 10. Quality of life (QoL) outcomes within treatment modality groups. Definitive chemoradiotherapy with or without neck dissection (Def. CRT ± ND) resulted in better QOL outcomes than surgery and radiotherapy (Sx + RT) and surgery and chemoradiotherapy (Sx + CRT). Statistically significant differences are marked with an asterisk (*). Significant differences in pairwise comparisons are marked with a line. In the MD Anderson Dysphagia Inventory (MDADI) subscales, high scores represent high QoL. In the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and its Head and Neck Module (EORTC QLQ-H&N35) symptom scales, high scores represent a high level of problems. QoL outcome values presented are mean ranks. From original publication I with permission from the copyright holders.

5.1.3 Smoking and long-term QoL

The long-term QoL of patients who were smoking at the time of OPSCC diagnosis was low compared to never smokers and previous smokers. The difference was significant across a wide range of QoL domains: 10/15 EORTC QLQ-C30 scales (global health status, physical, role, and social functioning, fatigue, nausea/vomiting, dyspnoea, appetite loss, constipation, and financial problems), 5/18 EORTC QLQ-H&N35 scales (weight loss, speech, social contact, sexuality, and feeling ill), and MDADI functional subscale (one out of six subscales).

In pairwise comparisons, previous smokers coughed more than never smokers ($p=0.027$), but no other significant differences in QoL domains were found between the smoking groups.

5.1.4 Heavy alcohol consumption and long-term QoL

Heavy alcohol consumption, both current and previous, was associated with poorer long-term QoL outcomes compared to patients with no history of heavy alcohol use across a vast variety of QoL domains: 9/15 EORTC QLQ-C30 scales (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, diarrhoea, financial problems), 5/18 EORTC QLQ-H&N35 scales (weight loss, weight gain, sexuality, social contact, and feeling ill), and MDADI functional subscale (one out of six subscales). All these differences were statistically significant.

5.1.5 p16 status and long-term QoL

In the Study I cohort, most patients had a positive p16 status (n=98 [89.1%], with information missing in 54 cases), which was used as a surrogate marker for identifying HPV-driven tumours. Only 12 participants (10.9%) had a negative p16 status. The p16-positive patients reported significantly better QoL results than p16-negative patients in EORTC QLQ-C30 cognitive function and EORTC QLQ-H&N35 dry mouth domains. No significant differences were found in the remaining QoL subscales.

5.1.6 Feeding tube dependency and long-term QoL

At the long-term follow-up, there were nine percutaneous endoscopic gastrostomy (PEG)-dependent patients (5.8%). All PEG-dependent patients had received RT: three were treated with single-modality CRT and six with combined surgery+(C)RT.

PEG dependency was associated with a notably poorer QoL: the EORTC QLQ-C30 global health status median was 33.3 (IQR 31.3) for PEG-dependent patients

and 75.0 (IQR 25.0) for patients without a PEG tube (p=0.008). In addition to global health status, the QoL differences were significant across all MDADI domains (global and composite scores and emotional, functional, and physical subscales), eight EORTC QLQ-H&N35 scales (pain, swallowing, senses, weight loss, social eating, sexuality, sticky saliva, and feeding tube), and four EORTC QLQ-C30 scales (role functioning, social functioning, appetite loss, and financial difficulties).

5.2 Study II: Persistent dysphagia, hypothyroidism, and osteoradionecrosis after RT for HNC

5.2.1 Long-term morbidity

5.2.1.1 Dysphagia

A total of 106 (45%) participants reported dysphagia that persisted for more than a year after RT. Most of the dysphagic patients (n=101, 95.3%) had changed their diet as a result, avoiding hard and crunchy foods, moistening and mechanically mincing all food or only consuming pureed foods. A total of 22 dysphagic patients (21%) had undergone oesophageal upper sphincter dilatations, the number of dilatations per patient ranging from one to 14. As a sign of severe dysphagia, 24 of the dysphagic patients (22.6%) had become PEG dependent. The impact of treatment modality on dysphagia results is presented in Table 1.

Table 1. Persistent dysphagia and its treatment within treatment modality groups. Modified from original publication II with permission from the copyright holders.

Column 1	Persistent dysphagia (n=106)	Percutaneous gastrostomy tube (PEG) dependence (n=24)	Oesophageal dilatations (n=22)	Nutrition therapy only (n=60)
Only surgery, advanced stage (III–IV) (n=7)	0	0	0	0
Only primary tumour radiated (n=15)	13.3%	0	6.7%	6.7%
Neck radiated, elective dose (median 50 Gy, n=79)	46.8%	10.1%	11.4%	25.3%
Neck radiated, definitive dose (median 65 Gy, n=139)	48.2%	11.5%	8.6%	28.1%
p	**0.004***	0.420	0.769	0.123

*Statistically significant differences are marked with an asterisk.

5.2.1.2 Hypothyroidism

Hypothyroidism was diagnosed in 67 patients (29%) after RT for HNC. The median time between the end of RT and starting thyroxine medication was 2.5 years (IQR 2.9 years, range 15 days to 9.1 years). In addition to the 67 new diagnoses, 18 participants had already been treated for hypothyroidism before RT.

5.2.1.3 Osteoradionecrosis

Of the Study II cohort, 29 patients (12%) were diagnosed with osteoradionecrosis. Two of them had very minor osteoradionecrosis and received no interventions but were followed up until the necrotised area had healed. In contrast, 23 of the patients diagnosed with osteoradionecrosis received surgical treatment, and in addition to surgery, six patients were treated with hyperbaric oxygen. Antibiotics for osteoradionecrosis were given to 12 participants.

5.2.2 Risk factors for long-term side effects of RT

5.2.2.1 Age

In younger patients, hypothyroidism was more common ($p=0.01$). The mean age of participants diagnosed with hypothyroidism was 58.4 years (SD 9.8), while the mean age of other participants was 62.2 years (SD 9.8). Older age was not associated with dysphagia or osteoradionecrosis.

5.2.2.2 Gender

Hypothyroidism was more common in women ($p<0.001$), affecting 52.8% of females (n=28) after RT for HNC, but only 23.5% (n=38) of males. The gender groups were comparable regarding age. Gender was not associated with dysphagia or osteoradionecrosis incidence.

5.2.2.3 Alcohol consumption

Hypothyroidism was less common in current heavy alcohol users (19.0%) compared to patients with previous (48.0%) or no history of heavy alcohol use (31.1%), ($p=0.045$). In contrast, heavy alcohol use was not associated with the incidence of dysphagia or osteoradionecrosis.

5.2.2.4 Primary tumour site

As expected, osteoradionecrosis was more common in the oral cavity cancer group (20.7%, n=92) compared to other primary tumour sites (7.2%, n=141), p=0.003. No other significant associations were observed between primary tumour site and treatment-induced morbidity.

5.2.2.5 RT to the neck

Persistent dysphagia was more common among patients receiving RT to the neck (both ipsilateral [66% of 12 patients] and bilateral [47% of 207 patients]) than in patients who did not receive neck radiation (0% of 14 patients) ($p<0.001$). Neck RT did not increase the risk of hypothyroidism or osteoradionecrosis.

