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GLOSSARY

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LIST OF ABBREVIATIONS

3D-CRT	Three-dimensional conformal
5-FU	5-fluorouracil
AC	Adjuvant chemotherapy
AUC	Area under curve
AEs	Adverse events
AJCC	American Joint Committee on Cancer
CBC	Complete blood count
CE	Contrast-enhanced
ChT	Chemotherapy
CPG	Clinical Practice Guideline
CRT	Chemoradiotherapy
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
cTNM	clinical Tumor-Node-Metastasis
CTV	Clinical target volume
CTVn	Nodal clinical target volume
CTVp	Primary tumor clinical target volume
DAHANCA	Danish Head and Neck Cancer Group
DNA	Deoxyribonucleic acid
DOI	Depth of invasion
DPD	Dihydropyridine dehydrogenase deficiency
DVH	Dose-volume Histogram
ECE	Extracapsular extension
EBNA	EB nuclear antigens
EBRT	External beam Radiotherapy
EBV	Epstein Barr Virus
ECOG	Eastern Cooperative Oncology Group

EMA	European Medicines Agency
END	Elective neck dissection
ENI	Elective neck irradiation
ENT	Ear-Nose-Throat
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESCAT	Scale for Clinical Actionability of Molecular Targets
ESMO	European Society for Medical Oncology
ESMO-MCBS	ESMO-Magnitude of Clinical Benefit Scale
EURACAN	European Reference Network for Rare Adult Solid Cancers
FDA	Food Drug Administration
FDG-PET	20-deoxy-20-[18F] fluoro-D-glucose
FNA	Fine-needle aspiration
GLCM	Grey Level Co-occurrence Matrix
GoR	Grade of recommendation
GTQ	Gothenburg Trismus Questionnaire
GTVn	Nodal gross target volume
GTVp	Primary tumor gross target volume
HER2	Human epidermal growth factor receptor 2
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
IARC	International Agency for Research on Cancer
ICD-O	International Classification of Diseases for Oncology
ICHT	Induction chemotherapy
IHC	Immunohistochemistry
IMPT	Intensity Modulated Proton Therapy
IMRT	Intensity Modulated Radiotherapy
LP	Lateral Pterygoid

LMPs	Latent membrane proteins
LoE	Level of Evidence
LPs	Leader proteins
LN	Lymph node
MDT	Multidisciplinary Team
MEC	Mucoepidermoid carcinoma
MIO	Maximal Inter-incisal Opening
mo	Month
mos	Months
MP	Medial Pterygoid
MRI	Magnetic Resonance Imaging
NMA	Network meta-analysis
NGS	Next-generation sequencing
NPC	Nasopharyngeal carcinoma
NP	Nasopharynx
NTCP	Normal tissue complication probability
ORR	Objective response rate
OS	Overall survival
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
PET	Positron Emission Tomography
PROs	Patient-reported outcomes
QoL	Quality of life
QLQ	Quality of Life Questionnaire
RBE	Relative biological effectiveness
RFS	Recurrence-free survival
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristic
ROM	Risk of malignancy
RP	Retropharyngeal

RTOG	Radiation Therapy Oncology Group
RT	Radiotherapy
SCC	Squamous Cell Carcinoma
SCCHN	Squamous Cell Carcinoma Head and Neck
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SGC	Salivary gland cancer
SRT	Stereotactic Radiotherapy
T	Temporal
T-DM1	Trastuzumab-emtansine
TLM	Transoral laser microsurgery
TMJ	Temporomandibular Joint
TNM	Tumour Node Metastasis
TPeX	Cisplatin/docetaxel/cetuximab
TORS	Transoral robotic surgery
TPS	Treatment Planning System
TRK	Tropomyosin receptor kinase
TSH	Thyroid-stimulating hormone
UICC	Union for International Cancer Control
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization

Contents

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1. Introduction

Trismus is a side effect that can be experienced by Head and Neck Cancer (HNC) patients undergoing radiotherapy (RT). The reported trismus incidence varies due to heterogeneous study populations, treatment modalities, and different methods of measuring and defining trismus. The incidence has been reported to be as high as 79% [1], while several studies indicate an incidence between 38% and 52% [2,3,4]. Trismus is defined as a maximum inter-incisor distance of ≤35 mm and is caused by impaired function of the masticatory muscles [5]. Trismus can manifest in poor dental hygiene, impaired chewing, malnutrition, and psychological difficulties, including low self-esteem, depression, and suicidal intentions, which all jeopardize health-related quality of life (QoL) [6,7]. The pathogenesis of trismus in patients with HNC can be related to several parameters and varies between individuals (Astradsson et al., 2018). It may involve a single cause or a combination of different factors, such as direct tumor interference with jaw opening, surgical scarring, RT-induced fibrosis in the muscles of mastication, as well as temporomandibular joint (TMJ) damage [8]. Patients with a history of surgery are more likely to have trismus already prior to having adjuvant RT [10]. On the other hand, in patients treated with definitive RT, the exact trismus onset underlying mechanism, biological and clinical underpinnings, and dosimetric parameters remain to be fully defined [11, 12,13]

Due to the extreme anatomical complexity and large number of organs-at-risk (OARs) to spare, radiation delivery for this district is challenging and notoriously burdened by considerable side effects [14]. Modern radiotherapy, namely image-guided intensity-modulated RT (IG-IMRT) and volumetric arc therapy (VMAT) have profoundly impacted the therapeutic index in HNC treatment improving patients' toxicity profile and tolerance [15,16.17].

The present research project aims at investigating trismus incidence, its consequences, and its association with baseline clinical and dosimetric variables in a series of consecutive HNC patients treated with radiation within the definitive setting (+/- chemotherapy). Thereupon, the present study has been designed to qualitatively evaluate

the interplay between modern RT, trismus, patients' toxicity profile, and quality of life (QoL).

The study was initiated with the believe that investigating the dose-volume metrics predictors, analyzing the clinical and radiological aspects of this toxicity item, and its impact on patients' outcomes may be of pivotal interest for the Research scenario in the HNC arena.

2. Background - Head and Neck cancer

2.1 Overview

Head and neck squamous cell carcinoma (HNSCC) refers to a group of malignancies that arise from the squamous cells lining the tissues of the head and neck region, including the oral cavity, hypopharynx, nasopharynx, oropharynx, lip, nasal cavity, paranasal sinuses, and salivary glands [18]. These organs function to facilitate respiration and swallowing, as well as filter and humidify the air inspired. HNSCC is a significant health concern worldwide, with its incidence and mortality rates displaying substantial variation across different geographic locations and demographic characteristics. Certain populations are particularly susceptible to HNSCC, with higher rates observed among men, older adults, and individuals of lower socioeconomic status. Understanding these epidemiological patterns is vital for effectively addressing the burden of HNSCC and implementing targeted preventive measures [18].

By examining the geographical and demographic factors that contribute to HNSCC disparities, we can gain insights into the underlying mechanisms and risk factors involved. These risk factors range from well-established ones, such as tobacco smoking and alcohol consumption, to emerging factors, such as viral infections, including human papillomavirus (HPV) and Epstein–Barr virus (EBV) infections. Understanding the multifaceted nature of these risk factors is crucial for devising effective prevention and intervention strategies that can help reduce the incidence of HNSCC [18].

2.2 Epidemiology

Per the latest GLOBOCAN estimates (2020), HNSCC is the seventh most common cancer globally, accounting for an estimated 890,000 new cases (roughly 4.5% of all cancer diagnoses around the world) and 450,000 deaths per year (roughly 4.6% of global cancer deaths). The incidence includes approximately 380,000 cases of cancer of the lip

and oral cavity, 185,000 of the larynx 133,000 of the nasopharynx, 98,000 of the oropharynx, 84,000 of the hypopharynx, and 54,000 of the salivary glands [19].

The incidence and mortality rates of head and neck squamous cell carcinoma vary widely by geographic region and demographic characteristics. Globally, HNSCC is more common in men than in women, with a male-to-female ratio of approximately 2:1, and in adults over 50 years of age [19]. The incidence rates of HNSCC are highest in South and Southeast Asia (where the chewing of the carcinogenic areca nut is prevalent) [20], followed by Central and Eastern Europe, and South America [19]. The highest incidence rates are observed in India, where tobacco (with or without the areca nut) accounts for up to 80% of all HNSCC cases [21]. The global incidence of head and neck squamous cell carcinoma has been increasing in many countries, particularly in younger populations, with a predicted 30% annual increase in incidence by 2030 [19]. This trend is partly attributed to changes in lifestyle factors, such as increased alcohol consumption and tobacco use in developing nations, as well as the growing prevalence of human papillomavirus (HPV)-related oropharyngeal cancer. It is estimated that HPV will overtake tobacco as the leading contributor to the global HNSCC cancer burden, causing the incidence of oropharyngeal HNSCC to surpass that of oral cancer (which is predominantly tobacco-related) [19,22]. Similarly, over the past decade, laryngeal cancer cases have increased by 23% [22]. Younger women in developed nations have seen a marked growth in incidence, likely due to changes in sex-specific cultural expectations for tobacco and alcohol consumption as well as a growing HPV burden [23,24]. In Japan, the incidence of oropharyngeal, oral cavity, and salivary gland tumors has gone up, more for women than men, while nasopharyngeal and laryngeal tumor incidence has gone down (which are more associated with the Epstein–Barr virus in East Asian populations than with HPV) [25]. Likewise, in the UK, oropharyngeal HNSCC has increased by 7.3% among men and 6.5% among women, and oral cancer has increased by 2.8% and 3.0% for men and women, respectively, with the greatest growth seen in those of lower socioeconomic status [26,27].

In the United States, per the SEER estimates, around 54,000 new cases of head and neck squamous cell carcinoma were diagnosed in 2022 (roughly 3% of all malignancies),

with an estimated 11,230 deaths, accounting for roughly 2% of all cancer deaths. Some 27% of cases are localized at diagnosis (stages I and II), 51% are locally advanced (stages III-IVB), and 15% are distantly metastatic (stage IVC). The 5-year survival is 68.5%, but it varies by stage at diagnosis. The 5-year survival is 86.6% for localized disease, 69.1% for locally advanced disease, and 39.3% for metastatic disease. The median age at diagnosis is 64, with around half of patients diagnosed between the ages of 55 and 74. The incidence among all males is 17.2/100,000 but is greatest for non-Hispanic White (20.1/100,000) and American Indian and Alaska Native (17.5/100,000) patients, with the lowest incidence in Hispanic (10.3/100,000) and Asian and Pacific Islander (12.0/100,000) patients. The incidence among females is nearly three times lower at 6.4/100,000 and is similarly highest for non-Hispanic White (7.1/100,000) and Asian and Pacific Islander (5.0/100,000) patients, with the lowest incidence in Hispanic (4.3/100,000) and Black (5.0/100,000) patients. The incidence rates of HNSCC in the United States have declined overall by approximately 14% since 1975, largely due to decreases in tobacco use. However, since the nadir in 2003, incidence rates have increased by 15.5% [28]. This growth has coincided with the replacement of tobacco related HNSCC with HPV-related disease, with oropharyngeal disease set to surpass oral disease [29].

Since 1975, head and neck squamous cell carcinoma mortality in the US has fallen by 44%, down to a mortality rate of 2.5/100,000 persons in 2020. This has been accompanied by an increase in 5-year survival from 54.6% in 1975 to 68% in 2018. Survival rates remain disparate based on the stage of diagnosis. The 5-year survival for localized disease is 86.3%, decreasing to 69.0% for locally advanced and 40.4% for metastatic disease [28,29]. The increase in survival among developed nations has been multifactorial, including the shift to HPV-related cases (which portend better prognosis), earlier detection due to screening, advances in robotic surgical resection and stereotactic radiation, as well as the development of immunotherapies (checkpoint inhibitors) for neoadjuvant [30], adjuvant [31], and metastatic systemic therapy [32,33]. Access to screening and advanced therapies remains a contributor to disparate survival statistics, with racial minorities and those living in low-socioeconomic-status urban and rural communities (e.g., Appalachia) suffering greater incidence and lower overall survival

[34,35]. An analysis of HNSCC diagnoses at one academic institution during the COVID-19 pandemic suggested a larger proportion of late-stage diagnoses and worsened tumor burden following quarantine, potentially exacerbating disparities in survival [36].

2.3 Risk Factors

The primary risk factors commonly linked to head and neck cancer encompass tobacco, alcohol consumption, using areca nut, human papillomavirus (HPV) infection (particularly for oropharyngeal cancers), and Epstein–Barr virus (EBV) infection (especially prevalent in Asia, particularly for nasopharyngeal cancers).

2.3.1 Tobacco

Tobacco use remains the leading risk factor for head and neck squamous cell carcinoma, accounting for an estimated 75% of all cases according to a study of cases in Western Europe [37]. A national survey from the UK implicated tobacco in 70% of oral and pharyngeal HNSCC cases [39], while data from East Asia have implicated tobacco in 2.8–25% of cases. Tobacco use is increasing across developing nations as economic progress increases household disposable income. In developed nations, tobacco use has declined overall but increased in certain demographics, commonly women [40,41]. Tobacco contains numerous carcinogenic chemicals such as polycyclic aromatic hydrocarbons, nitrosamines, aromatic amines, and aldehydes which are released during high-temperature combustion that are known to damage DNA in the cells of the oropharynx and lead to the development of cancer. Heavy cigarette smokers have a 5–25-fold increased risk of HNSCC as compared to non-smokers [42], while pipe and cigar smokers are at a lesser, yet still increased, risk [43]. Regular chewing tobacco use is also associated with a 1.7 odds ratio (OR) for HNSCC and 3.0 OR for oral cancer specifically [44]. Individuals with certain genetic and metabolic predispositions, including concurrent heavy drinking, are at the highest risk of developing HNSCC with smoking [43]. Second-

hand smoke exposure in childhood was found to have a 1.28 OR for HNSCC, adjusted for smoking, drinking, and HPV status [45].

2.3.2 Alcohol

Alcohol consumption among nonsmokers is estimated to account for 4% of head and neck squamous cell carcinoma cases globally [46]. The risk of HNSCC increases in a dose-dependent manner with the amount and frequency of alcohol consumption (relative risk 1.3× for all drinkers and 2.5× for heavy (>50 g/day) drinkers), with the highest risk observed among individuals who consume more than three alcoholic drinks per day [46]. The risk of HNC also varies by the type of alcohol consumed, with higher risks observed among individuals who consume spirits (e.g., whiskey or vodka) than among those who consume beer or wine, although this effect may be nonsignificant when adjusted for alcohol concentration [47, 48 ,49]. Alcohol's property as a solvent increases the mucosal tissue's susceptibility to carcinogens such as smoke or nitrites in food. Acetaldehyde is responsible for many of the symptoms of heavy alcohol consumption, such as headaches and flushing, and its conversion is blocked by disulfiram and other drugs with similar properties, such as metronidazole or abacavir, resulting in reactions with drinking [49,50]. Interestingly, patients with variants in acetaldehyde dehydrogenase, the enzyme that breaks down acetaldehyde, have been found to be associated with greater HNSCC risk with heavy alcohol consumption, greater risk of resistance to chemoradiotherapy, and overall poor prognosis.

Alcohol and tobacco have a multiplicative effect on head and neck squamous cell carcinoma. Increases in alcohol and tobacco consumption are projected to be the major contributors to growing global HNSCC incidence over the coming decades, particularly in developing nations. Studies from the UK [21], China [22], and Lebanon [51] all implicate alcohol consumption in 32–37% of oropharyngeal HNSCC diagnoses, with approximately 90% of these cases also reporting a smoking history [46,52]. Worldwide, tobacco or alcohol account for 72% (95% CI 61–79%) of HNSCC cases, with 35% (nearly half) attributed to both combined [46]. In fact, concurrent heavy alcohol and tobacco use has been shown to increase HNSCC risk 40-fold [49].

2.3.3 Areca Nut (Betel Quid)

Areca Nut (Betel Quid). In South and Southeast Asia and Polynesia, chewing of the *areca nut*, also known as betel quid, accounts for over half of oral and oropharyngeal head and neck squamous cell carcinoma cases [53]. The prevalence of consumption ranges from 33.8% in Sri Lanka [54] to 76.8% in the Solomon Islands [55]. Chewing can be part of rituals or recreational, as the compound has psychoactive effects via antagonism of GABA receptors, resulting in alertness, euphoria, and appetite suppression [56]. In fact, around 600 million people chew areca nuts worldwide, and it is considered the fifth most commonly used psychoactive agent after alcohol, nicotine, caffeine, and cannabis. In some of these nations, Areca nut is the most affordable and accessible stimulant and appetite suppressant, thus making its usage particularly prevalent in rural and underprivileged populations [53,56]. Areca nut can often be prepared with tobacco added, which may account for disparate risk calculations. A study from India found a 3 times-fold increased risk of HNSCC with areca chewing without tobacco and an 8 times-fold risk with tobacco, while a study from Taiwan reported a 10 times-fold risk without tobacco. Both studies reported positive dose–response curves [53].

2.3.4 Human Papillomavirus (HPV) Infection

HPV accounts for 72% of all head and neck squamous cell carcinoma cases in developed nations, as compared to 13% of cases in developing nations (as indicated by p16 positivity on immunohistochemistry) [57]. Over 20 high-risk HPV serotypes have been identified, distinguished by the protein capsid. HPV16 is responsible for 85–90% of HPV related oropharyngeal HNSCC cases in North America, in contrast to cervical cancer where HPV16 and 18 both account for 50–75% of cases [58]. Oncogenesis occurs with viral infection of basal keratinocytes, exposed to micro-abrasions caused by sexual contact [59]. The risk factors for HPV-associated oropharyngeal cancer include a history of multiple sexual partners, anal sex, oral sex (with the mouth on female genitalia conferring

the highest risk), and a weakened immune system. Comorbidity with human immunodeficiency virus (HIV) is common, with women with HIV having a 1.5–2.5 times greater risk of HPV. Globally, those with >4 oral sex partners have an OR of 2.25 (95% CI 1.42–3.58) of HNSCC [60]. The prevalence of HPV-associated oropharyngeal cancer has increased in developing nations in recent years (225% in the US from 1984 to 2004), particularly among young adults [61]. In the US, HNSCC has surpassed cervical cancer as the leading HPV-associated cancer [62]. Among US demographics, White men <45 years saw the greatest growth in incidence, with a 5.1% annual increase from 2008 to 2012. By contrast, the incidence of non-HPV associated HNSCC is roughly 50% higher among Black Americans [63]. Likewise, in the UK, cases of HPV-related HNSCC rose by 51% from 1989 to 2006 [64]. HPV-positive HNSCCs are associated with greater infiltration of B-cells into the tumor microenvironment, have fewer genetic mutations, and have an intact apoptotic response, which may explain the improved prognosis and superior response to radio- and immunotherapy [59,65]. HPV positivity portends a significantly longer median survival among HNSCC patients (130 vs. 20 months) [66], independently reducing the risk of death by 64% when adjusted for risk factors [67]. HPV-positive HNSCC is now staged differently due to the large disparity in survival [68].

2.3.5 Opium

Opium. The use of opium has been linked to an elevated risk of laryngeal cancer. Opium, an illicit substance derived from the poppy plant, is obtained from the juice of the unripe seedpod and contains several alkaloids. According to the International Agency for Research on Cancer, opium is classified as carcinogenic to humans when smoked or consumed in various forms, including raw, dross, or sap opium. For instance, findings from the Golestan Cohort Study (GCS), which examined 50,045 patients in Iran, demonstrated that opium use was associated with an increased risk of developing laryngeal cancer that correlated with the dosage [69].

2.3.6 Other Viral Infections

Other Viral Infections. Nasopharyngeal carcinoma, while uncommon in most populations, is prevalent in southern China, ranking among the most frequently diagnosed cancers in the region. Research has established the significant involvement of the Epstein–Barr virus (EBV) as the primary causative factor in the development of nasopharyngeal carcinoma. Additionally, chronic hepatitis C virus (HCV) infection has a robust association with the occurrence of hepatocellular carcinoma, and it has also been linked to various other malignancies such as lymphoproliferative disorders [18].

2.3.7 Immunodeficiency

Immunodeficiency resulting from HIV infection or solid organ transplantation has been linked to a heightened susceptibility to cancer in the head and neck area. HIV-infected individuals exhibit a higher occurrence of various non-AIDS-defining malignancies. Notably, there is a two- to threefold rise in the incidence of HNSCC among HIV-infected patients. Similarly, individuals who have undergone solid organ transplantation face an elevated risk of developing cancer, including malignancies originating in the head and neck. Moreover, patients who have received a bone marrow transplant, despite lacking conventional risk factors, are at an increased risk of head and neck cancer, particularly in the oral cavity [70].

2.3.8 Other Risk Factors

Other risk factors for head and neck squamous cell carcinoma include exposure to occupational or environmental carcinogens (e.g., asbestos or wood dust), poor oral hygiene, poor nutrition, and genetic predisposition. Chronic inflammation and infection of the oral cavity, such as chronic periodontitis, have also been linked to an increased risk of HNC [23,24,33,71]. Individuals diagnosed with Fanconi anemia face a substantial

predisposition to various malignancies, such as HNSCC, myelodysplastic syndrome, and acute myelocytic leukemia.

Certain dietary factors can play a role in either protecting individuals from head and neck cancer or heightening their vulnerability to specific diseases. Numerous studies have demonstrated a protective effect linked to higher intake of fruits and vegetables. Conversely, case-control studies indicate that frequent consumption of preserved meats, which contain elevated levels of added nitrites, may increase the risk of nasopharyngeal carcinoma.

The administration of prior radiation therapy, whether for malignant or benign conditions, has been associated with an increased incidence of thyroid cancer, salivary gland tumors, squamous cell carcinomas (SCCs), and sarcomas. While this connection is indeed present, it should be noted that there is a considerable time delay before any potential adverse effects manifest, and the overall risk remains relatively low [18].

2.4 Prevention

Prevention. The prevention of head and neck squamous cell carcinoma involves public health initiatives aimed at increasing oral screening and HPV vaccination, reducing exposure to tobacco, alcohol, and areca nut, and promoting a healthy lifestyle. The promotion of healthy diets, such as those high in fruits and vegetables, and good oral hygiene can also reduce the risk of HNSCC.

2.4.1 Smoking Cessation

Smoking Cessation. Counseling by healthcare practitioners and pharmacotherapy (nicotine replacement, varenicline, and/or bupropion) for smoking cessation in tangent have been shown to be most effective in promoting smoking cessation among head and neck squamous cell carcinoma patients in large systematic reviews. The average smoker requires over ten attempts to discontinue, though this figure can be dramatically reduced

by a combination of pharmaco and psychotherapy [70,71]. In the general population, maintained abstinence remains low (18–30%) even with varenicline therapy, highlighting the need for research into alternative mechanisms of targeting cravings. Other medications, including GLP-1 agonists such as semaglutide and naltrexone, are under investigation for tobacco addiction [72].

2.4.2 Decreasing Alcohol Consumption

Decreasing Alcohol Consumption. The World Health Organization (WHO) recommends a maximum daily intake of 30 g of alcohol for men and 20 g for women. Pharmacotherapy for alcohol use disorder (approved agents include naltrexone, acamprosate, nalmefene, and disulfiram) was found, in one US study, to be prescribed to only 3.6% of eligible patients [73]. Pharmacotherapy plus cognitive behavioral therapy, or other forms of evidence-based counseling, have been shown to improve cessation rates over pharmacotherapy alone [74]. Patients undergoing alcohol withdrawal are recommended for inpatient admission due to the risk of seizure and delirium tremens. Communities of lower socioeconomic status, such as Black Americans, are at higher risk of concurrent alcohol and tobacco consumption and should be targeted in public health initiatives to increase participation in regular wellness checkups and screenings, and substance use programs. Public health initiatives engaging community leaders such as pastors and barbers have proven especially effective in health promotion in US Black communities [75].

2.4.3 Ceasing Areca Nut Consumption

Ceasing Areca Nut Consumption. Studies from Taiwan, India, and China suggest that ceasing areca nut consumption would prevent roughly half of the oral cancers in those nations [36]. In northern Thailand, head and neck squamous cell carcinoma incidence dropped 2–3-fold from 1988 to 1999 due to concerted efforts to discourage Areca nut

consumption, particularly among young adults [76]. A study from Guam found that while the average tobacco smoker required 11.5 attempts before successfully quitting, that figure was only 5.2 for habitual areca users [77]. Programs aimed at increasing awareness of areca nut carcinogenicity have been successful in promoting cessation. The most successful interventions will involve engaging community leaders, particularly in refugee communities with lower medical literacy such as the Hmong and Karen [78,79].

2.4.4 HPV Vaccination

HPV vaccination is currently approved as a two-dose routine vaccine beginning at ages 11–12, though it may be administered through to the age of 26 according to the US Centers for Disease Control. As HPV vaccination was first approved in 2006 for adolescent females, the latency period has not yet been adequate to establish the impact of vaccination programs on the incidence of HNSCC [80]. Vaccination has been shown, in a US cross-sectional study, to reduce the prevalence of oral HPV 6, 11, 16, and 18 (the latter two being high-risk serotypes) by 88.2%. Following the implementation of the vaccine, the US Centers for Disease Control found a 64% decrease in high-risk HPV among sexually active women under 20, and a 34% decrease in women aged 20–24 [81]. Randomized trials for the Cervarix and Gardasil vaccines have also shown a significant reduction in cervical, vaginal, and vulvar HPV infection and HPV-associated precancerous lesions [82]. The quadrivalent vaccines were approved for adolescent and young adult men in 2009, and the most recent vaccines now cover nine HPV serotypes. The rate of adolescents who received the full two doses of the HPV vaccine increased from 54.2% in 2019 to 58.6% in 2020 [83], though the proportion may have since declined as the COVID-19 quarantine disrupted annual wellness exams.

2.4.5 Genital HPV

Genital HPV screening for cervical cancer consists of regular pap smears. The pap smear aims to sample cells from the cervix to look under the microscope for dysplastic changes, i.e., changes in the cell structure that suggest it has started on its path to becoming cancerous. This screening is recommended by the USPSTF for anyone with a cervix every three years beginning at age 21 until age 65. Microscopy can also be combined with HPV molecular testing via PCR. This combined approach can be started at 30 and only needs to be done every five years instead of every three. The ACS recommends HPV testing every five years beginning at 25 without the need for cervical sampling. HPV testing is not recommended before age 25–30, as many women may have the infection, but their immune system is robust enough to clear it, and thus the risk of cancer being caused by the HPV is much lower. Pap screenings have reduced US cervical cancer death rates by over 70% since the 1960s. Unfortunately, studies around the US found a significant reduction in screening rates during COVID-19, up to 80%, affecting Asian Americans and Pacific Islanders most severely. Patients found to have active HPV infection on a pap smear, or anal swab, can minimize transmission during oral sex, and thus minimize HNSCC risk, by the use of safe sex practices, such as the use of condoms and dental dams. The prevention of HPV-related HNSCC involves promoting awareness of sexual transmission and safe sex practices and increasing HPV vaccination rates [18].

2.4.6 Secondary Prevention

Secondary Prevention. As of 2017, US dentists are required to perform oral examinations as part of wellness encounters, though national uptake of the practice has been mixed. Data from 1998 found only 15–19% of adults aged >40 reported having had an oral cancer examination [84]. The US Preventative Screening Task Force has found insufficient evidence to recommend regular oral cancer screening for normal-risk adults, although the American Cancer Society does recommend screening [85]. However, among adults with risk factors for head and neck squamous cell carcinoma, there is data

to support annual screening. The greatest risk factor for HNSCC is a prior history, which increases the annual risk of a second primary tumor by 2–7%. Patients with premalignant oral leukoplakia have a roughly 12% lifetime risk of oral cancer [86]. Patients with hereditary cancer syndromes such as Fanconi anemia, and Li–Fraumeni and Plummer–Vinson syndromes, as well as immunosuppression, also associated with increased HNSCC risk, should undergo screening. A study of oral screening interventions from India found a greater detection of early-stage cases but did not find a statistically significant mortality rate reduction (0.8, 95% CI 0.5–1.2); however, for males with tobacco and alcohol use, the reduction was significant (0.6, 95% CI 0.4–0.9) [87]. Compared to visual examination, alternative methods such as toluidine blue staining, brush biopsy, or fluorescence imaging have not been found to reduce HNSCC mortality. Routine screening for HPV infection is not currently recommended [88].

2.5 Head and Neck Cancer Subsites

2.5.1 Squamous cell carcinoma of the oral cavity, larynx, oropharynx, and hypopharynx

2.5.1.1 Incidence and Epidemiology

Incidence and Epidemiology. In Europe, between 2000 and 2007, the annual crude incidence rates were 4.6/100 000 for laryngeal squamous cell carcinoma (SCC), 3.5/100 000 for oral cavity SCC, 3.3/100 000 for oropharyngeal SCC and 1.3/100 000 for hypopharyngeal SCC, corresponding to approximately 90 000 new cases per year.[89] Five-year relative survival was 61%, 49%, 41% and 25% for laryngeal, oral cavity, oropharyngeal and hypopharyngeal SCC, respectively [90]. Around 75%-85% of SCCHN is due to tobacco use and alcohol consumption, although human papillomavirus (HPV) infection as a cause of oropharyngeal cancer is increasing. The prevalence of oropharyngeal cancer attributable to HPV varies widely across the globe but is estimated at around 30%-35% [91]. HPV-positive patients with oropharyngeal cancer have a significantly better outcome than patients diagnosed with HPV-negative disease.[92] HPV-positive SCCHN outside of the oropharynx is rare (<6%). Other much weaker risk factors include radiation exposure, chronic infection, long-term immunosuppression, poor oral hygiene, poor nutrition, betel nut chewing and ill-fitting dentures. Fanconi anemia, ataxia telangiectasia, Bloom's syndrome, Li-Fraumeni syndrome and dyskeratosis congenita are rare inherited causes of SCCHN. Genetic counselling should be considered in cases of cytopaenia, young age and history of several cancers in the family, particularly in the absence of the other risk factors. Specific polymorphisms in genes encoding for enzymes that metabolise carcinogens such as glutathione S-transferase (GSTM1), glutathione S-transferase (GSTT1) or human microsomal epoxide hydrolase (EPHX1) have been associated with SCCHN development [67].

2.5.1.2 Diagnosis and Pathology/Molecular Biology

Diagnosis and Pathology/Molecular Biology. The following symptoms should prompt clinicians to examine patients for an SCCHN: chronic pain in the throat, persistent hoarseness, chronic sore tongue or non-healing ulcers or red/white patches in the mouth, painful or difficulty swallowing, and neck masses [89]. Clinical evaluation should include a history of symptoms, complete physical examination including neck palpation and flexible head and neck fiber optic endoscopy, performance status (PS), nutritional status with weight assessment, dental examination, speech and swallowing function, and psychosocial evaluation[89], A complete blood count, assessment of liver enzymes, serum creatinine, albumin, coagulation parameters and thyroid-stimulating hormone (TSH) should be routinely carried out, pathological confirmation is mandatory [89]. Examination and biopsy can be carried out transorally under local anesthesia. For pharyngolaryngeal tumours, this is often best carried out using an endoscopic route under general anaesthesia [89]. Stomatological evaluation with tooth extraction, when required [especially if radiotherapy (RT) is being considered], is also usually carried out. Systematic bronchoscopy and esophagoscopy are not advised but should be driven by symptoms and/or other diagnostic findings [89]. Contrast-enhanced (CE) computed tomography (CT) scan and/or magnetic resonance imaging (MRI) are mandatory to assess the primary tumour and regional lymph nodes as well as cartilage invasion for laryngeal or hypopharyngeal cancer. The two imaging techniques are complementary and their respective indications should be discussed with a radiologist specialised in head and neck cancer [89]. CT and MRI have similar diagnostic value in the radiological evaluation of the neck. Chest imaging is important to assess the presence of distant metastases in high-risk tumors (i.e., presence of neck adenopathies) or a second lung primary in heavy smokers. As a minimum, a chest CT should be carried out. The combination of 20-deoxy-20-[18F] fluoro-D-glucose (FDG) positron emission tomography (PET) and CE-CT of the chest have a higher sensitivity than chest CT or whole-body FDG-PET as separate modalities to detect tumors [93]. FDG-PET is also recommended for the work-up of a carcinoma of unknown primary to direct specific mucosal biopsy [94]. Finally, FDG-PET

is recommended to evaluate the neck response to RT or chemoradiotherapy (CRT) 10 e 12 weeks after completing treatment, or in cases of suspected recurrence.[95].

Pathology assessment. SCCHN should be classified according to the 4th edition of the World Health Organization (WHO) classification [96]. This classification recognizes the oropharynx as a distinctive subsite.

HPV evaluation using p16 immunohistochemistry (IHC) should be carried out on all patients with newly diagnosed oropharyngeal SCC. P16 IHC is a reliable surrogate marker for HPV positivity in the oropharynx, although 10%-15% of false-positive results occur [97]. For neck metastases of unknown origin, p16 status should also be assessed, and in case of positivity, another specific HPV test [e.g., DNA, RNA, or in situ hybridization (ISH)] should be carried out in order to confirm the HPV status[98, 99].In case of neoplastic lymph node(s) with an unknown primary, the Epstein-Barr virus (EBV) status should also be determined by Epstein-Barr-encoded RNA (EBER) using ISH to exclude a nasopharyngeal cancer.

The prognostic value of p16 has only been observed in oropharyngeal SCC and not in laryngeal, hypopharyngeal, or oral cavity tumors. Thus, for non-oropharyngeal cancers of the head and neck, determination of p16 status is not mandatory. Pathological assessment of the surgical specimens should include the size of tumour, growth pattern, depth of invasion (DOI) for oral cavity cancer, the total number of lymph nodes removed, number of invaded lymph nodes and their location, presence of extracapsular nodal extension, perineural and lymphatic infiltration and the surgical margins (i.e. R0 and R1 resection). These features are important for pathological staging and prognosis, and to determine the postoperative adjuvant treatment. For recurrent and/or metastatic SCCHN, tumor programmed death-ligand 1 (PD-L1) expression should be evaluated by an approved PD-L1 test within the framework of quality assurance [100]. PD-L1 expression is assessed either by the tumour proportion score (TPS), defined as the percentage of tumour cells with membranous PD-L1 staining, or by the combined positive score (CPS), defined as the number of PD-L1-positive cells (tumor cells, lymphocytes and macrophages) divided by the total number of tumor cells multiplied by 100. The CPS can help to define the first-line treatment strategy for recurrent/metastatic SCCHN.

Molecular Biology. Tobacco and/or alcohol-induced SCCHN and HPV-positive oropharyngeal cancer are two distinct entities that differ significantly at both a clinical and molecular level [101].