5.2.2.6 Factors that did not increase the risk for late toxicities of RT

In the Study II cohort, a combination of chemotherapy (n=193), definitive neck radiation to high-risk volumes (n=139), advanced cancer stage (n=142), and surgical interventions (n=140) were found to be neutral with respect to studied late RT toxicities.

5.3 Study III: Validation of the Finnish MDADI in patients with HNC

5.3.1 Reliability

For all MDADI subscales, internal consistency was high in the dysphagic group (Cronbach's alpha coefficients >0.80) (Table 2). Moreover, test-retest reliability, assessed in all participants who returned the second administration of the MDADI (n=55, 89.5%), was good for each domain (ICC>0.80) (Table 2).

Table 2. Internal consistency and test-retest reliability of the MD Anderson Dysphagia Inventory (MDADI) domains in dysphagic patients with head and neck cancer. ICC=intraclass correlation. CI=confidence interval. Modified from original publication III with permission from the copyright holders.

Domains	Items	Internal consistency (Cronbach's alpha), n=64	Test-retest ICC (95% CI), n=55
Global	1	Not applicable	0.972 (0.952–0.984)
Emotional	6	0.864	0.965 (0.941–0.980)
Functional	5	0.819	0.964 (0.931–0.981)
Physical	8	0.850	0.973 (0.954–0.984)
Composite (all questions but global)	19	0.941	0.983 (0.970–0.990)
Total (all questions)	20	0.944	0.984 (0.972–0.990)

5.3.2 Validity

Criterion and construct validities were analysed in the dysphagic group by examining correlations between the MDADI and the previously validated dysphagia questionnaire F-EAT-10. As expected, strong negative correlations were found between the F-EAT-10 total score and the MDADI total, composite, emotional, functional, and physical scores; higher QoL in the MDADI corresponded to lower symptom burden in the F-EAT-10 (Table 3). In addition, strong negative correlations were found between the F-EAT-10 item "reduced pleasure of eating" and the MDADI total, composite, emotional, and physical scores. Furthermore, the F-EAT-10 item "cough during eating" showed a strong negative correlation with the MDADI total, composite, emotional, and physical subscale scores.

Another aspect of validity, known-group validity, was assessed by the ability of the MDADI to distinguish between dysphagic and non-dysphagic participants (Table 4). In all MDADI subscales, there was a statistically significant difference between the groups ($p<0.001$). The mean composite score differed between the dysphagic (74.3, SD=18.3) and non-dysphagic (99.9, SD=0.5) groups ($p<0.001$).

Moreover, a full range of score distribution (20 to 100) was observed in the dysphagic group with HNC. No ceiling or floor effects were found. In contrast, in the non-dysphagic group, the ranges were narrow and ceiling effects were observed across all domains, as expected (Table 5).

Table 3. Criterion and construct validities. Scale-scale correlations (Spearman's correlation coefficient r) for MDADI and F-EAT-10 in dysphagic patients with head and neck cancer, n=64. MDADI=MD Anderson Dysphagia Inventory. F-EAT-10=Finnish version of the Eating Assessment Tool. Modified from original publication III with permission from the copyright holders.

	F-EAT-10										
MDADI	Weight loss	Ability to go out for meals	Swallowing liquids disorder	Swallowing solids disorder	Swallowing pills disorder	Painful swallowing	Reduced pleasure of eating	Food sticks in the throat	Cough during eating	Stressful swallowing	Total score
Global	-0.376	-0.319	-0.426	-0.613	-0.552	-0.447	-0.636	-0.434	-0.213	-0.492	-0.641
p	*0.002*	*0.01*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.092*	*<0.001*	*<0.001*
Total	-0.499	-0.641	-0.572	-0.757	-0.64	-0.445	-0.823	-0.478	-0.367	-0.525	-0.831
p	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.003*	*<0.001*	*<0.001*
Composite	-0.502	-0.648	-0.576	-0.753	-0.626	-0.438	-0.821	-0.47	-0.365	-0.516	-0.824
p	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.003*	*<0.001*	*<0.001*
Emotional	-0.434	-0.682	-0.54	-0.702	-0.581	-0.395	-0.79	-0.465	-0.373	-0.516	-0.799
p	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.001*	*<0.001*	*<0.001*	*0.002*	*<0.001*	*<0.001*
Functional	-0.427	-0.691	-0.505	-0.685	-0.636	-0.317	-0.706	-0.409	-0.397	-0.45	-0.762
p	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.011*	*<0.001*	*<0.001*	*0.001*	*<0.001*	*<0.001*
Physical	-0.513	-0.499	-0.531	-0.708	-0.612	-0.445	-0.795	-0.485	-0.324	-0.481	-0.773
p	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.009*	*<0.001*	*<0.001*

Table 4. Known-group validity: differences between dysphagic and non-dysphagic participants. MDADI=MD Anderson Dysphagia Inventory. SD=standard deviation. Modified from original publication III with permission from the copyright holders.

MDADI domains	Dysphagic group with head and neck cancer n=64		Non-dysphagic control group n=30		*p*
	Mean	SD	Mean	SD	
Total	73.6	18.2	99.9	0.4	<0.001
Composite	74.3	18.3	99.9	0.5	<0.001
Global	60.9	22.1	100	0	<0.001
Emotional	72.9	20.5	100	0	<0.001
Functional	80.2	19	100	0	<0.001
Physical	71.7	18.8	99.7	1.1	<0.001

Table 5. Score distributions of the MD Anderson Dysphagia Inventory (MDADI). SD=standard deviation. Modified from original publication III with permission from the copyright holders.

	Domains	Items	Range	Mean	Median	SD	%Floor	%Ceiling
Dysphagic group with head and neck cancer, n=64	Total	20	20-99	73.6	78	18.2	1.6	0
	Composite	19	20-100	74.3	78.4	18.3	1.6	3.1
	Global	1	20-80	60.9	70	22.1	12.5	0
	Emotional	6	20-100	72.9	76.7	20.5	1.6	12.5
	Functional	5	20-100	80.2	84	19	1.6	14.1
	Physical	8	20-100	71.7	72.5	18.8	1.6	3.1
Non-dysphagic control group, n=30	Total	20	98-100	99.9	99.9	0.4	0	90
	Composite	19	97.9-100	99.9	100	0.5	0	90
	Global	1	100-100	100	100	0	0	100
	Emotional	6	100-100	100	100	0	0	100
	Functional	5	100-100	100	100	0	0	100
	Physical	8	95-100	99.7	100	1.1	0	90

5.3.3 Feasibility

All participants fully completed the MDADI, with no missing values, indicating good feasibility. Also supporting this, voluntary written feedback regarding the MDADI from dysphagic participants with HNC was positive. In the open-text field, seven patients wrote that the questions were easy to understand. One participant remarked that the F-EAT-10 was easier and quicker to fill in than the MDADI. The rest of the HNC group (total n=64) provided no feedback.

5.4 Study IV: QoL in OPC patients during the first year after diagnosis

5.4.1 Changes in QoL

The mean global QoL score of the study cohort was lowest at the 6-month follow-up and highest at the 12-month follow-up, with mean scores of 69.7 (SD 18.4) at baseline, 65.0 (SD 19.5) at 6 months, and 70.2 (SD 18.7) at 12 months.

There was a clinically significant change over time in 4/18 EORTC QLQ-H&N35 symptom item scales: senses, dry mouth, sticky saliva, and feeling ill. For the first three (senses, dry mouth, and sticky saliva), QoL worsened during follow-up, while the latter (feeling ill) was the only score to improve at 12 months compared to diagnosis. The scores for senses (mean±SD) were 10.1±21.6 at diagnosis, 32.4±29.6 at 6 months, and 28.6±24.4 at 12 months. Dry mouth scores were 34.5±26.5 at diagnosis, 62.8±33.1 at 6 months, and 55.7±29.7 at 12 months. Sticky saliva scores were 24.7±30.3 at diagnosis, 49.8±35.5 at 6 months, and 41.1±30.1 at 12 months. The score for feeling ill was 25.6±26.5 at diagnosis, 28±26.6 at 6 months, and 13±21.1 at 12 months.

5.4.2 Patient-related factors predicting QoL

A poor global QoL at diagnosis predicted a lower global QoL at 1-year follow-up (correlation coefficient ρ 0.405, p=0.004).

Never smokers and previous smokers had better swallowing-related QoL 1 year after diagnosis than smokers (MDADI total score p=0.042, global score p=0.017, composite score p=0.049).

Heavy alcohol users had poorer swallowing-related QoL outcomes than patients with no history of heavy alcohol consumption at 12 months (MDADI total score p=0.040, global score p=0.003, composite score p=0.046).

5.4.3 Single-modality treatment compared to combined treatment in early-stage OPC

One year after diagnosis, patients in the early-stage (I–II) single-modality group reported higher QoL compared to those in the early-stage combined-treatment group. This was observed in the EORTC QLQ-H&N35 domains of swallowing- and sticky saliva-related QoL, and in the MDADI swallowing-related domains total, global, and physical (Figure 11). The superiority of single-modality treatment was both statistically significant and clinically meaningful in all these domains.

At the 6-month follow-up, the swallowing-related QoL results were already poorer among patients in the combined-treatment group (Figure 12).

In the Study IV cohort, the single-modality and combined-treatment groups were comparable regarding age, gender, tumour subsite, stage, smoking, heavy alcohol use, ACE-27 comorbidity score, ECOG performance status, p16 status, and N classification. The single-modality group consisted of patients treated with surgery alone (n=12), definitive RT (n=2), and definitive CRT (n=35). The combined-treatment group consisted of patients treated with surgery + RT (n=9) and surgery + CRT (n=9).

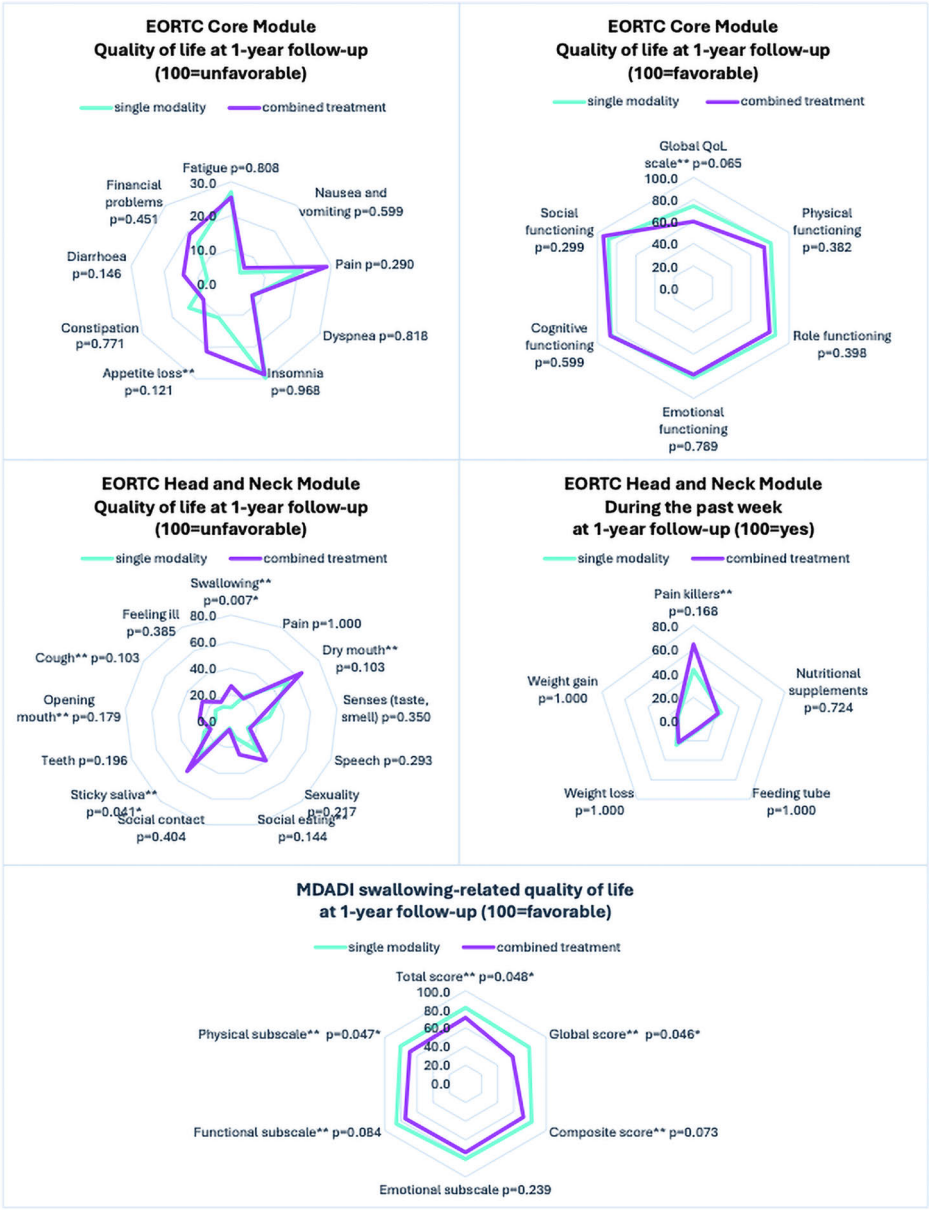

Figure 11. Early-stage (I–II) oropharyngeal cancer, quality-of-life outcomes at 1-year follow-up: single modality (n=49) vs combined treatment (n=18). Statistically significant differences between the groups are marked with an asterisk *. Clinically meaningful differences between the groups are marked with **. The single-modality group includes patients treated with surgery only (n=12), definitive radiotherapy (n=2), and definitive chemoradiotherapy (n=35). The combined-treatment group includes patients treated with surgery and radiotherapy (n=9), and surgery and chemoradiotherapy (n=9). EORTC=European Organisation for Research and Treatment of Cancer. MDADI=MD Anderson Dysphagia Inventory. From original publication IV with permission from the copyright holders.