For HPV-negative SCCHN, the two most frequent genomic alterations are p53 (83%) and CDKN2A (57%), according to The Cancer Genome Atlas (TCGA) data [101, 102][1] In HPV-positive oropharyngeal cancer, 56% harbor PI3KCA amplifications/ mutations, whereas other genetic alterations are rare. Different subgroups (mesenchymal, basal, classical, and atypical) have also been defined based on gene expression profiles [103,104, 105]. In addition, HPV-positive SCCHN can be subclassified [into different gene profile groups, some of which are prognostic [106]. However, despite a better understanding of the molecular biology of SCCHN, the current management of these patients is not based on genomic alterations or gene expression profiles.

Staging. The Union for International Cancer Control (UICC) Tumour Node Metastasis (TNM) Cancer Staging Manual 8th edition head and neck chapters introduce significant changes from the 7th edition [107]. The 8th edition takes new prognostic factors into account to better predict patient survival based on disease stage.

In this context, it is important to outline that TNM staging is a prognostic factor and that current treatment strategies of SCCHN should not be modified based on any new classifications. The main modifications to the UICC TNM 8th edition.

5.2.1.3 Pre-treatment risk assessment.

Pre-treatment risk assessment. The objective of any treatment strategy for SCCHN is to achieve the highest possible cure rate with the lowest risk of morbidity. As such, treatment proposals should integrate both objective tumor parameters (e.g., tumor location, tumor histology, T stage, N stage) and patient parameters (e.g., physiological age, comorbidities, previous history of cancer, occupation, expected functional outcome, personal preference) [89] .

In this framework, in addition to locoregional staging, every patient should undergo evaluation of their nutritional status, comorbidities, cardiopulmonary and renal function, frailty index (for geriatric patients), psychological and social status and dental status with rehabilitation in case of foreseen RT. In case of significant malnutrition, defined as weight loss of more than 10% during the six months before diagnosis, nutritional improvement via an enteral route through a feeding tube is highly recommended before starting treatment. Percutaneous gastrostomy is generally preferred to a nasogastric feeding tube for long-term enteral support [89].

The optimal treatment strategy must be discussed in a multidisciplinary team (MDT), including not only the main treatment disciplines (surgery, radiation oncology, medical oncology) but also the disciplines involved in diagnosis (radiology, nuclear medicine, pathology) and treatment support (e.g., nutritionist, research nurse, psychologist). Patients should also be treated at high-volume facilities as this has been reported as a strong and significant prognostic factor [108].

2.5.1.4 Treatment

2.5.1.4.1 Management of local/locoregional disease

Management of local/locoregional disease. All treatment recommendations are based on staging according to the UICC TNM 8th edition. In case of RT, all patients should be treated by intensity-modulated RT (IMRT) or its variant volumetric modulated arc therapy (VMAT). The overall treatment time of RT has been shown to influence the probability of local control, and any treatment delays should be avoided or compensated. International consensus guidelines have been published for the optimal selection of node levels as a function of tumour location as well as for the delineation of these levels in the neck [109, 110]. Consensus guidelines have also been published for the delineation of the primary tumour target volumes [111]. Although promising data have been published favoring the use of proton therapy instead of megavoltage X-rays, there are no randomized clinical

trial data available to recommend the routine use of intensity-modulated proton therapy (IMPT) [112].

2.5.1.4.1.1 Early-stage disease

Early-stage disease is defined as either T1-2N0 (stage I and II) oral cavity, laryngeal, hypopharyngeal, and p16-negative oropharyngeal cancer or T1-2N0 p16-positive oropharyngeal cancer according to the UICC TNM 8th edition [89].

In early-stage disease, conservative surgery, or RT [external beam RT (EBRT) or brachytherapy for selected stage I oropharyngeal or oral cavity subsites], gives similar locoregional control. In the absence of high-level evidence, the choice between these two modalities should be based on the assessment of functional outcome and treatment morbidity for an individual patient as well as institutional and patient preferences and experience. Early disease should be treated as much as possible with a single-modality treatment (surgery or RT) [89].

2.5.1.4.1.1.1 Surgery

Minimally-invasive surgical treatments, including transoral laser microsurgery (TLM) and transoral robotic surgery (TORS), offer the potential for organ preservation with less functional morbidity than open surgery and often less long-term toxicity than RT providing the extent of resection does not jeopardize the functional outcome (e.g. speech and swallowing) and is unlikely to require postoperative RT [113]. This is especially relevant given the increasing incidence of HPV-positive SCCHN, as these patients tend to be younger and have a better long-term prognosis than those with HPV-negative SCCHN. This changing patient profile has strengthened interest in functional organ preservation surgery to improve functional outcomes and quality of life (QoL) in these patients.

In early-stage disease, transoral surgery is usually recommended as a single-modality treatment for oral cavity, oropharyngeal, and laryngeal lesions. The surgical technique

will depend on the location of the tumours and patient-related factors. Despite the lack of randomized trials, recent data suggest that the oncological outcomes of TORS for oropharyngeal cancer are comparable to open surgery and IRT [114].

Despite the growing popularity of TORS in the treatment of oropharyngeal cancer, this approach has several potential drawbacks. Importantly, the use of TORS does not obviate the need for postoperative RT in some cases. Although the head and neck are relatively accessible, access and maneuverability are sometimes limited by anatomical restrictions. Although TLM is currently considered a standard of care for early glottic cancer, TORS has also been used to treat early-stage glottic carcinomas, but data are currently limited [115]. With the exception of T1-2 glottic cancer, ipsilateral selective neck dissection (bilateral in near-midline tumours) or sentinel node biopsy is recommended for cT1-2 SCCHN tumours that are treated with primary surgery [116,117,118].

2.5.1.4.1.1.2 Radiotherapy

Radiotherapy. Early-stage disease can be treated by RT alone without any use of concomitant or induction ChT. For stage I disease, a standard fractionation regimen with a primary tumor dose ranging from 66 to 70 Gy, depending on the tumor volume and location, is recommended. For stage II disease, a slightly more intense RT delivery is recommended with either hyper-fractionation with a slightly higher total dose (e.g. 80.5 Gy delivered in 70 fractions of 1.15 Gy twice daily over 7 weeks) or moderately accelerated RT with a similar RT dose (e.g. 66-70 Gy delivered in 33-35 fractions of 2 Gy over 5.5-6 weeks) [119]. Such regimens could also be offered to patients with T1 or T2 tumours and neck disease with a single positive lymph node of <3 cm. Several randomized controlled trials and a meta-analysis have demonstrated that the use of hypoxic sensitizers improved locoregional control and disease-specific survival after RT [120]. This radio sensitization is achieved irrespective of the RT fractionation regimen and the modification of hypoxia used. Except for T1 glottic laryngeal tumours, prophylactic nodal RT is required up to an equivalent dose of 50 Gy delivered in fractions of 2 Gy; in case of a single positive lymph node of <3 cm, the RT dose should be increased to 70

Gy. Altered fractionation RT results in a significant increase in acute grade 3-4 mucositis to around 40% compared with 25% for standard RT, an increase in the need for a feeding tube during RT and a non-significant increase in late RT induced morbidity [89]. Although HPV-driven SCCHN is known to be more sensitive to RT, there are no data to suggest that the total RT dose can be decreased in p16-positive oropharyngeal tumors [14].

No robust, mature clinical trial data are available to convincingly guide treatment between minimally invasive surgery or RT for node-negative p16-positive T1 or T2 tumours [86].

Finally, for appropriately selected stage I oral cavity and oropharyngeal tumours, brachytherapy remains an option [91]. The use of brachytherapy in the head and neck region is, however, on the decline due to lack of physician expertise, the need to combine it with EBRT (or surgery) to treat the neck, and the availability of alternative surgical options with very low morbidity, especially for oral cavity tumors [86,91].

2.5.1.4.2 Locally advanced disease.

Locally advanced disease is defined as either stage III or IV oral cavity, larynx, hypopharynx, and p16-negative oropharyngeal cancer, or T3-4/ N0-3 and T0-4/N1-3 p16-positive oropharyngeal cancer according to the UICC TNM 8th edition. Standard options for locally advanced SCCHN are either surgery plus adjuvant IRT or primary CRT alone. In principle, the use of hypoxic radiosensitisers can also be used with CRT, although the published meta-analysis only reviewed patients treated with RT alone. Primary combined concomitant CRT is the standard treatment in non-resectable patients and is also indicated in resectable patients when the anticipated functional outcome and/or the prognosis is so poor that mutilating surgery is not justified [89].

2.5.1.4.2.1 Surgery

Surgery in Locally advanced disease. Primary surgical treatment is recommended for T3/T4 oral cavity and T4 laryngeal cancers. Advanced hypopharyngeal cancers may also

be treated surgically, especially when there is laryngeal cartilage invasion (i.e. stage T4) or a non-functional larynx. Treatment of advanced oropharyngeal lesions is currently non-surgical for both HPV-positive and -negative disease, but surgery can be employed if RT is contraindicated [122]. For oral cavity cancers, wide surgical excision followed by appropriate reconstruction needs to be employed: a free vascularised soft tissue flap when the continuity of the mandible is intact and a bony flap if not. The radial forearm and anterolateral thigh flaps and the fibula flap are the preferred options, respectively. During total laryngopharyngectomy, the pharyngeal mucosa may need reinforcing or patching with a free soft tissue flap or a pedicled flap. The smaller oropharyngeal lesions may be resected transorally (with or without TORS), but the larger ones may require a mandibular swing approach [122].

Almost invariably, surgically treated tumours will need postoperative RT or CRT depending on the pathological report. When the patient has a relatively small primary tumour but a large neck mass, the appropriate treatment must be decided by an MDT. Except for oral cavity cancer, a primary non-surgical option will usually be chosen with surgery reserved for salvage treatment; occasionally, neck surgery before CRT may be considered [122].

2.5.1.4.2.2 Concomitant CRT

Concomitant CRT. For locally advanced disease, the use of concomitant CRT has resulted in greater locoregional control and improved overall survival (OS) compared with RT alone [123]. This benefit was observed irrespective of the tumor location in the oral cavity, pharynx, or larynx [124]. The largest benefit was observed with cisplatin-based RT, and a total dose of 200 mg/m2 cisplatin is recommended [125,126]. The benefit of concomitant CRT has been observed with a standard fractionation regimen as well as for altered fractionation regimens. However, when accelerated RT is used (i.e. 70 Gy in 6 weeks), the addition of two courses of cisplatin (100 mg/m2) has been shown to be equivalent to three courses given concomitantly to a 7-week RT regimen but with the advantage of improved ChT compliance [127]. A comparison of weekly cisplatin (30

mg/m2) and 3-weekly cisplatin carried out in a randomized trial of mainly postoperative patients showed that weekly cisplatin was inferior [128]. Whether weekly cisplatin at a dose of 40 mg/m2 is equivalent to 3-weekly dosing (at 100 mg/m2) has never been directly compared as the primary curative treatment, but for fit patients, the indirect evidence favours the latter [128]. Platinum combined with 5-fluorouracil (5-FU) has also been shown to improve survival and is a valid option in patients who cannot tolerate high-dose cisplatin [123, 129, 130].

2.5.1.4.2.3 *Radiotherapy with concomitant cetuximab*

RT with concomitant cetuximab has demonstrated improved locoregional control, progression-free survival (PFS), and OS compared with RT alone [131]. Recently, two randomized trials have reported results in patients with p16-positive oropharyngeal SCCHN treated with either concomitant 3-weekly cisplatin (100 mg/m2) and RT (70 Gy) or weekly concomitant cetuximab (250 mg/m2) and the same RT regimen. Although these two trials enrolled slightly different patient populations (i.e. low-risk patients in the UK De-Escalate study and all-risk patients in the RTOG 1016 study), both demonstrated a shorter OS in the cetuximab arm with no reduction in acute or late morbidity rates [132,133]. How concomitant cetuximab-RT compares with concomitant cisplatin-RT in patients with locally advanced, HPV-negative tumours is unknown, but CRT is recommended, with cetuximab reserved for patients considered unfit for platinum-based CRT. In these patients, the use of altered fractionation RT should be considered since this improves survival [119,134] Also, the use of cetuximab has not been shown to improve OS or PFS when given with concomitant 3-weekly cisplatin and RT in patients with locally advanced, stage III and IV SCCHN. Finally, the use of induction ChT followed by concomitant CRT irrespective of tumour response for non-laryngeal or hypopharyngeal tumours has not been shown to be superior to concomitant CRT alone [135]. There are findings suggesting that treatment intensity should be de-escalated in patients with p16-positive oropharyngeal SCC [IV, A], so omitting concomitant ChT or replacing ChT with cetuximab is not endorsed [136].

The use of concomitant CRT results in a significant increase in acute and late treatment-related morbidity, including treatment-related death, underlining the need for careful patient selection [137]. RT-induced swallowing impairment and aspiration are thought to be responsible for the lower 10-year OS of concomitant CRT compared with induction ChT followed by RT for responders in locally advanced laryngeal SCC, although the larynx preservation rate is higher for concomitant CRT [89].

2.5.1.4.2.4 Induction ChT.

Induction ChT. For larynx preservation, two approaches are validated: concomitant CRT and induction ChT (three courses) followed by RT alone. The rate of larynx preservation is higher with concomitant CRT but survival is similar to induction ChT followed by RT[138]. In patients with locally advanced laryngeal or hypopharyngeal SCCHN who would require a total laryngectomy or pharyngolaryngectomy, the use of induction ChT with a platinum-based combination has been associated with organ preservation by identifying those patients who could benefit from RT alone[139, 140}. The introduction of taxane/platinum/5-FU (TPF) combinations has proven superior to platinum/5-FU schedules and TPF is now the standard induction ChT regimen [141,142,143]. The use of organ preservation with induction ChT (three courses) has not been shown to improve OS compared with surgery, although patients undergoing organ preservation tend to have a reduction in distant metastasis. it should be emphasised that induction ChT followed by concomitant CRT has not been shown to improve outcome and the overall toxicity of this approach can be substantial, thus compromising the final results [89].

Also, not all patients with locally advanced laryngeal or hypopharyngeal cancer should be offered induction ChT. Patients with massive larynx cartilage invasion (T4a), extra-laryngeal extension (T4a) or with severely impaired laryngeal function should be excluded from a larynx preservation strategy and offered upfront surgery [89].

Outside of a laryngeal-preservation strategy, the role of induction ChT is not recommended, and the standard regimen is concomitant CRT with high-dose (100 mg/m2) cisplatin when a non-surgical approach is preferred. In the locally advanced

setting, induction ChT has been prospectively compared with concomitant CRT in five trials without any strong evidence of improving patient outcomes [144, 145, 146, 147,148].

2.5.1.4.2.5 *Neck dissection after CRT*

Neck dissection after CRT. For patients with nodal disease treated by RT or concomitant CRT, the necessity to carry out a systematic neck node dissection before or after the locoregional treatment has always been debated. A randomized trial compared systematic neck node dissection before or after concomitant CRT for locally advanced nodal disease to a neck node dissection carried out only in patients with a positive or equivocal FDG-PET/CT at 12 weeks after the completion of locoregional treatment [96]. With a median follow-up of 36 months, the 2-year OS rate was similar in both arms (81.5% in the systematic neck dissection group and 84.9% in the surveillance group), thus validating a surveillance policy in case of negative FDG-PET and normal size lymph nodes at 12 weeks post-CRT. However, evaluation of FDG-PET response can be challenging. The five-point scale (Hopkins Criteria) to assess response is therefore recommended [149].

2.5.1.4.2.6 Postoperative RT

Postoperative IRT. When a surgical option is preferred as the primary treatment modality, postoperative RT may be required to decrease the risk of locoregional recurrence. Several risk factors for locoregional recurrence have been identified, such as pT3-4 (UICC TNM 8th edition), positive margin (tumour 1 mm from the margin), close resection margin (between 1 and 5 mm), perineural infiltration, lymphovascular spread, >1 invaded lymph node and the presence of extracapsular nodal infiltration [150]. It should be noted that these risk factors have been established mainly for oral cavity cancers; margins at other sites (especially oropharynx and larynx) should be interpreted with caution, and lesser distance to the margin is often appropriate [89].

For patients with one or more of these risk factors, prospective studies have validated the use of postoperative RT up to a dose of 58 Gy (only one risk factor) or 63-64 Gy (several risk factors) [150, 151]. For patients with only one lymph node invaded without other adverse features, postoperative RT is optional as long as at least 15 lymph nodes have been analysed. Furthermore, pooled data from two randomised studies (EORTC 22931 and RTOG 9501) have shown that for patients with an R1 resection and extracapsular spread, concomitant CRT (66 Gy) with high-dose cisplatin (100 mg/m2 every 3 weeks) improved OS compared with the same dose of RT alone [152,153], Recently, weekly cisplatin at a dose of 40 mg/m2 plus RT has been shown to be non-inferior to high-dose cisplatin (100 mg/m2) plus RT for postoperative high-risk SCCHN patients[154], Irrespective of the regimen, postoperative RT should be started within 6-7 weeks after surgery and/or the treatment regimen of surgery and postoperative RT should be delivered within 11 weeks [155].