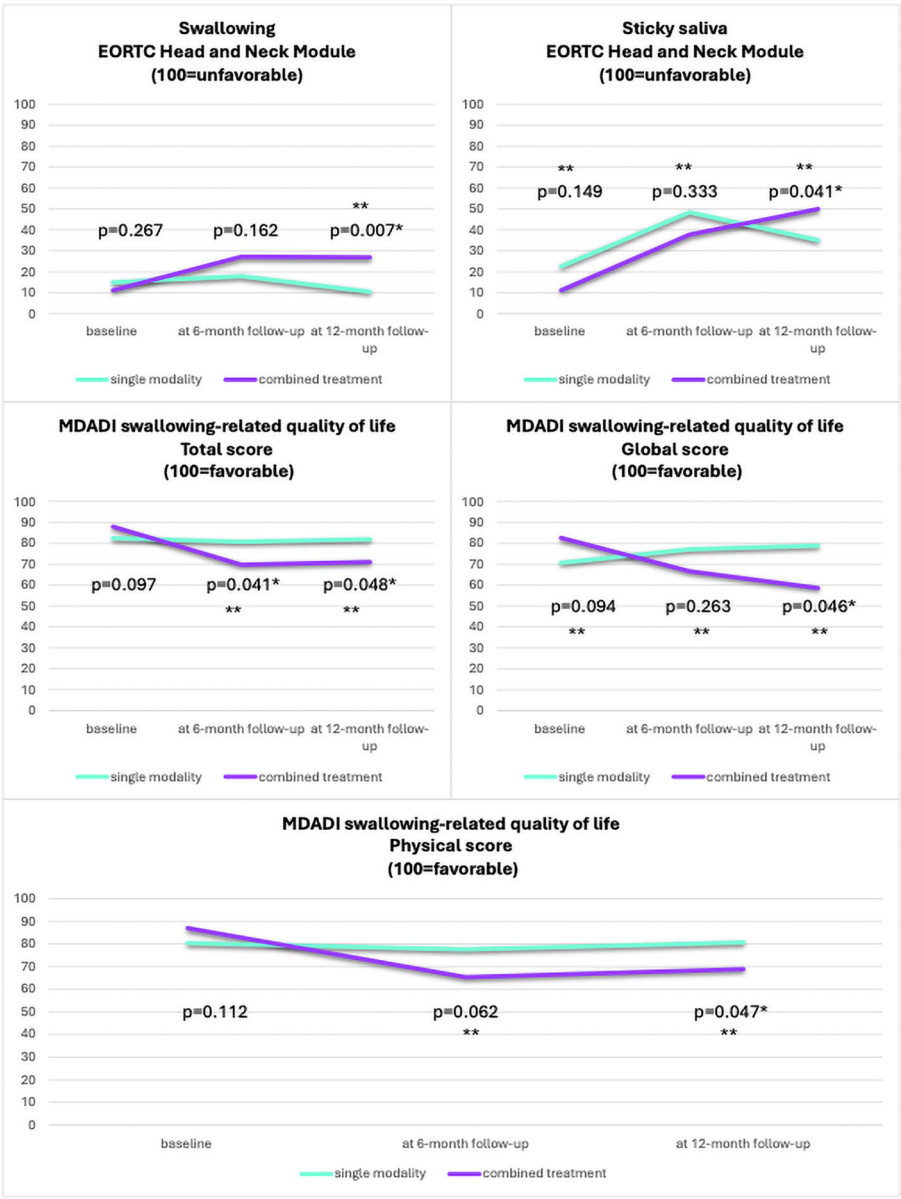

Figure 12. Early-stage (I–II) oropharyngeal cancer, quality-of-life outcomes at baseline, 6-month, and 12-month follow-up: single modality (n=49) vs combined treatment (n=18). Statistically significant differences between the groups are marked with an asterisk *. Clinically meaningful differences between the groups are marked with **. Only the subscales with statistically significant differences between the groups at 12-month follow-up (see Figure 11) are presented in this figure. The single-modality group includes patients treated with surgery only (n=12), definitive radiotherapy (n=2), and definitive chemoradiotherapy (n=35). The combined-treatment group includes patients treated with surgery and radiotherapy (n=9), and surgery and chemoradiotherapy (n=9). EORTC= European Organisation for Research and Treatment of Cancer. MDADI=MD Anderson Dysphagia Inventory. From original publication IV with permission from the copyright holders.

5.4.4 Surgical treatment compared to CRT in early-stage OPC

The early-stage (I–II) surgically treated patients reported better QoL outcomes than early-stage patients treated with CRT at both the 6-month and 12-month follow-ups.

At 12 months, the superiority of surgical treatment was statistically significant and clinically meaningful in the EORTC QLQ-C30 global health status and in the EORTC QLQ-H&N35 domains of senses, teeth, dry mouth, and sticky saliva.

At 6 months, the superiority of surgical treatment was statistically significant in the EORTC QLQ-C30 domains of global health status and pain; in the EORTC QLQ-H&N35 domains of pain, swallowing, senses, speech, social eating, social contact, dry mouth, sticky saliva, and feeling ill; and in the MDADI total, functional, and physical scores. All these differences, except for social contact, were also clinically meaningful.

In the Study IV cohort, the early-stage surgery-only group and the early-stage CRT group were comparable regarding age, gender, tumour subsite, smoking, heavy alcohol use, ACE-27 comorbidity score, ECOG performance status, p16 status, and N classification. However, in the CRT group, there were more stage II diseases (p=0.019) and N1–2 tumours (p=0.009) than in the surgery-only group.

5.4.5 Weight loss and feeding tubes

Weight loss was the most pronounced during the period from diagnosis to 6 months, with a median loss of 5.5 kilograms (IQR 11.2), corresponding to a median decrease of 8.0% from the weight at diagnosis. During the period from 6 to 12 months, most patients regained some weight (mean 1.1 kilogrammes, SD=9.8). Despite this, the weight at 12 months remained lower than at diagnosis for most patients (median weight loss 2.5 kilogrammes, IQR 11.2, median decrease of 3.8% from the weight at diagnosis).

The early-stage patients treated with CRT lost more weight in the first 6 months after diagnosis than the early-stage patients treated only surgically (p=0.018).

Weight loss was more pronounced in patients with PEG than in patients without PEG, both during the period from diagnosis to 6 months (p=0.011) and from diagnosis to 12 months (p=0.040). None of the patients treated with surgery alone needed PEG. In contrast, many patients with stage I OPC in the CRT group required PEG (43.5%, n=23).

6 Discussion

6.1 Single-modality treatment compared to combined treatment in OPC

This thesis provides evidence that the long-term QoL outcomes of single-modality treatment for OPC are superior to those of combined treatment. The retrospective Study I and prospective Study IV both supported this finding in a patient cohort diagnosed between 2000 and 2023.

In the retrospective Study I, with a median follow-up of 11.8 years, the single-modality group demonstrated better QoL results across multiple domains. These included the MDADI swallowing-related composite score and the emotional, functional, and physical subscales; the EORTC QLQ-C30 domains of pain and appetite loss; and the EORTC QLQ-H&N35 domains pain and opening mouth. Consistent with these findings, the prospective Study IV showed that at the 1-year follow-up, the early-stage single-modality group had superior QoL scores in the MDADI swallowing-related domains total score, global score, and physical subscale, and in the EORTC QLQ-H&N35 domain of swallowing and sticky saliva. According to both HNC-specific QoL instruments in use (MDADI and EORTC QLQ-H&N35), combined treatment resulted in poorer long-term swallowing-related QoL.

In Study IV, we also compared QoL outcomes in early-stage (I–II) OPC within different single-modality groups: surgical alone versus CRT. At the 1-year follow-up, surgery alone was superior to CRT in the EORTC QLQ-C30 global health status and in the EORTC QLQ-H&N35 domains of senses, teeth, dry mouth, and sticky saliva. Considering the inferior outcomes of multimodal treatment, we concluded that primary surgical treatment should only be offered to patients who, based on imaging findings, can be cured with surgery alone.

The superiority of single modality treatment has been previously established by several retrospective studies analysing long-term QoL in OPC and HNC survivors. (Broglie et al., 2013; Ramprasad et al., 2023; Taylor et al., 2024; Xu et al., 2019) Broglie et al., Xu et al., and Ramprasad et al. drew similar conclusions to those of Study IV, whereby surgery alone is associated with fewer QoL-impairing problems

than (C)RT or multimodality treatments, and should be considered when oncologically safe.

Taylor et al. (2024) conducted an international cross-sectional study involving 1105 HNC survivors with a median follow-up of 8 years, and summarised that the most prominent differences between single-modality and multimodal treatments were in symptoms of dry mouth and sticky saliva. Additionally, the clinically meaningful superiority of single-modality treatment was observed in domains such as fatigue, insomnia, pain in the mouth, swallowing, sensory problems, trouble with social eating, teeth, and opening the mouth. Consistent with our Study IV results, the fewest swallowing-related problems were found in patients treated only surgically compared to those treated with RT, CRT, (C)RT+ND, and surgery+(C)RT. However, the differences between the symptom burdens of patients treated with surgery alone and RT, both being single-modality treatments, were relatively small and clinically meaningful only in dry mouth and sticky saliva.

To our knowledge, only one prospective study assessing the QoL outcomes of single-modality and combined treatment in OPC was published before Study IV. (Amit et al., 2019) Amit et al. found that single-modality surgical treatment had better QoL outcomes than RT at 6 months, whereas multimodality upfront surgical treatment and multimodality nonsurgical treatment had comparable QoL at 6 months. Amit et al. did not report any comparison of QoL between single-modality and combined treatment. However, in line with the findings of Broglie et al., Xu et al., Ramprasad et al., and Study IV, Amit et al. also found surgery alone to be superior to RT regarding dry mouth, mucus, and taste disturbances at 6 months post-treatment.

Single-modality treatment, whether IMRT or TORS, has shown favourable oncological outcomes and is a widely accepted treatment strategy in early-stage OPC. (Meccariello et al., 2022) Especially HPV-positive OPCs respond well to treatment. (Wang et al., 2015) However, the optimal treatment strategy for advanced-stage OPC remains unresolved. (Tsai et al., 2021) According to current guidelines, definitive CRT and upfront surgery are the primary options. (Pfister et al., 2020) Nonetheless, patients undergoing upfront surgery are at increased risk of requiring multimodal treatment; adjuvant (C)RT may be indicated following pathological examination of the surgical resection specimen. Tsai et al. studied advanced-stage OPC and found that in the upfront surgical treatment group, 427 patients (87.9%) ended up receiving adjuvant (C)RT, whereas in the CRT group, only 20 patients (2.9%) needed salvage surgery and were therefore classified as multimodally treated patients. However, upfront surgical treatment was associated with better 3-year OS compared to CRT.

In large cohorts, upfront surgical treatment appears to have similar survival rates than CRT in early-stage OPC, regardless of HPV status. (Kelly et al., 2017, 2018)

Nevertheless, in these studies, postoperative CRT was given to 59–64% of patients in the upfront surgery group.

Some OPC patients seem to benefit from trimodality therapy (surgery + CRT): In a cohort of 2,974 patients with HPV-positive locally advanced OPSCC, this resulted in improved OS. (Sanford et al., 2019) Conversely, trimodality therapy was not associated with improved OS in patients with early-stage disease, regardless of HPV status, nor in HPV-negative patients, regardless of stage. However, analysis of the QoL of the life years gained was not included. Further studies are needed to reveal whether trimodality therapy can offer better outcomes than mono- or bimodality treatments when QoL is also considered.

It is also noteworthy that HPV status is not the only important factor impacting therapeutic decision-making in OPC; the oropharyngeal subsite often influences treatment strategies. For example, OPCs of the tonsils are surgically treated more frequently than cancers of the base of the tongue, for which CRT is the preferred treatment modality. (Culié et al., 2018) Non-tonsillar (soft palate, uvula, posterior and lateral pharyngeal wall) HPV-positive OPCs are also associated with worse cause-specific survival than tonsillar (tonsillar fossa and pillar, base of tongue, lingual tonsil) HPV-positive OPCs. (Tham et al., 2019) In our studies, we were not able to reliably compare the QoL results of oropharyngeal subsites because of the limited number of participants.

6.2 Treatment impact on QoL in HNC

In the long-term OPC cohort of Study I, CRT±ND resulted in better QoL outcomes than upfront surgical multimodal treatment (Sx+[C]RT). Superior scores were observed in EORTC QLQ-C30 pain and appetite loss, EORTC QLQ-H&N35 pain, speech, and opening mouth, and in MDADI composite, emotional, functional, and physical domains. These results were not unexpected, as CRT±ND can be classified as a single-modality treatment, whereas Sx+RT and Sx+CRT are multimodal therapies (see Chapter 6.1).

In pairwise comparisons between Sx+RT and Sx+CRT, no differences in QoL outcomes were observed. Consistent with the findings of Study I, the Study II cohort showed no correlation between concurrent chemotherapy and persistent dysphagia. Nevertheless, in the shorter term, concurrent chemotherapy has been associated with increased PEG dependence. (Sher et al., 2018) Moreover, although not visible in our long-term follow-ups, chemotherapy is known to cause acute toxicities such as neutropenia, mucositis, and nausea. (Lere-Chevaleyre et al., 2022)

In the early-stage OPC population of Study IV, we compared different single-modality treatment groups and found that surgery alone was superior to CRT in QoL outcomes at both 6-month and 12-month follow-ups. At 12 months, the difference

was statistically significant in the EORTC QLQ-C30 global health status and in the EORTC QLQ-H&N35 domains of senses, teeth, dry mouth, and sticky saliva. At 6 months, the superiority of surgical treatment was significant in even more QoL domains, including EORTC QLQ-C30 global health status and pain, and its Head and Neck Module domains of pain, swallowing, senses, speech, social eating, social contact, dry mouth, sticky saliva and feeling ill; and the MDADI total, functional, and physical scores.

In contrast, a recent meta-analysis concluded that TORS and RT result in similar QoL outcomes in early-stage OPSCC, except for xerostomia, where TORS appeared more favourable. (Gupta et al., 2024) However, there was a notable limitation in the meta-analysis, where the majority of TORS-treated patients (54.7%) had received postoperative (C)RT, making it multimodal therapy. Hence, Gupta et al. were not actually comparing single-modality treatments against one another, but upfront surgical treatment against RT. In any case, careful patient selection is essential in considering upfront surgical treatment; surgery alone may result in better QoL than upfront CRT, but possible adjuvant postoperative (C)RT is likely to worsen the outcome.