2.5.1.4.3 Unknown Primary.

Unknown primary. An SCCHN with an unknown primary is an SCC 41 localized in (a) neck lymph node(s) but without any mucosal primary identified. The diagnostic work-up of these patients includes an FDG-PET, head and neck imaging (preferably MRI), and a panendoscopy under general anaesthesia with bilateral tonsillectomy and a mucosectomy of the base of the tongue in case of HPV-positive disease [156]. For p16-positive SCC, HPV status should be confirmed with a specific HPV (DNA, RNA or ISH) test. However, the treatment of HPV-positive and negative disease is the same. Treatment of SCCHN with an unknown primary is either primary surgery (neck dissection) alone or followed by RT or CRT based on the same postoperative risk factors as other SCCHN subsites, [150,151] or primary RT or CRT (see above for doses and combinations with ChT) followed by neck dissection in case of residual disease [152,153]. The type of neck dissection should be based on the extent of nodal disease both in the non-operated situation and after prior nodal excision [e.g. for a single level II node, selective (levels Ib, II and III) dissection is indicated]. Patients with pN1 disease and no other risk factor do not require postoperative RT if at least 15 nodes have been analysed. Total mucosal RT

is controversial; it is associated with significant morbidity even in the IMRT/VMAT era and is not recommended. Oropharynx RT can be considered as an option in some cases [157].

2.5.1.5 Management of recurrent and/or metastatic disease

Few patients (<5%) present with upfront metastases. Around 50% of patients with locally advanced SCCHN will recur after primary treatment with distant metastases and/ or local or regional disease [158]. In selected patients with oligometastatic disease at diagnosis, local and/or regional treatment (with surgery or RT) can be considered for treatment with curative intent, especially after a response to upfront systemic treatment [158]. On the other hand, in the presence of a high burden of distant metastases (e.g. more than two distant sites, mainly visceral involvement), starting systemic treatment is a priority and locoregional treatment should be carried out only if symptoms occur. Patients with a good PS and an early-stage laryngeal recurrence occurring more than 2 years after primary treatment can be offered salvage surgery with a reasonable oncological outcome. Patients with locoregional recurrence not amenable to surgery and/or RT, as well as those with metastatic disease, are eligible for systemic treatment [89]. The standard of care first-line therapy for recurrent and/or metastatic disease changed recently. The KEYNOTE-048 study showed that a combination of ChT (cisplatin or carboplatin plus 5-FU) plus pembrolizumab, a monoclonal antibody targeting programmed cell death protein 1 (PD-1), significantly improved OS compared with the EXTREME regimen (cisplatin or carboplatin plus 5-FU plus cetuximab): median OS 13 versus 10.7 months (P ¼ 0.0034) [159]. Objective response rate (ORR) and PFS were similar between the ChT plus cetuximab and ChT plus pembrolizumab arms [ORR 35.6% and 36.3%, PFS 4.9 and 5.1 months, grade 3-5 adverse events (Aes) 85.1% versus 83.3%, respectively]. In the same trial, pembrolizumab monotherapy also improved median OS in patients with PD-L1-expressing SCCHN: 14.9 versus 10.7 months in the CPS 20 subgroup and 12.3 versus 10.3 months in the CPS 1 subgroup [159] However, PFS with pembrolizumab monotherapy was not satisfactory compared with EXTREME: 3.4 versus 5.0 months in CPS 20 and 3.2 versus 5.0 months in CPS 1. Similarly, ORR for pembrolizumab

monotherapy versus EXTREME was 23.3% versus 36.1% and 19.1% versus 34.9% in the CPS 20 and CPS 1 groups, respectively. Therefore, based on the KEYNOTE-048 results, two different approaches are validated for patients with locoregional relapse not amenable to locoregional salvage treatment and/or with distant metastases [89].

A ‘chemo-free’ approach with pembrolizumab monotherapy in patients with CPS 1 SCCHN should be considered, especially when a rapid tumour shrinkage is not needed [I, A]. A second option, independent of PD-L1 status, is the combination of pembrolizumab and ChT (cisplatin or carboplatin plus 5-FU), particularly in symptomatic patients or when a rapid tumour shrinkage is needed. Of note, based on current evidence, we do not know if platinum/5-FU/ pembrolizumab improves survival compared with platinum/5-FU/cetuximab in patients with SCCHN not expressing PD-L1. The impact of pembrolizumab on survival in patients with SCCHN and a CPS between 1 and 19 also needs to be clarified [159].

The Food and Drug Administration (FDA) recently approved pembrolizumab in combination with ChT as first-line treatment regardless of PD-L1 expression and pembrolizumab alone for patients with PD-L1-expressing tumours (CPS 1).

In contrast, the European Medicines Agency (EMA) has approved pembrolizumab with or without ChT only for patients with a CPS 1 [ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4]. EXTREME improves OS compared with platinum/5-FU (10.1 versus 7.4 months) and is EMA-approved as first-line treatment in patients with recurrent or metastatic SCCHN [ESMO-MCBS v1.1 score:3] [160]

Cisplatin/docetaxel/cetuximab (TPeX) showed comparable results to EXTREME in a phase III trial [161]. A retrospective analysis from French sites showed an ORR of 30%, a median PFS of 3.6 months and a median OS of 7.8 months with salvage ChT for patients who progressed on immune checkpoint inhibitors.[162].

In the first-line treatment of recurrent SCCHN, EXTREME is the standard of care for patients with contraindications to antiPD-1 inhibitors and in patients with a tumor not expressing PD-L1. EXTREME can also be considered as second-line treatment after progression on an immune checkpoint inhibitor in fit patients considered eligible for

platinum-based ChT. Similarly, TpeX can be considered as a treatment alternative to EXTREME for some patients [for example, in the case of dihydropyrimidine dehydrogenase deficiency (DPD)]. For patients who progress within 6 months of platinum therapy, given either as palliative treatment or with multimodal curative treatment, nivolumab has been shown to improve OS compared with single-agent systemic treatment (cetuximab, docetaxel or methotrexate): 7.5 versus 5.1 months (CheckMate 141) [163]. In a very similar study design (KEYNOTE-040), pembrolizumab prolonged median OS compared with standard of care (8.4 versus 6.9 months), although the difference was not statistically significant [164]. In the population with a PD-L1 TPS of 50%, median OS was 11.6 months with pembrolizumab and 6.6 months with standard of care. Nivolumab is both FDA- and EMA-approved in this setting [ESMO-MCBS v1.1 score: 4]. Pembrolizumab is also approved by the FDA for the same indication and is approved by the EMA for patients whose tumours express PD-L1 with a TPS of 50%. After progression on platinum-based ChT and anti-PD-1 inhibitors, no standard of care exists. Cetuximab is approved by the FDA after platinum failure.

This approval was not based on a randomized trial but on data from prospective single-arm studies, which showed that patients progressing on platinum-based ChT treated with cetuximab had a median OS of between 5.2 and 6.1 months [165].

Taxanes with or without cetuximab and/or methotrexate are frequently used after platinum failure, although no randomized trials have demonstrated their benefit in this setting [161].

2.5.1.6 Treatment Recommendations, according to ESMO

1. The optimal treatment strategy must be discussed in an MDT including not only the treating physicians but all the supportive specialties.
2. Patients should be treated at high-volume facilities.
3. In case of RT, all patients should be treated by IMRT or VMAT.

4. The treatment strategy for HPV-positive SCCHN should be the same as HPV-negative SCCHN.
5. The recommended treatment option should be based on patient- and treatment-related factors (e.g. side effects, complications, etc.) since conservative surgery and RT may often provide similar locoregional control.
6. Early disease should be treated as much as possible with a single-modality treatment.
7. Standard options for locally advanced disease are either surgery plus adjuvant (C)RT or primary concomitant CRT.
8. Primary surgical treatment followed by RT or CRT is the preferred treatment for T3/T4 oral cavity and T4 laryngeal cancers.
9. A hypoxic radiosensitiser increases locoregional control and disease-free survival compared with RT alone.
10. Concomitant CRT increases locoregional control and OS compared with RT alone.
11. The standard of care for ChT is cisplatin at a dose of 100 mg/m2 given on days 1, 22 and 43 of concomitant RT (70Gy).
12. In patients unfit for cisplatin, carboplatin combined with 5-FU or cetuximab concomitant to RT as well as hyperfractionated or accelerated RT without ChT are treatment alternatives.
13. For larynx preservation, induction ChT with TPF (three courses) followed by RT alone is a validated treatment option.
14. Besides larynx preservation, induction ChT is not routinely recommended.
15. Neck dissection is not recommended in cases of negative FDG-PET and normal size lymph nodes at 12 weeks postCRT.
16. Postoperative RT is recommended for patients with pT3 e 4 tumours, resection margins with macroscopic (R2) or microscopic (R1) residual disease, perineural infiltration, lymphatic infiltration, >1 invaded lymph node and the presence of extracapsular infiltration.
17. Postoperative CRT is recommended for patients with an R1 resection and extracapsular rupture.
18. Postoperative RT or CRT should start within 6e7 weeks of surgery [II, A].

19. Pembrolizumab in combination with platinum/5-FU and pembrolizumab monotherapy are two approved regimens for patients with recurrent/metastatic SCCHN expressing PD-L1 (CPS 1) [ESMO-MCBS v1.1 score:4]. ChT plus pembrolizumab is recommended when rapid tumour shrinkage is needed.
20. Platinum/5-FU/cetuximab remains the standard therapy for recurrent/metastatic patients with SCCHN not expressing PD-L1 [ESMO-MCBS v1.1 score: 3]. TPeX is also a treatment option in this population.
21. Nivolumab is both FDA- and EMA-approved for recurrent/metastatic patients who progress within 6 months of platinum therapy [ESMO-MCBS v1.1 score: 4].
22. DPD testing is recommended before initiating 5-FU.

2.5.2 Nasopharyngeal Carcinoma, Diagnosis, Treatment, and Follow-up

2.5.2.1 Incidence and Epidemiology

Nasopharyngeal carcinoma (NPC) is a disease with unique epidemiological features. The distribution of the disease demonstrates a clear regional, racial and gender prevalence. In 2018, the global age-standardised incidence rates (ASIRs) varied from 2.1 to 0.4 per 100 000 in Asia and Europe, respectively [166].[1] The highest ASIRs per 100 000 were in East and South East Asia (e.g. seven in Singapore, the Maldives and Indonesia; six in Malaysia and Vietnam; three in China). There were more than 129 000 new cases of NPC reported in 2018, including more than 5000 in Europe [166]. In recent decades (1970-2007), the incidence of NPC has declined worldwide, with substantial reductions in South and East Asia, North America, and the Nordic countries [167].

NPC has several features that differ according to geographic area. For example, age distribution differs in low-incidence areas compared with endemic areas. In low-incidence areas, the incidence of NPC increases with age and has a bimodal peak: the first in adolescents and young adults and the second after 65 years of age, whereas in endemic

areas, the incidence increases after 30 years of age, peaks at 40-59 years and decreases thereafter. The male-female incidence ratio is 2.75 [90].

In Europe, during the period of 2000-2007, the 5-year survival rate for adults with NPC was 49% (www.Rarecarenet.eu). Survival rates increased during 1999-2007 in Europe, except in Eastern Europe where it declined over time [168].

In the USA, during the period of 2009-2015, the 5-year relative survival rate was 60%, with differences seen across ethnic groups[169].[Asians seem to have a disease specific survival advantage independent of gender, age at diagnosis, grade, TNM (tumour-node-metastasis) staging and treatment 170].In addition, the hazard rate patterns for NPC-related mortality appear significantly different between histological subtypes[171].[7] The effect of age on survival is marked. Five-year survival rates were 72% in the youngest age group (15-45 years) and 36% in the oldest group of patients (65-74 years) [172]. In general, the prognosis is better for women than men 173,174].

2.5.2.2 Diagnosis and Pathology/Molecular Biology

Diagnosis. Definitive diagnosis is made by endoscopic-guided biopsy of the primary nasopharyngeal tumour. In case of no clinical primary tumour visible at endoscopy, a biopsy of nasopharyngeal tissue positive at magnetic resonance imaging (MRI) FDG-PET is suggested [175]. Since the first sign of disease is often the appearance of neck nodes, it is frequent that patients undergo neck biopsy and/or neck nodal dissection. This procedure is not recommended since it may reduce the probability of cure and have an impact on late treatment sequelae. Nevertheless, if carried out (for example, if the primary tumor is not visible), node dissection without capsular effraction or ultrasonography-guided, transcutaneous tru-cut biopsy is the best option; node surgical biopsy should be avoided. Determination of Epstein-Barr virus (EBV) on the histological sample by in situ hybridization (ISH) is indicated.

The histological type should be classified according to the 4th edition of the World Health Organization (WHO) classification [176]. The term ‘nasopharyngeal carcinoma’ refers to

all squamous cell cancers, which are categorized into keratinizing, non-keratinizing (subdivided into differentiated and undifferentiated), and basaloid carcinoma subtypes. Keratinizing cancer is more frequent in nonendemic than endemic areas, whereas non-keratinizing cancer comprises the vast majority of cases and is linked to EBV infection.

EBV expression. EBV is considered in 'Group 1' by the International Agency for Research on Cancer (IARC) with respect to NPC, i.e., a virus for which there is sufficient evidence of carcinogenicity in humans [177, 57], EBV is identified by ISH by the presence of EBV-encoded RNAs in NPC tissue. Latent EBV has been found in high-grade dysplasia and NPC cells but not in normal epithelium or low-grade dysplasia [178]. EBV has also been identified in a clonal pattern in pre-invasive lesions of the nasopharynx that contain EBV RNAs characteristic of latent infection. EBV-infected cells express several latent proteins, both as EB nuclear antigens [EBNAs 1, 2, 3A, 3B, and 3C and EBNA leader proteins (LPs)] and as latent membrane proteins (LMPs 1, 2A, and 2B) [179]. However, the EBV latent-gene expression in NPC is predominantly restricted to EBNA1, LMP2A and LMP2B. The role of EBV genomic variants on NPC development has not been completely clarified; however, whole genome sequencing of EBV has revealed a high variability in many genomic regions of NPC biopsy specimens [180]. EBV is almost always a necessary, even if not sufficiently causative, factor for non-keratinizing NPC; its role in keratinizing cancer is less pronounced.

Human papillomavirus expression. In regions where NPC is endemic, p16 positivity and human papillomavirus (HPV) expression (screened using RNA probes to detect 13 high risk and 5 low-risk HPV types) is reported in up to 8% of non-keratinising undifferentiated carcinoma, and carries a better prognosis than its EBV counterpart [181]. In nonendemic areas, the presence of HPV data is limited, with a higher frequency seen in keratinizing cancer; however, an association with prognosis is not as clear [182]. Whether HPV is involved in carcinogenesis and disease progression has yet to be established.

Molecular analysis. Although no actionable mutations in NPC have been identified, a role for gene signature discovery is increasing. However, gene expression analysis may be useful in identifying patients at higher risk of developing distant metastases [183]. In

addition, mutational signatures relevant to DNA repair pathways show prognostic value with potential clinical implications [184].

Other risk factors. Genetic susceptibility plays a clear role in the development of NPC, as witnessed by the discovery of susceptibility loci and candidate genes in NPC patients or high-risk individuals [186]. Environmental factors are also causal agents, mainly related to the consumption of salted fish, while there is less evidence to support other agents or dietary products [186].

2.5.2.3 Screening

In regions where NPC is endemic, the use of plasma EBV DNA with a primer/probe assay targeting the BamHI-W region of the EBV genome, carried out in duplicate (at least 4 weeks apart) and coupled with endoscopic examination and MRI, showed a sensitivity and specificity in screening NPC of 97.1% and 98.6%, respectively [187]. The number of subjects needed to be screened to detect one case was 593. Its use can therefore only be recommended for detecting early asymptomatic NPC in endemic areas and is limited to those considered at higher risk (i.e. males aged 40-62 years). Although overall survival (OS) data for the screened population are not available, the 3-year progression-free survival (PFS) was significantly improved compared with a matched historical cohort [97% versus 70%; hazard ratio (HR) 0.10; 95% confidence interval (CI) 0.05-0.18] [192] One of the issues related to plasma EBV DNA is the poor standardization between the different assays used.

2.5.2.4 Staging and Risk Assessment

NPC is clinically staged according to the American Joint Committee on Cancer (AJCC) staging classification 8th edition [188]. Compared with the previous edition, the new classification better delineates the T2 stage to also include prevertebral muscle and medial or lateral pterygoid involvement, and the T4 stage now includes parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle, thus

eliminating other ambiguous terminology. Nodal extension to the supraclavicular fossa has been substituted by the limit of the caudal border of the cricoid cartilage and so better delineates the ‘lower neck’ extension; the N3 definition includes both the previous N3a and N3b groups. Moreover, EBV-positive cervical nodes in cancer of unknown primary are staged according to the NPC classification [192].

Routine staging procedures include a medical history, physical examination (including cranial nerve examination), complete blood count (CBC), serum biochemistry [including liver and renal function tests and lactate dehydrogenase (LDH)], nasopharyngoscopy, computed tomography (CT) scan or MRI of the nasopharynx and base of the skull and neck (up to the clavicle) and FDG-PET/CT imaging. MRI is the most accurate way of defining local tumor staging as it is sensitive in depicting small mucosal thickening, parapharyngeal, and masticatory space involvement, and skull base and cranial nerve infiltration, and it should therefore be preferred whenever available and according to the center’s expertise. Accuracy of nodal involvement detection is higher with MRI compared with CT; FDG-PET adds further accuracy in nodal staging. The best imaging for detecting distant metastases is FDG-PET in terms of sensitivity and specificity, and it is recommended at least in locally advanced disease [189]. Moreover, a systematic review and meta-analysis showed that baseline metabolic values of FDG-PET were able to predict survival outcomes for NPC patients [199]. Baseline audiometric testing, dental examination, nutritional status evaluation, and ophthalmological and endocrine evaluation should be carried out as appropriate. Pretreatment quality of life (QoL) scales [e.g. the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ)-C30], mainly physical functioning, have been found to be a more accurate predictor of OS than performance status (PS)[191]. Their application in clinical practice may better delineate the individual risk and prompt medical or physical support before the start of treatment. Due to the variability in assessments between laboratories, EBV DNA measurement needs further harmonization [193]. Both the pre- and post-treatment plasma/serum load of EBV DNA with a primer/probe set targeting the BamHI-W region of the EBV genome has shown prognostic value. A pre-treatment cut-off value of between 1500 and 4000 copies/ml has been proposed in endemic areas [194, 195]. The prognostic role of pre-treatment EBV DNA has also been reported in non-endemic

areas using PCR, which amplifies the gene coding for the EBNA-1 protein [196]. Incorporation of plasma EBV DNA both in the pre and post-treatment setting may improve the prognostic capacity of the TNM staging system [197, 198]. At this time, however, plasma EBV DNA detection has no impact on treatment strategy. Biomolecular signatures with gene expression and microRNA have been shown to add prognostic value to clinical and radiological staging [199, 200].

2.5.2.5 Treatment

2.5.2.5.1 Management of local/locoregional disease

The optimal treatment strategy for patients with advanced NPC should be discussed within a multidisciplinary team (MDT). Treatment of patients in high-volume facilities is recommended as this was reported as an independent prognostic factor for improved survival, at least in areas where the disease is endemic [201]. A proposed treatment algorithm for local and locoregional NPC is shown in Intensity-modulated RT (IMRT) is an important milestone in the management of NPC, providing enhanced outcomes and less severe late effects compared with previous RT techniques [conventional two-dimensional (2D) and three-dimensional (3D) by parallel improved dosimetric parameters]. Indeed, a meta-analysis showed a significant improvement in 5-year OS and 5-year local control (LC), favoring IMRT over other techniques [201].

Regarding late effects, a significant reduction in late xerostomia, trismus, and temporal lobe injury was reported in favor of IMRT compared with older RT techniques [202]. The largest Asiatic series reported that 5.1% of patients had cranial nerve palsies, 7.1% had severe hearing loss, 3% had dysphagia requiring long-term tube feeding and 0.9% had symptomatic temporal lobe necrosis (TLN) at a median follow-up of 80 months [IV, A] [203] In addition, IMRT improved QoL for long-term survivors over time compared with older techniques both in endemic and non-endemic regions[204,205] Although IMRT represents the current standard RT technique for NPC, particle therapy, including protons and carbon ions, is gaining popularity based on its physical and biological properties. In

particular to maintain a high RT dose and avoid neurological structures. Proton therapy represents a promising approach for patients with locally advanced NPC. A few small studies with a relatively short follow-up have shown a benefit in terms of clinical outcome when proton therapy was added as a boost for locally advanced disease [III, C] [206, 207,208, 209]. In particular, significantly lower rates of severe (grade 3) mucositis and salivary dysfunctions were reported in NPC patients receiving IMRT followed by proton therapy boost (55.6% of whom had T4-stage disease) compared with patients receiving a full course of IMRT only (41.2% of whom had T4-stage disease [206].

Target volume definition represents a major issue during IMRT planning for NPC, as witnessed by the need for international guidelines for appropriate target contouring [210]. Overall, RT is targeted according to the primary tumour and pathological nodes, but also to the adjacent regions considered at risk of microscopic spread from the tumour and generally to both sides of the neck (levels II-V and retropharyngeal nodes) because of the high incidence of occult neck node involvement [210]. A total dose of 70 Gy is needed for the eradication of macroscopic disease and 50- 60 Gy for the treatment of potential at-risk sites, usually by conventional or moderately accelerated RT [211]. IMRT may be applied using either a sequential boost or a simultaneous integrated boost (SIB). A recent randomised trial comparing these two techniques found no difference in terms of clinical outcome and toxicities. Due to the convenience of an SIB strategy, this approach can be considered the technique of choice for NPC treatment [212]. Recently, many trials have investigated the opportunity to reduce the extension of target volumes in order to reduce the toxicity burden. In node-negative NPC, upper versus whole-neck prophylactic RT led to a similar lower neck control rate, suggesting that a reduced nodal volume approach may be feasible [213].

When obtaining tumour shrinkage with induction chemotherapy (ICT), the strategy of planning IMRT with reduced primary gross tumour volume (GTV) based on post chemotherapy (ChT) MRI scan volumes may be adopted. This approach tested on a limited number of patients appears not to show any detrimental effect on LC and survival if the pre-induction tumour areas received at least an intermediate dose (64 Gy); an

improvement in QoL score was shown compared with the planning of GTV based on pre-ChT MRI scans [214, 215].

Planning optimisation in terms of prioritisation and dose constraints for target and radiosensitive structures is fundamental in order to avoid missing tumour coverage while maintaining organs at risk at their tolerance dose levels. International guidelines on dose prioritisation and acceptance criteria with IMRT for NPC have been recently established [210].

In most cases, conventional or moderate hypofractionation regimens are used to a total dose of 70 Gy in 33-35 fractions. A scheme used in a dose escalation trial with a total dose to macroscopic primary disease of 76 Gy is also reported [216]. However, extreme caution should be exercised when increasing the total dose due to the high risk of developing late toxicities (e.g. osteoradionecrosis, carotid pseudoaneurysm and neurological toxicities).

Stage I disease is treated by RT alone, whereas patients with stage II NPC benefit from concurrent chemoradiotherapy (CRT) with cisplatin 30 mg/m2/week when 2D-RT is used [217]; a non-significant difference in survival outcomes was shown for CRT versus RT alone when IMRT was adopted [218].

Stage III and IVA diseases are treated by CRT. The standard agent used is cisplatin [219]. This provides a benefit in terms of OS and both locoregional and distant control. The most commonly used regimen is cisplatin 100 mg/m2 every three weeks with concomitant RT [220]. Weekly cisplatin (40 mg/m2/week) has also been shown to improve OS [221]. The optimal cumulative total dose of concurrent cisplatin should be higher than 200 mg/m2 [222]. Concurrent nedaplatin was found to be non-inferior to cisplatin in one randomised trial [223]. Concurrent carboplatin is considered an available option but the evidence is conflicting [224, 225]. The addition of bevacizumab to platinum based ChT concurrently with RT showed a substantial rate of high-grade toxicities and is not recommended [226]. the role of anti-epidermal growth factor receptor (EGFR) agents (such as nimotuzumab) concurrently with RT, in addition to or instead of ChT, requires further clarification as there are no unequivocal data in this setting.

The propensity of NPC to develop distant metastases is a major cause of treatment failure and death [227]. Intensification of the systemic treatment is therefore needed for stage III-IVA non-keratinising NPC. Adjuvant ChT (AC) is generally difficult to complete, with only ~60% of patients completing the planned treatment cycles and half of patients require a dose reduction [228]. In contrast, ICT offers the possibility of delivering an adequate dose intensity of ChT. However, as a prerequisite, ICT added to CRT should not hinder the subsequent delivery of full-dose CRT, and the time between the end of ICT and the start of RT should be kept as short as possible. Recently, a phase III trial comparing ICT with cisplatin and gemcitabine followed by CRT versus CRT alone in patients with stage III/IVB (according to AJCC 7th edition) NPC showed a benefit in favour of ICT in recurrence-free survival (RFS), OS and distant RFS, with higher acute but not late toxicities [229]. Importantly, 96.7% of patients randomised to the ICT arm completed the 3 cycles of cisplatin/gemcitabine and 92% received at least 2 cycles of cisplatin 100 mg/m2 concomitantly with RT. Long-term results of a randomised trial of ICT with cisplatin and 5-fluorouracil (5-FU) followed by CRT versus CRT alone confirmed the benefit of ICT on survival outcomes and the comparable late toxicities [230]. Moreover, a recent update of an individual patient data network meta-analysis (NMA) showed that ICT with taxanes followed by concomitant CRT ranked as the best treatment in terms of OS versus concurrent CRT alone or with AC[231], Long-term data from a multicentre, randomised, factorial trial showed that shifting from the concurrent-adjuvant to the induction-concurrent sequence achieved significant improvements in PFS and marginal improvements in OS without an adverse impact on late toxicity [232].

The selection of patients to receive more ChT or immunotherapy in addition to CRT in the form of either ICT or AC is a therapeutic area that is being explored in the following randomised, controlled trials (see later for individualised risk assessment) [192].

Two NMAs have analysed the impact of different ChT regimens added to RT, although they do not include the most recent data from induction trials [233,234]. In the first NMA, AC added to CRT proved to be the best approach for all clinical endpoints except distant control, where ICT followed by CRT was superior [233]. In the second NMA, which was

limited to studies with IMRT, ICT followed by CRT was superior for all clinical endpoints except locoregional RFS, where AC achieved better results [234].

Evaluating the risk profile of each patient is a key issue. Advanced nodal and primary stage, as well as high basal EBV DNA, have been proposed as a means to select patients for ICT in order to improve the therapeutic ratio [235]. Persistent EBV DNA at 6-8 weeks after completion of RT or CRT is a negative prognostic factor that has been used as an inclusion criterion for a randomised trial of AC versus observation. No improvement in RFS or OS has been seen with adjuvant cisplatin and gemcitabine in this high-risk population; therefore, this approach is not recommended in clinical practice [236]. In case of persistent, high EBV DNA values after definitive treatment, a personalised approach with non-cross-resistant drugs or participation in a clinical trial is suggested.

Elderly patients have been under-represented in clinical trials testing the addition of ChT to RT. In the cited meta-analysis, unlike data from other non-nasopharyngeal subsites, no interaction was observed between treatment effect on OS and patient age, whereas for PFS, the benefit was dependent on the age range (HR 0.72; 95% CI 0.65-0.80 for patients <50 years and HR 0.84; 95% CI 0.70-1.01 for patients 60 years) [220]. However, as a general principle, concurrent ChT is not tolerated as well in elderly patients compared with younger patients, and consequently, it is reccomented with a reduced dose intensity for elderly patients.

2.5.2.5.2 Management of advanced/metastatic disease

Treatment of locoregional recurrences. Small local recurrences are potentially curable [237]. The main therapeutic options include nasopharyngectomy, brachytherapy, radiosurgery, stereotactic RT (SRT), IMRT or a combination of surgery and RT, with or without concurrent ChT. No comparative trials have been carried out to compare reirradiation versus a surgical approach. Treatment decisions are tailored to the specific situation of each individual case, taking into consideration the volume, location/extent of the recurrent tumour, previous treatments, disease-free interval (DFI), comorbidities and any pre-existing organ dysfunction [192].

For surgical salvage treatments, prognostic factors include T and N stage at recurrence, surgical approach (with a better outcome reported for endoscopic surgery), and feasibility of adjuvant re-irradiation [238].

Patients with local recurrences not invading the carotid artery and not extending intracranially are candidates for nasopharyngectomy; local recurrence stage rT1-rT3, might benefit more from endoscopic nasopharyngectomy than from IMRT [239].

Lymphatic recurrences in the neck can be treated with neck dissection. The extent of neck dissection depends on the nature of the recurrence (N stage and extracapsular extension) and can range from selective to radical neck dissection [192].

Pre-treatment circulating EBV DNA has been shown to be a prognostic factor for distant metastasis in candidates for surgery [240].

For re-irradiation, patient selection is crucial due to the high incidence of major late complications, even with modern RT techniques. Disease- and treatment-related prognostic factors for re-irradiated patients are: T and N stage at recurrence, tumour volume, DFI, dosimetry calculations (recurrence within the previous fields of radiation or outside), dose to target and fractionation schedule, window dose for organs at risk and RT technique (IMRT, SRT) [241,242,243}.[77-79]

Preliminary results have shown activity and limited toxicity with proton and carbon ion therapy for locally recurrent NPC [244,245].

Treatment of metastatic disease or locoregional recurrences not amenable to curative approaches. In metastatic NPC, palliative ChT should be considered for patients with an adequate PS. A treatment combination of cisplatin and gemcitabine is the first-line choice and improves OS [246]. In patients with newly diagnosed metastatic NPC, the addition of locoregional RT to systemic therapy improves locoregional control and, ultimately, OS [247].

No standard second-line treatment exists. Active agents include paclitaxel, docetaxel, 5-FU, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin, oxaliplatin and cetuximab, which can be used as single agents or in selected combinations [248]. Poly-

ChT is more active than monotherapy [overall response rate (ORR) of 64% versus 24%] at a cost of increased and cumulative toxicities. The estimated PFS and OS with second-line therapy are around 5 and 12 months, respectively [248]. In this context, treatment choice should be based on previous treatments, patient symptoms, PS, patient preference, and the expected toxicity.

Immunotherapy represents a promising strategy in this disease, especially because of the causal role of EBV and the possibility to elicit a response against its antigens. To-date, no phase III trials have been published in NPC and available evidence is derived from phase II studies, mainly with checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1), or adoptive immunotherapy. Nivolumab, pembrolizumab and camrelizumab have been shown to be safe and active as monotherapy for recurrent and/or metastatic NPC, with ORRs of 20%, 25% and 34%, respectively, with most of the best responses occurring at first radiological evaluation. However, their therapeutic positioning is still to be defined [249,250,251]. Cytotoxic T-cell lymphocyte (CTL) adoptive immunotherapy has demonstrated activity in highly pretreated patients [252,253]. Oligometastatic patients may achieve long-term survival after aggressive treatment, including ChT, surgery or definitive RT to the metastases [254,255]

Pre-treatment plasma EBV DNA and clearance rates are prognostic factors in metastatic patients treated with firstline ChT [256].

2.5.2.5.3 Treatment Recommendations according to ESMO

1. The optimal treatment strategy for patients with advanced NPC should be discussed in an MDT. Patients should be treated at high-volume facilities.
2. IMRT is the mainstay of treatment.
3. Overall, RT is targeted according to the primary tumour, pathological nodes and adjacent regions considered at risk of microscopic spread from the tumour, and generally to both sides of the neck (levels II-V and retropharyngeal nodes).

4. A total dose of 70 Gy is needed for the eradication of macroscopic disease and 50-60 Gy for the treatment of potential at-risk sites.
5. Planning optimisation in terms of prioritisation and dose constraints for target and radiosensitive structures is fundamental.
6. Stage I-II disease is treated by RT alone; for stage II disease, this approach is only used when IMRT is adopted.
7. Stage III and IVA disease are treated by CRT . The standard agent used is cisplatin.
8. The most commonly used regimen is cisplatin 100 mg/m2 every 3 weeks concomitantly to RT. Weekly cisplatin (40 mg/m2/week) has also been shown to improve OS [II, A]. The optimal cumulative total dose of concurrent cisplatin should be higher than 200 mg/m2.
9. Concurrent nedaplatin was found to be non-inferior to concurrent cisplatin.
10. Concurrent carboplatin is an available option but the evidence is conflicting.
11. Intensification of the systemic treatment is needed for stage III-IVA non-keratinising NPC.
12. ICT with cisplatin and gemcitabine followed by CRT for locally advanced NPC is associated with a benefit in RFS, OS and distant RFS, with more acute but not late toxicities versus CRT alone.
13. The selection of patients to receive more ChT in addition to CRT in the form of either ICT or AC is a therapeutic area that is being explored in ongoing randomised, controlled trials.
14. In cases of persistent, high EBV DNA values after definitive treatment, a personalised approach with non-cross resistant drugs or participation in a clinical trial is suggested.
15. Small, local recurrences are potentially curable. The main therapeutic options include nasopharyngectomy, brachytherapy, radiosurgery, SRT, IMRT or a combination of surgery and RT, with or without concurrent ChT.
16. Patients with local recurrences not invading the carotid artery or extending intracranially are candidates for nasopharyngectomy; local recurrence stage rT1-rT3 might benefit more from endoscopic nasopharyngectomy than IMRT.

17. Lymphatic recurrences in the neck can be treated with neck dissection.
18. In metastatic NPC, palliative ChT should be considered for patients with an adequate PS. A treatment combination of cisplatin and gemcitabine is the first-line choice and improves OS.
19. In patients with newly diagnosed, metastatic NPC, the addition of locoregional RT to systemic therapy improves locoregional control and ultimately OS.
20. No standard second-line treatment exists. Active agents include paclitaxel, docetaxel, 5-FU, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin, oxaliplatin and cetuximab, which can be used as single agents or in selected combinations.
21. Immunotherapy represents a promising strategy in this setting but its therapeutic positioning is still to be defined.
22. CTL adoptive immunotherapy has demonstrated activity in highly pre-treated patients.
23. Oligometastatic patients may achieve long-term survival after aggressive treatment, including ChT, surgery or definitive RT to the metastases.

2.5.2.5.4 Management Metastatic disease or locoregional recurrences

Treatment of locoregional recurrences. Small local recurrences are potentially curable [159]. The main therapeutic options include nasopharyngoscopy, brachytherapy, radiosurgery, stereotactic RT (SRT), IMRT, or a combination of surgery and RT, with or without concurrent ChT. No comparative trials have been carried out to compare reirradiation versus a surgical approach. Treatment decisions are tailored to the specific situation of each individual case, taking into consideration the volume, location/extent of the recurrent tumor, previous treatments, disease-free interval (DFI), comorbidities, and any pre-existing organ dysfunction.