In the Study II HNC cohort, radiation-induced persistent morbidities were common: dysphagia, hypothyroidism, and osteoradionecrosis affected 45%, 29%, and 12% of survivors, respectively. These percentages were consistent with previous studies. (De Felice et al., 2020; C. L. Huang et al., 2019; Patterson et al., 2018; Pezdirec et al., 2019) RT to the neck increased the risk of persistent dysphagia, although we did not find differences in dysphagia incidence between high-dose definitive neck RT (median dose 65 Gy, IQR 3 Gy) and elective neck irradiation (median dose 50 Gy, IQR 0 Gy) or ipsilateral and bilateral neck RT. The published data regarding these factors has been inconsistent; radiation doses to the superior pharyngeal constrictor and tongue appear to correlate with late dysphagia (Gharzai et al., 2020). While there is evidence that ipsilateral RT reduces dysphagia (A. M. Chen et al., 2018), dysphagia scores do not significantly differ between uni- and bilateral IMRT groups (Chin et al., 2017). However, it is likely that reductions of volume and dose mitigate toxicities (Nutting et al., 2023), and unilateral elective neck RT is currently considered sufficient in selected patients by many researchers. (García-Anaya et al., 2023; Nuyts et al., 2021)

Feeding tube dependency had a strong negative impact on QoL in Study I. The median EORTC QLQ-C30 global health status was 33.3 (IQR 31.3) for PEG tube-dependent patients and 75.0 (IQR 25.0) for patients without a PEG tube. PEG dependence decreased QoL scores across all MDADI scales, across the EORTC QLQ-C30 domains of role functioning, social functioning, appetite loss, and financial problems, and across the EORTC QLQ-H&N35 domains of pain, swallowing, senses, weight loss, social eating, sexuality, sticky saliva, and feeding

tube. In the Study IV cohort, none of the patients treated with surgery alone needed a PEG tube. In contrast, PEG tubes were inserted in many patients treated with CRT across all stage groups: 43.5% of those with stage I disease and 59.4% of those with stage II–IV disease. Our finding that surgery alone seems superior to CRT in reducing the need for PEG tubes aligns with previous HNC studies. (Kouka et al., 2024; Sher et al., 2018; Van Der Linden et al., 2017)

Another treatment-related aspect affecting the QoL of HNC survivors is chemotherapy-induced cognitive impairment (CICI), or "chemobrain", although our studies were unable to find evidence of this. The only way we measured cognitive impairment in this thesis was through patient self-assessment in two items of the EORTC QLQ-C30: memory and difficulty concentrating. The underlying mechanisms of CICI are suggested to include direct neurotoxicity, blood-brain barrier disruption, decreased hippocampal neurogenesis, white matter abnormalities, secondary neuro-inflammatory response, and increased oxidative stress. (Mounier et al., 2020) In HNC patients, CRT has been found to decrease neuronal glucose metabolism in FDG PET imaging-based analysis. (Bishay et al., 2024) Additionally, a prospective study found neurocognitive problems up to 2 years following definitive (C)RT in HNC survivors. (Zer et al., 2018) The potential to avoid risk for CICI may guide HNC patients, especially younger ones with early-stage disease and good prognosis, towards upfront surgical treatment.

6.3 Impact of patient-related factors on QoL and treatment-induced morbidity in HNC

In the 12-year follow-up of Study I, current smokers reported poorer QoL outcomes compared to never smokers and previous smokers across a wide range of scales. These included ten EORTC QLQ-C30 scales (global health status, physical, role, as well as social functioning, fatigue, nausea/vomiting, dyspnoea, appetite loss, constipation, and financial problems). Poorer outcomes were also noted in five EORTC QLQ-H&N35 scales (weight loss, speech, social contact, sexuality, and feeling ill), as well as in the MDADI functional subscale. The only difference in reported QoL between never smokers and previous smokers was cough, with never smokers coughing less. Study IV supported the findings of Study I: smokers had worse QoL in swallowing-related MDADI total, global, and composite domains at 12 months compared to never and previous smokers. Our findings are consistent with a systematic review and meta-analysis, which concluded that HNC patients who continue smoking have poorer QoL outcomes. (J. Smith et al., 2019)

Another finding in Studies I and IV was the effect of heavy alcohol consumption on QoL. Alcohol dependence has been shown to affect overall QoL, physical and mental health, general and social functioning, and activities of daily living. (Levola

et al., 2014) In Study I, previous or current heavy alcohol use at diagnosis was associated with worse QoL across several domains: nine EORTC QLQ-C30 scales (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, diarrhoea, financial problems), five EORTC QLQ-H&N35 scales (weight loss, weight gain, sexuality, social contact, and feeling ill), and the MDADI functional subscale. In Study IV, the inferiority of QoL results among heavy alcohol users was significant in three MDADI domains: total, global, and composite scores. In contrast, in Study III, heavy alcohol use was associated with a lower incidence of radiation-induced hypothyroidism. This may be attributed to a known phenomenon in which moderate alcohol consumption appears to confer protection against many autoimmune diseases, including hypothyroidism. (Carlé et al., 2012)

In addition to a more favourable prognosis, HPV-positive HNC patients are also associated with better QoL outcomes and less anxiety and depression. (Henry et al., 2022) In Study IV, as there were only 11 p16-negative participants, we chose not to conduct QoL analyses comparing p16 groups. However, in Study I, we found that p16-positive cancer patients experienced better self-reported QoL in the EORTC QLQ-C30 cognitive functioning scale and the EORTC QLQ-H&N35 dry mouth item, although the p16-negative group was small.

In Study IV, a low baseline QoL was associated with poorer QoL at 12 months. Consistent with these findings, there is evidence that baseline anxiety, depression, and a lifetime history of suicidal ideation predict lower post-treatment QoL in HNC patients. (Henry et al., 2022) Especially for HNC patients with a history of psychological distress, psychosocial counselling should be made available.

6.4 The value of reliable QoL measurements

In Study III, we validated the first HNC-specific swallowing-related QoL questionnaire in Finnish. The Finnish MDADI demonstrated good feasibility, internal consistency, score distribution, and test-retest reliability. Against the previously validated general dysphagia questionnaire F-EAT-10, correlations were strong, suggesting criterion and construct validity. The Finnish MDADI also successfully distinguished between the non-dysphagic control group and the dysphagic group; across all subscales, the latter reported worse QoL outcomes than the non-dysphagic group ($p<0.001$). The difference in composite score between these groups (25.6 points) was clinically meaningful (≥10 points) according to previous literature. (Hutcheson et al., 2016) Patient feedback was positive. The only neutral/negative comment was that the F-EAT-10 was easier and quicker to complete than the MDADI. This was expected, as the MDADI, which includes 20 items, is twice as long as the 10-item F-EAT-10. Outside of research settings, particularly in

clinical practice, a shorter questionnaire may be preferable, at least for older patients and men. (Mehanna, Carter, et al., 2023) Therefore, a recently developed shortened version of the MDADI, the 5-item "MiniDADI" by Lin et al. (2022), offers promising future potential.