For surgical salvage treatments, prognostic factors include T and N stage at recurrence, surgical approach (with a better outcome reported for endoscopic surgery), and feasibility of adjuvant re-irradiation [165]. Patients with local recurrences not invading the carotid artery and not extending intracranially are candidates for nasopharyngectomy; local recurrence stage rT1-rT3, might benefit more from endoscopic nasopharyngectomy than from IMRT [258].

Lymphatic recurrences in the neck can be treated with neck dissection. The extent of neck dissection depends on the nature of the recurrence (N stage and extracapsular extension) and can range from selective to radical neck dissection. Pre-treatment circulating EBV DNA has been shown to be a prognostic factor for distant metastasis in candidates for surgery [162].

For re-irradiation, patient selection is crucial due to the high incidence of major late complications, even with modern RT techniques. Disease- and treatment-related prognostic factors for re-irradiated patients are: T and N stage at recurrence, tumor volume, DFI, dosimetry calculations (recurrence within the previous fields of radiation or outside), dose to target and fractionation schedule, window dose for organs at risk and RT technique (IMRT, SRT) [163, 164,165].

Treatment of metastatic disease or locoregional recurrences not amenable to curative approaches. In metastatic NPC, palliative ChT should be considered for patients with an adequate PS. A treatment combination of cisplatin and gemcitabine is the first-line choice and improves OS [259]. In patients with newly diagnosed metastatic NPC, the addition of locoregional RT to systemic therapy improves locoregional control and, ultimately, OS [260]. No standard second-line treatment exists. The estimated PFS and OS with second-line therapy are around 5 and 12 months, respectively [261]. In this context, treatment choice should be based on previous treatments, patient symptoms, PS, patient preference, and the expected toxicity.

Immunotherapy represents a promising strategy in this disease, especially because of the causal role of EBV and the possibility to elicit a response against its antigens. Oligometastatic patients may achieve long-term survival after aggressive treatment, including ChT, surgery, or definitive RT to the metastases Pre-treatment plasma EBV

DNA and clearance rates are prognostic factors in metastatic patients treated with first-line ChT [192].

2.5.3 Salivary gland cancer, diagnosis, treatment, and follow-up

2.5.3.1 Incidence and Epidemiology

Major salivary gland cancers (SGCs) comprise 5% of head and neck cancers in Europe. The worldwide crude and age adjusted incidence rates are 0.69 and 0.57 cases per 100,000 people per year, respectively, with 53,583 new patients in 2020. In Europe, crude and age-adjusted incidence rates are 1.3 and 0.67 cases per 100,000 people per year, respectively, with 9917 new patients in 2020[166]. Data for minor SGCs are limited, but the RARECARENet project estimated the crude incidence of minor salivary gland-type cancers of the head and neck to be 0.4 cases per 100 000 people in the 2000-2007 diagnosis period; minor SGCs have a slight predominance in males and the incidence is highest in the elderly (>65 years) [257]. History of head and neck cancer and cervicofacial radiotherapy (RT) have both been associated with an increased risk of major SGC [odds ratio (OR) 17.06, 95% confidence interval (CI) 4.34-67.05 and OR 31.74, 95% CI 2.48-405.25, respectively] [258.259]. Industries such as cereal and other crop production, furniture manufacturing, interurban road transport, and industrial cleaning have also been associated with an increased risk of major SGC [258.259,260]

Smoking only seems to increase the risk of developing major SGCs other than mucoepidermoid carcinoma (MEC) (OR 5.15, 95% CI 2.06- 12.87) [261]; however, ionizing radiation is the only well-established risk factor [262,263] . SGCs include >20 distinct histological subtypes. Given their rarity and heterogeneity, population-based epidemiological studies providing incidence rates according to histology are limited. SGC typically occurs in the sixth and seventh decades of life and has a male predominance [257]; however, age at diagnosis and gender predominance vary by histology. MEC, adenoid cystic carcinoma (AdCC), and acinic cell carcinoma (ACC) tend to occur at an earlier age than adenocarcinoma and squamous cell carcinoma (SCC). MEC, AdCC and

AcCC are more common in females up to ~50 years of age; however, incidence of AdCC and AcCC is similar for females and males at older ages, whereas MEC has a higher incidence rate among older males [262]. The ratio of tumour diagnoses in parotid, submandibular, minor and sublingual subsites is 100:10:10:1, and the proportion of malignant tumours at these sites is 20%, 50%, 50% and 80%, respectively [265]. SGC incidence has not increased between 1995 and 2007 in Europe[10] or between 1995 and 2010 in the United States [262]. The 5-year relative survival rate (estimated as the ratio of observed to expected survival in the general population, matched by age, sex, calendar year and geographical area) for patients with major SGC is 63% (95% CI 62% to 63.7%) in Europe [91]. This decreases with age, from ~90% (95% CI 91% to 97%) in patients aged <25 years, to 70% (95% CI 69% to 71%) in patients aged 25-64 years and 53% (95% CI 52% to 55%) in those aged >65 years. Five-year relative survival is higher in females (72%, 95% CI 71% to 74%) than in males (55%, 95% CI 54% to 56%). Furthermore, 5-year relative survival differs across European regions, with the highest rate of 74% (95% CI 71% to 78%) reported in Nordic countries (Finland, Iceland, Norway) and the lowest rate of 52% (95% CI 50% to 54%) reported in Eastern European countries (Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Poland, Slovakia). SGC relative survival has not improved in Europe between 1999 and 2007[257]. The 5-year relative survival rate for minor salivary gland-type cancers of the head and neck is 67% and is higher in females than in males. Five-year survival rates are highest in children (>90%) and patients aged <25 years and then decrease to 60% in patients aged >65 years. In Europe during the period 1999-2007, 5-year survival remained stable and was highest in Nordic countries (84%) and lowest in Eastern European countries (55%) [257].

2.5.3.2 Diagnosis, Pathology and Molecular Biology

SGC should be classified according to the World Health Organization (WHO) Classification of Head and Neck Tumours [176]. Including both benign and malignant tumours, there are over 30 distinct salivary gland tumour types in the latest WHO classification system.

Diagnostic work-up. The symptoms of SGC depend on tumour location. Symptoms that should prompt consideration of SGC include pain in the face or mouth, an externally or submucosally growing lump, or (facial) nerve paralysis.

Cytology or histology. Cytology or histology is mandatory. Ultrasound-guided salivary gland fine-needle aspiration (FNA) cytology has become the accepted minimally invasive method for evaluating parotid and submandibular gland tumours preoperatively. This can distinguish malignant from benign disease in 90% of cases if examined by a pathologist experienced in salivary gland disease [265]. The Milan system for reporting salivary gland cytopathology is recommended. It facilitates standardized reporting and links each diagnostic category to a risk of malignancy (ROM); risks were recently confirmed in a large meta-analysis [266].

If FNA is non-diagnostic or if the clinical situation requires more information on histotype, core needle biopsy, while more demanding and with a slightly increased risk of complications,[267] has less inadequate sampling (risk ratio 0.85) and a higher diagnostic yield than FNA [268]. It is thus an accepted next step in the diagnostic work-up[269]. Open biopsies should be avoided in major salivary gland lesions due to the risk of complicating definitive surgical treatment and the risk of spillage, with the exception of skin ulcerating tumours. For minor salivary gland tumours, an experienced surgeon should take a biopsy of the tumour and surrounding stroma [270]. Incisional biopsy is recommended for submucosally extending tumours, and an incisional or forceps biopsy should be taken for ulcerating lesions. Ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and FDG-PET are the imaging techniques most commonly used to assess lesions in the major salivary glands, with MRI being the preferred modality.

2.5.2.2.3 Histological tumour type and molecular biology

The SGC histological type essentially defines its biological behaviour, which influences prognosis and patterns of recurrence, and thus clinical management. Some SGC types, such as basal cell adenocarcinoma, low grade MEC, intraductal carcinoma and conventional AcCC, are indolent, with high risk of locoregional recurrence but low rates

of nodal involvement and distant metastases [271]. Immunohistochemistry (IHC) on the surgical specimen provides supplementary visualisation of cell compartments and cell populations, thus improving SGC taxonomy. The role of molecular diagnostics in SGC is evolving. Many monomorphic SGCs are now known to harbour defining balanced translocations, some of which are readily evaluable on paraffin-embedded materials either by FISH, RT-PCR or next-generation sequencing (NGS)[272]. Recently, NGS has provided significant input on the molecular characterisation of SGC subtypes, improving diagnostic differentiation between morphologically similar tumour types and also identifying novel driver pathways that determine tumour biology and which may be amenable to targeted therapy.

Clinical classification [cTNM (clinical tumor-node-metastasis)] should be carried out before treatment by the referring physician during initial patient evaluation using the Union for International Cancer Control (UICC) TNM eighth edition staging classification [108].[1] Preoperative diagnostics are mainly based on imaging methods and pathological findings, especially FNA. Pathological staging is carried out after surgical resection of the primary tumour. There is currently no clear recommendation on the differential staging of intra-parotid versus cervical nodal metastases; findings from a recent study suggest that these differences should be addressed in future editions of the TNM classification [273].

Pathological report and staging. For correct management of major SGC, the pathological report should follow the International Collaboration on Cancer Reporting guidelines [274]. Operative procedure; specimens submitted; tumour site, focality and dimensions; histological tumour type and grade; perineural invasion; lymphovascular invasion; extent of invasion and margin status are required [275] Minor SGCs are staged similarly to SCC, according to the site in which they arise (e.g. oral cavity, pharynx, sinuses, etc.).

2.5.3 Treatment

2.5.3.1 Management of Local and Locoregional Disease

Management of Local and Locoregional Disease. SGCs are a rare and complicated subgroup of head and neck cancers. As such, local/locoregional disease should be managed by expert surgeons, radiation oncologists, medical oncologists and other specialists working as a multidisciplinary team in specialised head and neck units, such as the centres that are designated members of the European Reference Network on Rare Adult Solid Cancers [276].

2.6.3.1.1 Surgery

Surgical management of the primary in parotid gland cancer. The treatment of parotid gland cancer is based on complete surgical excision with free margins [277]. The difficulty of this surgery lies in achieving free margins without functional and aesthetic sequelae. Revision surgery following an unexpected post-operative diagnosis of malignancy carries a great risk to an already dissected facial nerve; therefore, every effort should be made to identify malignancy preoperatively, allowing for immediate surgical removal [278]. It is imperative, if preoperative MRI, FNA or core needle biopsy suggests malignancy, to warn the patient of a possibly more extensive procedure. In case of extra parotid or facial nerve extension, an extended surgery sacrificing these elements [e.g. seventh nerve (nVII), infratemporal fossa, mandible, skin] with possible reconstruction must be considered. Functional or aesthetic disorders arising from resection should be considered during treatment planning [275]. Resectability should be assessed in a multidisciplinary team meeting, bearing in mind that surgery, if possible, is the optimal treatment. A cancer should be considered unresectable if macroscopic tumour is likely to be left behind.

The reference procedure is a total parotidectomy. For low-grade, early-stage (cT1-T2N0) tumours in the superficial lobe, a superficial parotidectomy can suffice, especially if malignancy is a post-operative discovery on the definitive histology. For advanced-stage (all but cT1-T2N0) and/or preoperatively known intermediate- or high-grade tumours, a

total parotidectomy is preferable. No consensus exists in the literature on how many millimetres thick a margin must be to be considered ‘free’ [276].

The presence or absence of facial nerve paralysis before surgery influences the choice of procedure: it is logical to try to preserve the facial nerve if there is no preoperative paralysis and to sacrifice it in case of preoperative paralysis [275]. In the absence of preoperative paralysis and in case of intra-operative macroscopic invasion of the facial nerve, sacrifice or preservation of the nerve is decided on a case by-case basis, depending on the histology of the tumour and extent of invasion of the nerve, as well as the age and wishes of the patient. It is important to collect as much information as possible about the tumour before surgery, discuss scenarios with the patient and be able to do a graft during the ablative procedure. A remote dissection of the nerve branches with an extended resection and frozen section analysis of the nerve section limits may be necessary, especially in AdCC, which is characterised by tumour extensions along and in nerves [278]. Preoperative facial paralysis is a major negative prognostic factor.[24] It imposes a wide surgery with often unsatisfactory excisional limits. Addressing the nerve deficit during resection is the appropriate therapeutic approach [275,279].

Surgical management of the primary in minor SGC and cancer of the sublingual gland. Minor SGC, a rare entity, may arise in all mucous membranes of the head and neck (including the nasal cavity, nasopharynx, oropharynx, hypopharynx, cervical oesophagus, larynx, trachea and oral cavity). Cancer of the sublingual gland is 10 times less frequent than minor SGC [264].

Surgery is the mainstay of treatment for primary resectable disease with the traditional open approach being the most widely used, although endoscopic and robot-assisted approaches have recently been described [280]. In a series of 450 patients with minor SGC, multivariate analysis showed advanced clinical stage and unfavourable histological subtype to be associated with poor disease-specific survival [281]. This was confirmed in a large Surveillance, Epidemiology and End Results (SEER) database study of 1426 patients with minor SGC of the oropharynx [282]. It is generally accepted that a 1-cm free margin is adequate in most tumours; however, it is often the case that only millimetric margins are achievable. AdCC is particularly known for perineural spread (as described

earlier), requiring detailed surgical planning and wide margins, including resection of bony structures [275]

Surgical management of the primary in submandibular gland cancer. The most common submandibular gland malignant tumour type is AdCC [283,284]. Tumours confined within the submandibular gland require resection of the gland and the surrounding level Ib lymph nodes to ensure negative margins. In case of high-grade malignancy without clinical evidence of cervical lymph node involvement, selective neck dissection involving level I, II and III lymph nodes is standard procedure as the prevalence of cervical lymph node metastasis in submandibular gland malignancies is high, exceeding that of the parotid malignancies [275,284,285]. Careful surgical planning is needed for AdCC, as clear margin surgery may require resection of important structures such as the lingual, hypoglossal and marginal mandibular nerves, floor of the mouth muscles and the skin. Although the risk of nodal metastasis in AdCC is low, this tumour has a propensity for infiltrating the adjacent lymph nodes and perineural spread [275, 283, 284, 287]. While it can be difficult to distinguish between direct invasion and embolic lymph node metastasis, some studies have identified a higher nodal spread than expected [288]. Elective Neck Dissection (END) for submandibular gland malignancies should be planned based on cytological and radiological findings. Whenever malignancy is suspected, frozen section analysis can dictate extension of surgery locally and to involve at least level Ib but most frequently level I, II and III lymph nodes [284].

Management of the cND neck in salivary gland malignancies. The reported incidence of positive neck nodes in parotid carcinomas varies between 10% and 40% and they occur more frequently in patients with high-grade malignancy, advanced T status, facial nerve involvement and extraglandular invasion[288, 289].The most frequently involved lymph node levels are II, III and IV[290]; however, involvement of levels I and V is also non-negligible[287, 291].When carrying out therapeutic neck dissection for clinically or radiologically positive lymph nodes (cNþ), the recommendation is to carry out a comprehensive neck dissection of levels I-V [287, 291].

The incidence of lymph node metastasis for submandibular carcinomas at initial presentation is around 8%-33% [292]. Positive lymph nodes are often found in level I

followed by levels II and III, although all lymph nodes can be involved with the possibility for skip metastases in levels IV and V. Some series have even shown positive lymph node involvement of 40% and 25% in levels IV and V, respectively, warranting a level I-V neck dissection for submandibular gland carcinomas with cNþ disease [283].

For minor SGC, the same applies, but depending on the origin of the primary, lymph nodes outside the neck may be involved that are relatively inaccessible for surgery, such as retropharyngeal or mediastinal nodes.

END for the cN0 neck in parotid gland carcinoma. In a cN0 neck parotid gland carcinoma with clinical and histopathological factors indicating a 15%-20% chance of occult regional metastasis, END is strongly recommended. Clinical prognostic factors for pathologically positive lymph nodes (pNþ) are age >54 years, pain, nVII dysfunction and >T2 status[293, 294].A study using END in T1-T2 N0 patients reported a cN0 pNþ rate of 17%.[43] Histopathological factors (that unfortunately only become clear once the primary is resected) include histological type, intermediate- or high grade tumor, extra glandular soft tissue invasion, and lymphatic invasion[292, 294,296,297].Histological types with a high prevalence (>50%) of cN0 pNþ disease are salivary duct carcinoma, undifferentiated carcinoma, adenocarcinoma NOS, high-grade MEC, SCC and high-grade transformed AdCC [288,292].AcCC and low-grade MEC were previously considered to have low pNþ rates but routine ENDs have revealed higher than expected rates, especially for high-grade AcCC [288, 290, 291, 295 ,296, 298].Regarding the best treatment strategy, some clinicians use END followed by postoperative RT, while others prefer to use elective neck irradiation (ENI) (see RT section)[289, 297, 299, 301].

Some clinicians propose a routine END for every patient with suspected or known parotid gland cancer; reported rates of cN0 pNþ range from 22% to 45% in series where all patients underwent END[288, 295, 302, 303].The lymph node levels to address are II, III and IV[291, 292]. A significant proportion (53%- 80%) of patients with pNþ disease on neck dissection will also have metastatic deposits in the ‘first echelon’ intraparotid lymph nodes (see earlier Surgical management of the primary in parotid gland cancer section) [275, 292, 302, 304].In one study, 1-11 parotid lymph nodes were retrieved, with 80% of parotid nodes involved in cN0 pNþ patients[290].There is still no direct evidence that

resection of these nodes increases locoregional control. Taken together, three scenarios exist:

1. Low risk of occult nodal disease (T1-T2 tumours, low-grade tumours, young patients)

- After resection of the primary, a watch-and-wait policy to the neck can be defended [291]
- Most clinicians will carry out a level II dissection with frozen section, converting into a comprehensive neck dissection in the rare pNþ cases [275], but leaving the neck untreated if pN0.
- Systematic END [288, 290, 295, 302, 303].