To improve HNC treatments, understanding QoL is essential. QoL measures describe not only the disease but also the comprehensive patient perspective, including personal and social contexts. The use of appropriate QoL measures helps focus on the patient rather than the disease. (Higginson & Carr, 2001) The obvious benefit of measuring QoL is the ability to compare, develop, and target both primary and rehabilitative treatments. QoL questionnaires can also facilitate patient communication, screen for potential problems, prioritise concerns, and monitor changes. QoL results can also support patient education, facilitating treatment decisions and furthering understanding of the disease. Furthermore, QoL domains have been shown to predict survival in patients with HNC. (Meyer et al., 2009; Scharpf et al., 2009)

However, how best to implement QoL measures into clinical practice remains unresolved. There is currently no gold-standard QoL questionnaire (QLQ) for HNC patients, and the use of various QLQs complicates cross-study comparisons. Moreover, different individuals may be content with different QoL scores. A high-quality QoL measure should be validated for the target culture and population, impose a reasonable burden on both respondents and administrators, and be able to detect changes over time. (Ojo et al., 2012) A long history of consistent international use is an asset. However, new instruments are emerging that feature better patient inclusion in the development process and incorporate questions related to novel treatments with distinct complications (A. I. Mendez et al., 2022). Researchers should remain informed on any such instruments. General QLQs may provide information about clinically meaningful symptoms that HNC-specific QLQs fail to capture. However, offering many different, potentially overlapping QLQs may be burdensome for HNC patients, who often suffer from fatigue and depression, which may impact their ability and motivation to complete questionnaires. Nevertheless, most HNC survivors find QLQs useful for communication with their clinicians, especially the when the tools are structured and disease-specific. (Mehanna, Carter, et al., 2023)

In the future, QLQs are likely to be completed via mobile apps. Already in 2018, a prototype app for the EORTC QLQ-C30 was developed and well received by patients. (Kessel et al., 2018) Digital health implementations also have the potential to facilitate clinical research.

QoL outcomes are also widely used in calculating Quality-Adjusted Life Years (QALYs) and economic evaluations of health interventions. However, it has been argued that the QALYs are unjust and discriminate against people in poor health.

(Schneider, 2021) In contrast, most people report being willing to give up some of their remaining lifetime in exchange for improvements in their HRQoL. When interpretating QALYs, health policy decision-makers should critically assess their underlying assumptions and ethical implications.

6.5 Strengths and limitations

Study I was based on a nationwide population-based survey of the 12-year follow-up of OPSCC survivors, representing the longest published QoL follow-up in OPC patients. Most survivors participated in the study, and the gender balance was good compared to previous research. The limitations of Study I included the absence of pretreatment QoL data, an unequal balance of treatment modalities across cancer stages, and a small surgery-only group, making it impossible to analyse the QoL outcomes of surgery alone versus nonsurgical treatments.

In Study IV, the same limitation of a small surgery-only group persisted, although the group size was sufficient for analyses. Given the multicentre design of the study, variations in local clinical practices were possible. Additionally, in Study IV, a small subset of patients failed to complete the pretreatment QoL questionnaires, although many participants returned all QLQs at the three timepoints. Another strength of Study IV was that it included many p16-positive patients with early-stage disease, few comorbidities, and good performance status, offering valuable insights into the outcomes of a patient group for whom treatment strategies remain controversial. Moreover, the set of QLQs used in both Studies I and IV was comprehensive, including a general QLQ, a disease-specific QLQ covering a wide range of HNC symptoms, and an elaborate dysphagia-specific HNC-specific QLQ.

In all Studies I–IV, selection bias may be present, due to the retrospective nature of Studies I–III, or non-randomised treatment decisions in the prospective Study IV.

In Study II, the excess amount of missing data and/or the small sample sizes in the late toxicity subgroups limited the reliability of analyses regarding smoking and p16 status. Moreover, no systematic information about weight changes was available. A strength of the study was that the same comprehensive patient cohort had been used in a previous publication by our coauthors, which provided a detailed description of RT techniques and recurrence analysis. (Nissi et al., 2021) Moreover, all patients were treated using modern IMRT techniques.

In Study III, no structured interviews were conducted to assess the comprehensibility of the MDADI translation, and no data on the participants' diets were available. Additionally, responsiveness analysis was not performed; however, the responsiveness of the MDADI was recently proven in a Swedish study. (Tuomi et al., 2020) The strengths of the study included the inclusion of an age- and gender-matched control group, balanced representation of age, gender, education and marital

status, and a high rate of return for the test-retest measurement. The study cohort was also representative of a wide range of HNC sites, and positive written patient feedback was received regarding the translated MDADI.

6.6 Future aspects

QoL results are essential for supporting clinical decision-making between upfront surgical and primarily non-surgical treatment options, which in many cases are considered oncologically equivalent. A winning treatment arm has yet to be identified; more prospective studies and randomised controlled trials (RCTs) assessing QoL outcomes of surgical treatment compared to (C)RT in patients with early-stage OPC are needed and ongoing. Major RCTs in progress include EORTC420 (Stelmes et al., 2019) and PATHOS (Owadally et al., 2015). Of special interest are the QoL outcomes of surgery alone without postoperative adjuvant (C)RT, and how to identify patients at low risk of requiring multimodality therapy after upfront surgery. Regardless of future evidence comparing surgical and non-surgical approaches, HNC treatments are likely to become increasingly rooted in even more personalised health strategies and include informed patient decision-making. Therefore, QLQs should be implemented in routine clinical use to facilitate both patient-clinician communication and the comparison of treatment options. Some patients may benefit from professional supervision and support when completing the QLQs.

There has been substantial effort to investigate deintensification options for selected HPV-positive OPC patients, with the aim of reducing treatment-related toxicities and improving long-term QoL, as many cancer patients prioritise QoL over OS. (Douglas et al., 2019; Seghers et al., 2022). The deintensification options include the comparison of chemotherapy drugs and reducing RT intensity and volume. However, identifying low-risk patients suitable for deintensification trials remains challenging, and currently there is insufficient evidence to support treatment deintensification in clinical settings. (S. H. Huang et al., 2023)

The future incidence of OPCs is likely to drop thanks to HPV vaccination programmes. Since its first approval in 2006, the vaccine has already reduced the prevalence of oral vaccine-type HPV infections by 72–93%. (Kaczmarczyk & Yusuf, 2022; Rosenblum et al., 2021) In the United States, catch-up HPV vaccination is recommended for all individuals aged up to and including 26 years who are not adequately vaccinated (Meites et al., 2019). This policy could be considered for implementation in Finland, where catch-up vaccinations are limited to students in secondary school, upper secondary school, and vocational institutions. Furthermore, there is early evidence suggesting that vaccine-based therapies for

HPV-related OPC are safe and show preliminary signs of efficacy. (Filippini et al., 2025)

Another minimally invasive tool with a possibly emerging role in HNCs is liquid biopsy. As a liquid biopsy biomarker, circulating tumour DNA has been associated with the prognosis of HNSCC patients (Yang et al., 2024), and may also be useful in detecting recurrences. (Galot & Machiels, 2020) If liquid biopsy results indicate a favourable prognosis, it may indicate a potential for treatment deintensification. Nevertheless, challenges remain regarding the use of liquid biopsies in HNC patients, including limited specificity and sensitivity, as well as a lack of standardisation. (Kong & Birkeland, 2021)

In a recent Finnish study, a novel immunohistochemical staining-based method (LIMA1-alpha staining) predicted curative intent surgery response in HPV-negative HNC. (Qiao et al., 2025) The search continues for prognostic and predictive biomarkers capable of capturing the heterogeneity of HNCs.