2. Risk factors for cN0 pNþ discovered at the histology of parotidectomy

- ENI is recommended [291, 301].

3. High risk of occult nodal disease preoperatively

- END (levels II, III and IV) and post-operative neck RT based on pathology. Level I (anteriorly located primary) and level V (large tumour located in the parotid tail with increased risk of spread to level V) dissection on indication [289,297],
- ENI, especially if adjuvant RT for the primary tumour is already likely [291, 300, 301].
- Level II dissection, extended to a comprehensive neck dissection if cN0 pNþ on frozen section. If no pNþ, ENI to the neck follows the findings in the pathology report of the resected primary [275].

END for the cN0 neck in minor SGC. For minor SGC, when the neck is surgically entered as an approach to the primary, it is logical to also address the neck surgically. The occult metastatic rate for laryngeal, sinonasal, external acoustic meatus and lacrimal gland origin is too low to justify END. In oral cavity (levels I, II, III and IV) and oropharyngeal (levels II, III and IV) minor SGC, and in high-grade MEC and AdCC, the occult rates largely exceed 20% and END is indicated [305, 306]. END is frequently advocated for all high-stage and high-grade tumours. In a recent French study, however, no benefit in terms of event-free survival was demonstrated when comparing patients with cN0 AdCC

undergoing END with those who did not, except when the site of origin was the oral cavity. In this series, the majority (58%) of 322 cases were of minor salivary gland origin[307] In a large series of 3005 patients with MEC of the oral cavity and oropharynx, END was associated with a survival benefit for patients with high-grade and clinical stage T3-4 disease[308].

END for the cN0 neck in submandibular gland carcinoma. For preoperatively known submandibular gland cancers with otherwise cN0 neck, inclusion of the submandibular gland in a selective neck dissection (levels I, II and III) is considered the standard procedure, revealing occult metastasis rates of 21%-23% [285, 309]. For completely intraglandular tumours, if preoperatively certain to not be high grade, resection of the gland and the surrounding level Ib lymph nodes may suffice [284],

2. 5.3.1.2 Radiotherapy

2.5.3.1.2 1 Post-operative RT for SGC

Post-operative RT for SGC. Historically, SGCs were considered radioresistant. There are no randomised studies comparing surgery alone versus surgery combined with post-operative RT. Nevertheless, many retrospective studies have reported beneficial outcomes with a combined approach in patients with advanced disease and negative prognostic factors for locoregional control.

Based on literature using matched pair analysis or large retrospective cohort studies, post-operative RT at the primary tumour region is recommended in case of T3-T4 disease, high/intermediate-grade disease, close or incomplete resection margins and/or perineural growth.[45,58] The use of intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) is recommended. For parotid gland cancer invading the deep lobe, the infratemporal fossa and the parapharyngeal space should be included in the field. After incomplete resection, a dose of 33 x 2 Gy is described for the primary tumour region

plus a 1 cm margin, with 30 x 2 Gy after a clear resection.[45,58] In case of extensive perineural invasion the nerve pathway to the base of the skull should be delineated [311].

Indications for ENI (25 x 2 Gy over 5 weeks) are the same as the indications for END. In general, ENI is indicated in case of T3-T4 cN0 tumours and high- or intermediate-grade subtypes, and also depends on the primary site [310]. The ipsilateral neck node levels II and III should be treated in parotid gland tumours and ipsilateral levels I, II and III in submandibular gland tumours. Bilateral ENI is indicated for tumours crossing the midline. For minor SGC, the highest risk for subclinical neck disease is a pharyngeal location, high-grade disease and T3-T4 tumours. Ipsilateral ENI is recommended for levels I, II and III.

Post-operative RT is indicated for all cases of pNþ neck. A dose of 30 x 2 Gy is recommended for the involved level, and 33 x 2 Gy in case of extranodal disease. For the ipsilateral elective levels I-V, a dose of 25 x 2 Gy is recommended [310].

2.5.3.1.2.2 Combining post-operative RT with Chemotherapy

Combining post-operative RT with chemotherapy. There are no large studies that have analysed the role of combined chemotherapy (ChT) and RT in the post-operative setting in SGC. In the phase II Radiation Therapy Oncology Group (RTOG) 1008 study (NCT01220583) both scenarios are being compared, but no results are available yet.

Combining post-operative ChT with RT in major SGC has been evaluated retrospectively using data from the US National Cancer Database. The addition of ChT was restricted to late-stage tumours with adverse features and did not result in a survival benefit [312].The level of evidence for combining ChT with RT is low, and this treatment is not recommended outside of a clinical study.

2.5.3.1.2.3 Primary RT for unresectable SGC

Primary RT for unresectable SGC. There are no large studies that have analysed the role of combined chemotherapy (ChT) and RT in the post-operative setting in SGC.

The primary treatment for SGC without distant metastasis is surgery with postoperative RT when indicated; however, curative primary RT is indicated for patients with functionally unresectable disease or who are unsuitable for surgery due to comorbidities.

Taking locoregional control, survival and complications into account, the treatment options are photon treatmentor particle treatment with protons, neutrons or carbon ions (C12). In most institutes, primary photon therapy up to 70 Gy is still applied. Particle treatment, particularly C12 and especially for AdCC and tumours involving the base of

the skull, may be an alternative with a potentially higher locoregional cure rate compared with photons; however, these treatment options have limited availability.

No randomised studies have been carried out to compare primary treatment with chemoradiotherapy versus RT alone. Most published studies report small series with different histological subtypes, using a variety of ChT regimens [313].

There is currently no evidence to support the combination of particle therapy and simultaneous ChT in SGC [314].

2.5.3.2 Management of Locally Recurrent and Metastatic Disease

2.5.3.2.1 RT for recurrent disease

RT for recurrent disease. Local recurrence within the highdose area following initial RT remains a challenge. When surgery is not an option, systemic treatments (either ChT or targeted agents) offer limited benefit with very moderate overall response rates and are, therefore, rarely successful in alleviating local symptoms. Before the introduction of particle therapy, re-irradiation with photons was used with utmost caution, especially in anatomically challenging sites. Meanwhile, three groups have shared their experience of

reirradiation using scanned C12 in SGC, [315,316] reporting 1-year and 2-year overall survival (OS) rates of up to 90% and 64%, respectively, although late toxicities were observed. Based on these studies, re-irradiation with C12 appears feasible with response rates of around 60% and moderate toxicities in heavily pre-treated patients; however, C12 has limited availability in Europe. Protons are becoming more widely available, but evidence is lacking to support the added value. Further dose escalation should be employed cautiously. There is no evidence to support the combination of re-irradiation and ChT for primary treatment of SGC.

2.5.3.2.3 RT for palliation.

RT for palliation. the RTOG 8502 study, an RT regimen of 4 x 3.7 Gy over 2 days was repeated in cycles of 4 weeks. Seven out of 75 patients had salivary gland histology. Palliative response was observed in 65% of patients, significantly correlating with the number of cycles [317]. For palliative RT of head and neck cancer, the 'Christie scheme' (16 x 3.125 Gy over 4 weeks) resulted in a 45% complete response rate and 28% partial response rate [318]. This schedule may also be considered in patients with metastatic SGC with a relatively long-life expectancy. For patients with AdCC or AcCC and a WHO performance status score of 0-1, an even more prolonged RT schedule for palliation of locoregional disease or symptomatic distant metastases might be considered. Nevertheless, in case of short life expectancy or a WHO performance status of 2-3, a short fractionation schedule is usually preferred.

2.5.3.3 Oligometastatic disease

Oligometastatic disease. For oligometastatic disease, locoregional treatments such as surgery [319, 320, 321], radiofrequency ablation [322] or stereotactic RT75 can be considered in selected cases, especially in AdCC. In one study, a prolonged disease-free

interval (>36 months) and radical resection were the main prognostic factors in 109 patients with AdCC and lung metastases who underwent metastasectomy [319].

2.5.3.4 Systemic treatment for recurrent and/or metastatic disease

Systemic treatment for recurrent and/or metastatic disease. In the case of R/M disease, systemic treatment is challenging but can be urgent, depending on tumor subtype and behavior. For all types of SGC with distant metastases (71% of patients will present or develop R/M disease), the median OS is 15 months, and 1-, 3- and 5-year OS rates are 54.5%, 28.4%, and 14.8%, respectively [323] This, however, varies widely between subtypes.

Mucoepidermoid Carcinoma (MEC). The reported risk of distant metastasis in MEC is 16% at 10 years [324]. In R/M MEC, responses with cisplatin alone or in combination with other agents [e.g., cisplatin-adriamycin-cyclophosphamide (CAP) or cisplatine-gemcitabine] and paclitaxel as monotherapy have been observed in small patient cohorts (three responses on paclitaxel monotherapy in 14 patients in the largest MEC cohort) [325]. The CRTC1-MAML2 gene fusion, which is commonly present in MECs, causes up-regulation of the epidermal growth factor receptor (EGFR) ligand amphiregulin,[326] suggesting a potential role for EGFR inhibitors. Reports of clinical benefit with an EGFR inhibitor in patients with MEC are, however, anecdotal and require further investigation.

Adenoid Cystic Carcinoma (AdCC). To date, no systemic treatment has been shown to improve OS in patients with R/M AdCC. Metastatic AdCC is generally characterized by multiple locoregional recurrences accompanied by distant metastases in about half of the cases. The lung is the most common site of distant spread, followed by the lymph nodes, bone, liver, etc. Despite these characteristics, survival of patients with R/M AdCC is generally prolonged, with an OS rate of 40% at ten years [317]. In this context, active surveillance could be a rational proposal in highly selected patients (asymptomatic, low tumour burden, lung metastases and stable disease). Lung metastasectomy should be considered in patients without other R/M tumour deposits, provided that a complete surgical resection is feasible and disease-free interval from primary diagnosis is >36

months [317]. Systemic treatment should be reserved for patients with progressive and/or symptomatic disease that is not otherwise manageable. Strategies focused on pathogenetic targets seem more promising.

Polymorphous adenocarcinoma. The prognosis of patients with polymorphous adenocarcinoma is generally good and distant metastases are rare, reported in only 4.3% of patients at presentation [289] No data on ChT or targeted therapy are available.

Adenocarcinoma NOS. CAP, paclitaxel monotherapy, and gemcitabine or vinorelbine in combination with cisplatin have led to limited response rates in adenocarcinoma NOS. If the tumor is androgen receptor-positive and/or has HER2 amplification, it is most likely a salivary duct carcinoma and must be treated in the same way as salivary duct carcinoma (see below) [327].

Salivary duct carcinoma. Fifty-four percent of patients with salivary duct carcinoma treated with curative intent will develop locoregional recurrences and/or distant metastases. In patients with distant metastases, spread to lungs (54%) and bones (46%) has been reported most frequently, but a high rate of brain metastasis has also been observed (18%) [328]. Given the dismal prognosis and high prevalence of distant metastasis (also in case of local or locoregional recurrence), systemic therapy is often required. The median OS for patients with R/M disease receiving the best supportive care is only five months [329]. Agents targeting androgen receptors and/or HER2 are promising and are the best-studied therapies in patients with salivary duct carcinoma.

Androgen deprivation therapy (ADT) may also be beneficial in the adjuvant setting. Based on retrospective data, adjuvant ADT results in significantly improved 3-year disease-free survival in patients with stage IVa androgen receptor-positive salivary duct carcinoma [48.2% (95% CI 14.0% to 82.4%) versus 27.7% (95% CI 18.5% to 36.9%) in the control group, which did not receive adjuvant ADT] [330].

In HER2-positive salivary duct carcinoma, trastuzumab combined with taxane-based ChT is the best-studied regimen, with an overall response rate of 70.2% (95% CI 56.6% to 81.6%) and median OS of 39.7 months (95% CI not reached) reported for trastuzumab-docetaxel in 57 patients with salivary duct carcinoma [330]. This combination could

potentially be amplified with the addition of another agent targeting HER2 (e.g. pertuzumab, lapatinib) or, after progressive disease, replacement of trastuzumab with the antibody-drug conjugate trastuzumab-emtansine (T-DM1). In analogy with the positive results achieved in HER2-positive breast cancer by adding pertuzumab to docetaxel-trastuzumab and the cases reported for this combination in salivary duct carcinoma, this triple combination deserves pursuit in clinical studies in salivary duct carcinoma. The most frequently used ChT regimen in R/M salivary duct carcinoma is carboplatin-paclitaxel [325]. Although 30%- 60% of salivary duct carcinomas demonstrate IHC positivity for programmed death-ligand 1, no phase II data with immune checkpoint inhibitors are available [331].

Secretory carcinoma. The body of evidence for the efficacy of tropomyosin receptor kinase (TRK) inhibitors (e.g. larotrectinib, entrectinib, repotrectinib, LOXO-195) in patients with secretory carcinoma and NTRK gene fusions is expanding [332]. A recent phase II trial evaluating the efficacy of larotrectinib in NTRK fusion-positive patients included 12 patients with secretory carcinoma and reported a response rate of 75%. Median PFS was not reached after a median follow-up of 9.9 months [335]. Responses in patients with secretory carcinoma have also been observed with entrectinib and repotrectinib [333, 334].

Other SGC subtypes. For some histological subtypes, little or no clinical evidence is available to make hard recommendations for additional IHC staining or molecular evaluation to identify therapeutic targets. For these subtypes, IHC staining for androgen receptors and evaluation of HER2 expression, preferably by IHC staining and FISH, are advocated. Besides this, the use of an NGS panel, which includes frequently affected genes in other cancers that are currently targetable with anticancer drugs (e.g. PIK3CA, BRAF, NRAS, MET), is suggested. Regarding gene fusions, which are often not present in commercially available panels, it is important to test specifically for NTRK gene fusions, as these have great implications for individual patients [276].

2.5.3.12 Treatment Recommendation According to ESMO

1. ***Surgical management of the primary: parotid gland cancer***

   - The reference procedure is total parotidectomy.
   - For low-grade tumours, especially post-operatively discovered, a superficial parotidectomy can be considered sufficient,
   - If the nVII is not infiltrated or grossly encased by tumour, the nerve should be preserved.
   - A preoperatively paralysed nVII requires nVII resection and primary reconstruction and/or reanimation procedures.
   - It is important to collect as much information as possible about the tumour before surgery, discuss scenarios with the patient and be able to do a graft during the ablative procedure.

2. ***Surgical management of the primary: submandibular gland cancer***

   - Malignant tumours confined within the submandibular gland require at least resection of the gland and the surrounding level Ib lymph nodes.
   - In case of high-grade malignancy without clinical evidence of cervical lymph node involvement, including the gland in a selective neck dissection involving levels I, II and III is indicated.

3. ***Surgical management of the cND neck in SGC***

   - Patients with positive lymph nodes (clinical or radiological) should undergo a comprehensive lymph node dissection involving levels I-V.

4. ***Surgical management of the cN0 neck in parotid gland cancer***

- Patients at low risk for cN0 pNþ before surgery (T1-T2, low grade, <54 years of age) have three options: (i) watch-and-wait; (ii) selective level II dissection (followed by watch-and-wait if pN0 or extend neck dissection to levels I-V if pNþ); (iii) END to levels II, III and IV.
- Patients with risk factors for cN0 pNþ discovered postoperatively should undergo ENI (cN0 at least levels II and III unilaterally; pNþ levels I-V).
- Patients at high risk for cN0 pNþ (T3-T4, high grade, >54 years of age) have three options: (i) selective level II dissection (followed by watch-and-wait if pN0 or extend neck dissection to levels I-V if pNþ); (ii) END to levels II, III and IV (followed by watch-and-wait if pN0 or RT to levels I-V if pNþ); (iii) ENI to levels I-V.

5. Surgical management of the cN0 neck in minor SGC

- As a general rule, END should be carried out when the neck is entered as an approach to the primary or for reconstruction.
- In tumours of laryngeal, sinonasal, external acoustic meatus and lacrimal gland origin, pNþ rates are too low to justify END.
- For oral cavity, oropharynx, T3-T4 and high-grade tumours, END or ENI should be carried out. Levels depend on tumour location and are comparable with treatment for cN0 head and neck SCC.

6. Surgical management of the cN0 neck in submandibular gland cancer

- Including the gland in a selective neck dissection involving levels I, II and III is indicated, unless the tumour is intraglandular and if low-grade histology is proven (in which case resection of the gland and level Ib lymph nodes may suffice).

7. Post-operative or primary RT or chemoradiotherapy

- Post-operative local RT is recommended for T3-T4 and intermediate/high-grade tumours and in cases with close resection margins (1-5 mm; 30 x 2 Gy), incomplete resection margins (33 x 2 Gy) or perineural growth.
- Post-operative regional RT is recommended for cases with pNþ (30 x 2 Gy) and extranodal extension (33 x 2 Gy). Unilateral ENI (25 x 2 Gy) is recommended based on the same inclusion criteria as for END.
- There is no proof of a beneficial effect of adding ChT to post-operative RT of the primary tumour and neck.
- Curative primary RT is indicated for patients with functionally unresectable disease or who are unsuitable for surgery due to comorbidities.
- Primary IMRT/VMAT photon RT up to 35 x 2 Gy to the primary tumour and positive neck nodes with ENI with equal indications as for primary surgery may result in w50% locoregional control.
- Primary particle treatment, namely C12, may result in higher locoregional control rates compared with photon RT (but with limited availability).
- There is no proof of a beneficial effect of adding ChT to primary RT in patients with unresectable SGC or those who are unsuitable for surgery.