As novel treatment modalities, immunotherapies including the programmed death 1 (PD-1) inhibitors pembrolizumab and nivolumab are promising, especially in metastatic and recurrent HNSCC. (Vallianou et al., 2023) The combination of immunotherapy with vaccines and chemotherapy may also hold potential. Biomarkers able to predict immunotherapy response are of special interest, as only a few patients respond to immunotherapy. In addition to PD-1 inhibitors, other immuno-based treatment modalities, such as programmed death-ligand (PD-L1) blockers, are currently being studied. (Vallianou et al., 2023)

In conclusion, a future goal is to find a balance between oncological outcomes and long-term QoL in HNC patients. Artificial intelligence (AI) holds potential to enhance HNC patient care in many areas, including early detection (histopathological analysis and imaging techniques), diagnosis (classification algorithms), treatment planning (AI predictions of patients' responses to different treatment modalities and genomics integration), monitoring and surveillance (recurrence detection and patient compliance tracking), drug discovery, and AI-assisted surgery. (Mäkitie et al., 2023; Pham et al., 2024) Furthermore, subtyping of HPV and integrating intratreatment response assessments may hold promise in the field of precision medicine. (Costantino et al., 2025; Kang et al., 2023)

7 Conclusions

This thesis analysing QoL outcomes and treatment-induced morbidity in patients with HNC leads to the following conclusions:

1. Single-modality treatment is superior to combined treatment in long-term QoL outcomes in patients with OPC and should be pursued whenever oncologically safe.

2. Surgery alone appears to be superior to CRT regarding QoL outcomes in patients with early-stage OPC. However, combining adjuvant postoperative (C)RT with surgical treatment may lead to worse QoL outcomes than upfront CRT. This emphasises the importance of patient selection: primarily surgical treatment should only be offered to those who, based on imaging findings, can be cured with surgery alone.

3. Smoking, heavy alcohol consumption, and PEG dependence are associated with poor QoL results in OPC patients.

4. Common long-term side effects of RT for HNC include dysphagia, hypothyroidism, and osteoradionecrosis. Susceptibility to these is influenced by age, gender, tumour subsite, and neck RT.

5. The Finnish version of the MDADI is a valid measure of the swallowing-related QoL of patients with HNC, offering clinical and research utility.

Acknowledgements

The studies of this thesis were conducted at the Department of Otorhinolaryngology – Head and Neck Surgery at Turku University Hospital and the University of Turku during 2018–2025. The studies were financially supported by the Vaasa Medical Foundation, Competitive State Research Funding, the Emil Aaltonen Foundation, the Finnish ORL-HNS Foundation, the Irja Karvonen Cancer Foundation, the Juhani Aho Medical Research Foundation, Cancer Foundation Finland, the Paulo Foundation, the Cancer Foundation of South-West Finland, the Turunmaa Duodecim Society, and Kirsti and Tor Johansson's Heart and Cancer Foundation. I am grateful to the organisations and individuals who support science and make the realisation of many research projects possible.

First and foremost, I owe my gratitude to my supervisors, Professor Heikki Irjala and Professor h.c., Docent Ilpo Kinnunen. I thank both Heikki and Ilpo for always taking the time to encourage me with positive feedback. Heikki, you likely have the fastest average email response time of all Finnish professors, combined with efficient problem-solving skills, knowledge, and contacts that have been essential for all progress in this thesis work. Ilpo, as my supervisor and the medical director of our clinic, you have shown how to combine power and skill with kindness and insight in a unique and inspiring way.

I also sincerely thank my co-authors Petri Koivunen, Eero Kytö, Linda Nissi, Pauliina Tiitto, Lauri Jouhi, Tero Vahlberg, Heikki Minn, Elina Halme, Leif Bäck, Timo Autio, Matti Pukkila, Eeva Haapio, and Lassi Nelimarkka for their input into the original publications of this thesis. I wish to express my gratitude to Miia Mokka for her support as a member of my supervisory committee. I also wish to thank Susanna Helkkula, Kirsi Nurmi, Teija Silomäki, Anne Koivisto, Miia Saarinen, Eija Vasarainen, Susanna Sinervo, and Peppi Kaavi for their help with the recruitment and follow-up of study participants.

I am grateful to the pre-reviewers of this thesis manuscript, Elina Penttilä and Mari Markkanen-Leppänen, for their valuable comments and input. I also wish to thank Dr. Ricard Simo for accepting the invitation to serve as the opponent at the public defence of this thesis.

I send my wholehearted thanks to the ENT Clinic at Vaasa Central Hospital, especially to Annika Mecklin, for the family-like and motivating work atmosphere. I also extend my heartfelt appreciation to my current workmates at Turku University Hospital, who have always been there for me through the ups and downs and the lessons learned; and who are some of the best party people I know.

To my dear friends, I am deeply grateful for the steadfast support, understanding, the special occasions shared, and the joy you bring to ordinary days. To name a few: Sofia and Jaakko, our former landlords and jolly friends, you were my most trusted science tutors. Hanna, Iris, Riku, and Santeri, I am grateful for our close-knit circle; thank you for the moments shared in Turku, Vaasa, Pellinki, Nuuksio, Helsinki, and London throughout the years of this project. Tiia and Elina, my Art Club, and Saara and Anni, my childhood friends, thank you for your captivating presence and undying friendship. Jonna, Ilmari, Anni, Jaakko, and Riku, thank you for your peer support during the final stages of my PhD journey. Elina, you were the first to inspire me to take the plunge into research. Sara, thank you for being so genuine and inventive. Mira, thank you for your sincerity and straightforwardness, and for sharing the ENT path. Aino, Eino, and Peppi, thank you for your close and quirky friendship. And Lissu and Ilmari, thank you for being the most highly valued players in the Tilhi Competition.

I owe my immense gratitude to my family: Tiiju, Esa, and Kalle. Thank you for always being there for me, for fostering my lifelong love of reading and languages, and for instilling in me both self-confidence and the trust in others for help. My mother, Tiiju, also set an example of perseverance through her own PhD work investigating mandibular advancement device therapy for sleep apnoea.

Finally, I wish to thank my dearest, my husband Aleksi for his playful everyday vibes, sense of humour, wit, and wisdom, for his skills in original thinking, caring listening, and generative improvisation, and for his genuine interest in rather unexpected topics such as arachnid nomenclature, statistical analysis, small creatures in muddy ditches, church history, and gardening in clay soil. You are an endless inspiration and my unwavering support through thick and thin. With you, I want to share my days.

September 2025
Pihla Ranta

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TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2025

ISBN 978-952-02-0336-8 (PRINT)
ISBN 978-952-02-0337-5 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)