3. Background - Radiotherapy and Trismus

3.1 Radiotherapy

Radiotherapy (RT) is a critical treatment modality for head and neck cancers (HNC), particularly in cases where surgery is unfeasible or as part of a multimodal approach. Despite its effectiveness in tumor control, radiotherapy is associated with both acute and long-term side effects, which can vary in severity and significantly affect the patient's quality of life. Below is an expanded description of the side effects, their varying levels of severity, and the associated risks, along with strategies to mitigate them.

3.2.1 Side Effects

*Side Effects*Radiation-induced side effects typically occur during or shortly after the course of radiotherapy and may range from mild to severe, depending on the radiation dose, fractionation schedule, and individual patient factors. Hereby, the main side-effects are reported according to CTCAE v5.0 as per the table below:

Figure 1: Summary Table of Main Side Effects According to CTCAE v 5.0

Adverse Event	**CTCAE v5.0 Definition**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Oral Mucositis	A disorder characterized by inflammation of the mucous membrane of the mouth.	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Dry Mouth (Xerostomia)	A disorder characterized by reduced salivary production, leading to dryness of the mouth.	Asymptomatic (Grade 0)	Symptomatic (e.g., dry or thick saliva); without significant dietary alteration	Moderate symptoms; significant oral intake alteration (e.g., increased fluid intake, altered diet)	Inability to adequately aliment orally; tube feeding or total parenteral nutrition indicated	N/A
Dermatitis	A disorder characterized by inflammation of the skin occurring as a result of exposure	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneou	Death

Adverse Event	CTCAE v5.0 Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	to ionizing radiation.				s bleeding from the involved site; skin graft indicated	
Dysphagia	A disorder characterized by difficulty in swallowing.	Symptomatic; able to eat regular diet	Symptomatic and altered eating/swallowing; oral intake decreased	Severe symptoms; inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Trismus	A disorder characterized by reduced ability to open the mouth due to inflammation and spasms of the masticatory muscles.	Mildly reduced range of motion without significant pain	Limitation of range of motion, ability to eat/drink	Adequate but minimal oral function; requires dietary modification	Severely limited range of motion; unable to aliment orally or speak adequately; medical intervention (e.g., tube feeding) indicated	Death

Trismus following radiation is an additional side-effect together with the abovementioned ones. However, it has historically received less attention in the literature of definitive radiotherapy for HNC if compared to the other ones (particularly dysphagia, mucositis and

xerostomia). The definition of trismus in the HNC setting has varied but, after Dijkstra et al. presented their study in 2006, a cut-off point at 35 mm of maximum interincisal opening (MIO) is widely accepted [**8,5**]. Common Terminology Criteria for Adverse Events (CTCAE) defines trismus as a disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the mastication muscles (National Cancer Institute, 2009). Trismus is a potentially devastating late oral morbidity following RT [8, 6, 336, 12, 10, 337, 338], with an incidence rate of 5% to 50% in patients with mixed sites of HNC [336]. Patients with trismus experience restricted or painful mouth opening that may limit oral intake, impair speech and worsen oral hygiene [336]. Thus, these sequelae jeopardize QoL and may impact survival [8, 5, 336, 12, 10, 337]. The mouth opening is driven by the paired muscles of mastication including the medial and lateral pterygoids and masseters [336]. In HNC patients treated with definitive radiotherapy, trismus, a late normal-tissue complication, is most probably caused by radiation-induced damage to the neuromuscular masticatory structures resulting in radiation-induced fibrosis and denervation muscle atrophy [337]. Although to a lesser extent, a co-contributing factor is represented by temporomandibular joint (TMJ) radiation-induced damage [337]. At present, the adverse impact of trismus is well known, but the exact mechanism and best prevention plans are not well defined. While RT fractionation did not appear to impact, data showed that IMRT could better prevent this side-effect than the 3D-conformal technique [337]. Moreover, studies have demonstrated that both the site of disease and the volume of irradiated tissue contribute to the development of trismus [8, 5, 336, 12, 10, 337, 338]. For example, patients receiving RT for laryngeal or hypopharyngeal cancer can experience minimal trismus rates [12]. In comparison, as reported in a study by Rao et al., about 14% of patients receiving RT for OPC can experience chronic trismus at 33 months (range, 6–68) [12]. In a series by van der Geer et al., at six months after RT, 28.1% of the HNC patients without trismus prior to RT developed trismus for the first time [10]. In contrast with the study by Rao et al. [8], this series included postoperative cases, and a history of surgery resulted as significantly associated with trismus prior to RT [10]. Indeed, the adjuvant setting can represent a confounding factor when evaluating RT-induced trismus.

While structures such as the temporomandibular joint (TMJ) and the mandible are routinely contoured for RT planning, bilateral masseter, temporalis, lateral pterygoid, and medial pterygoid muscles are not. Therefore, these structures are usually exposed to an unintended irradiation bath even when intensity-modulated gradients are employed. Several retrospective dosimetric analyses have taken into account this muscular compartment [336, 12, 10, 337, 338]. In 2020, MD Anderson dosimetric data on trismus in OPC patients were published by Kamal et al. [336], and, to the best of our knowledge, this is the most consistent dosimetric analysis published in this setting of HNC patients. The most striking dosimetric differences among patients with and without late trismus were observed to be related to the ipsilateral lateral pterygoid (ILP) muscles, both the low dose bath to this muscle and mean dose (specifically, V27 of at least of 98.6 % and D_{mean} of 61 Gy) [336]. The authors suggested that applying the proposed dosimetric constraints could reduce the prevalence of late trismus after IMRT for OPC patients. Nonetheless, detailed dosimetric studies regarding RT-related trismus in HNC patients are eagerly awaited [336, 12, 10, 337, 338]. Finally, literature data support the use of magnetic-resonance (MR) to evaluate and eventually identify specific muscle alterations following RT (changes in morphology and signal intensity), and this is certainly worth further investigation [339]. Imaging findings can support clinical suspicion, evaluate the extent of the alterations, confirm the significance of baseline dosimetric parameters, exclude tumor recurrence involving the muscular compartment, and, lastly, guide eventual therapeutic intervention for trismus. The latter include different options: physiotherapy, therabite exercises, electrotherapy, and pentoxifylline. However, data on trismus therapy remain scarce.

4. Aim of the study

4.1 Significance of the study.

In patients treated with definitive RT, the exact trismus onset underlying mechanism, biological and clinical underpinnings, and dosimetric parameters remain to be fully defined. This study aims to prospectively evaluate clinical and dosimetric trismus predictors in nonmetastatic HNC treated with definitive RT (eventually combined with chemotherapy schedules). RT plus concomitant chemotherapy has become an accepted treatment modality in advanced HNC in order to guarantee organ preservation. Unfortunately, it is not synonymous with function preservation ([340]. Patient-reported outcomes (PROs) instruments are becoming increasingly important because reliable measures of how the patients experience their symptoms can be considered equally important in clinical research as survival and mortality [341]. Trismus is a detrimental radiation-induced side-effect, jeopardizing the QoL of HNC patients. Additionally, the study will prospectively collect not only clinical, dosimetric, and radiological findings but also patient-reported outcomes through specific questionnaires. The investigation of the impact of trismus on the quality of life, including the health of the oral cavity, is a parallel direction investigated by this study, which correlates with the dosimetric findings. In the case of positive characterization of pre-existing conditions of the oral cavity, masticatory muscles, temporomandibular joint and structural craniofacial features that correlate with increased trismus severity and reduced quality of life, it would be possible to identify patients in need of additional care early, in the framework of precision medicine. The outcomes drives to increased attention of the clinicians toward these aspects of the Head and Neck cancer patients that are important for the overall wellbeing and performance of the patients under or post RT treatment. The findings of the research will inform clinicians' clinical decision-making, including the oral cavity health check and QoL check in the overall treatment approach for these cancer patients.

4.2 Objectives and Research Questions

Primary outcomes of this research include the following:

- Trismus occurrence up to 2-years post-RT according to MIO evaluation, employing *TheraBite* range of motion scale for the evaluation [10, 337] and stratifying results according to the disease site, treatment, and clinical variables.

  QoL assessment through EORTC HN 35 QoL questionnaire with a focused analysis on Q32 ("Have you had pain in your jaw?") and Q40 ("Have you had problems opening your mouth wide?) [337] along the timepoints of the 2 years FU.

Secondary outcomes are:

- Dose-volume trismus-predictors identification: association/correlation between extracted baseline dose-volume metrics (V1-V75, Dmean) of trismus-related muscles (masseter, temporalis, and medial and lateral pterygoids) and trismus occurrence [336, 12, 10, 337, 338].
- Linac-based IMRT/VMAT vs Tomotherapy plan comparisons with regard to trismus related-muscles baseline metrics and muscular-sparing plan comparison.
- Trismus-related muscular morphological changes and structural damage evaluation through MR scans [339], along the timepoints of the 2 years follow-up (FU, 1- and 2-years). Eventual computed tomography (CT) findings can be included in the radiological analysis [343].
- CTCAE toxicity profile, acute and chronic (>6 months following treatment).
- Association between trismus and survival outcomes: evaluation of eventual association/correlation between trismus occurrence and overall survival (OS) at 2 years
- Association between trismus occurrence and dental status (baseline number of teeth present) before the beginning of RT.

- Association between trismus occurrence and craniofacial structural variables (cephalometric values) as well as masticatory muscles and temporomandibular joint condition.

Regarding QoL analysis, the Q32 and Q40 of the QLQ-HN35 EORTC questionnaire systematically evaluate the extent of patient discomfort by focusing on two primary areas:

- *Jaw Pain*. Module Q32 quantifies the level of jaw pain experienced by patients, a common direct manifestation of trismus. This dimension is crucial for understanding the pain's interference with daily activities and overall performance.

- *Mouth Opening Limitations*. Module Q40 evaluates the difficulties patients face in opening their mouths widely (OMW) — a direct measure of the mechanical limitations imposed by trismus. This assessment provides critical insights into the functional challenges that impact oral intake, speech, and non-verbal communication.

Through a scoring mechanism ranging from 1 (not at all) to 4 (very much), these questionnaires deliver granular insights into the severity of symptoms and their progression over time. This structured scoring system facilitates the analysis of trismus' impacts, informing both clinical management and therapeutic innovations.

By integrating these specific modules with the CTCAE framework, this study not only enriches the understanding of trismus-related quality of life impairments but also sets a foundation for targeted interventions aimed at alleviating these burdens.

Figure 2: Study Protocol Details

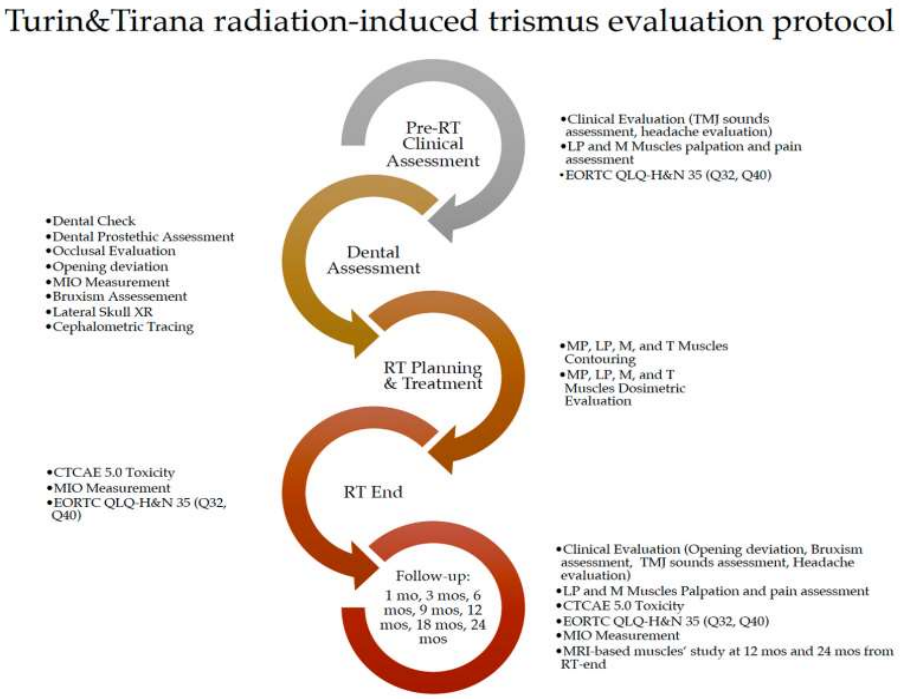


Figure 1: *Turin & Tirana radiation-induced trismus evaluation protocol. Abbreviations: mo, month; mos, months; XR, x-rays; RT, radiotherapy; MRI, magnetic resonance imaging; MIO, Maximal Interincisal Opening; TMJ, Temporomandibular Joint; MP, Medial Pterygoid; LP, Lateral Pterygoid; M, Masseter; T, Temporal; QLQ, Quality of Life Questionnaire; EORTC, European Organization for Research and Treatment of Cancer; CTCAE, Common Terminology Criteria for Adverse Events; H&N, Head and Neck.*

4.3 Materials and Methods (Study Protocol)

The present, two-center (AOU Città della Salute – Torino, Italy & Nënë Tereza –Tirana, Albania), no-profit, the longitudinal-observational study aims to evaluate trismus and its predictors in a consecutive series of HNC patients undergoing IMRT (including Step-and-Shoot)/VMAT (+/-ChT). Radiotherapy is delivered according to both Institutions' standards in line with international prescription guidelines.

Turin's RT department employs Tomotherapy-Radixact (Accuray, Madison, WI, USA); Tirana RT department employes ELEKTA Sinergy (Stockholm, Sweeden).

The accrual has begun in 15 November 2022. The study duration is expected to be four years overall. Follow-up will last 2 years for each patient. The study is currently ongoing. Thus, the data presented hereby are intended as an interim analysis.

Clinicians involved in the study are the following: treating Radiation Oncologist, referring Ear-Nose-Throat (ENT)/Oral-Maxillo-Facial (OMF) specialist, and eventually the treating Medical Oncologist (if ChT administered), and the dentistry specialist.

4.3.1 Inclusion Criteria – Eligibility

1. Patients with a histologically verified HNC.
2. Patients 18 years old or older, with ECOG performance status 0-2, suitable for definitive RT (+/- ChT according to disease and clinical presentation; induction ChT is allowed).
3. Early-stage or locally advanced HNC (American Joint Committee on Cancer, AJCC - 8th).
4. Patients must have signed informed consent.

4.3.2 Exclusion criteria

1. Patients who have undergone any previous HN radiotherapy earlier.
2. 3D-conformal RT (3D-CRT) delivery.
3. Adjuvant setting.
4. Palliative RT.
5. ECOG PS >2.
6. Patients unable to co-operate or suffering from any other form of disease that would interfere with the planned treatment.
7. The patients with any evidence of distant metastases.
8. The following HNC histologies: sarcomas, lymphomas, neuroendocrine tumors, and mucosal melanomas.
9. Thyroid cancer & Ear cancer
10. Early-stage (stage I-II) larynx cancer.

4.3.3 Study Design

At baseline, clinical and radiological evaluations, following histologic diagnosis, include:

- Anamnesis collection and performance status evaluation;
- ENT endoscopy, CT and MR (for staging and baseline masticatory muscles compartment evaluation), eventually positron emission tomography (PET) scans according to standard diagnostic and staging requirements.
- Dental evaluation, including: number of teeth at baseline and number of teeth needing extraction before the beginning of RT; assessment of present removable prosthodontic rehabilitation; measurement of overbite [mm].
- orthopantomography; lateral cephalogram with corresponding cephalometric tracing
- Complete Head and Neck clinical exam, including: MIO measurements using TheraBite; opening deviation; temporomandibular joint (TMJ) sounds evaluation; TMJ and muscular compartment palpation; bruxism assessment; headache (if present) evaluation.
- Lastly, the first patient-reported QoL assessment through the administration of EORTC HN 35 questionnaire.
- Follow-up (FU) will take place at 1 month (mo) – 3 months (mos) – 6 mos – 9 mos - 1 year (yr) – 15 mos -18 mos - 2 years (yrs) from the end of RT.

  At every timepoint, the complete Head and Neck clinical exam (as previously reported) is being repeated, along with the CTCAE 5.0 treatment-toxicity assessment and the EORTC HN 35 questionnaires administration.
  Dental-care FU is routinely performed according to both Institutions' standards.
  MR – based evaluation of masticatory muscle alterations (as T2 hyperintensity and post-gadolinium enhancement) is performed mandatorily at 12 and 24 months following the end of RT. Eventually, the referring radiologist can report post-treatment CT findings, as muscles' size alterations (thickening) or contrast-enhancement [342].
  Restaging imaging during FU is performed according to both Institutions' standards.
  For RT planning, trismus-related muscles' contouring follows Hague et al. recommendations [5].

Plan comparisons (Helical TomoTherapy delivery vs. IMRT/VMAT) involves two different treatment planning system solutions: Raystation TPS Platform and Monaco TPS Platform.

All data elements are currently being stored in a database managed by the Radiation Oncology Unit of the A.O.U. Città della Salute e della Scienza Hospital.

4.4 Study population

Target Study population*:* estimated population, n=100; We designed the present study to prospectively evaluate the incidence of trismus and its impact on QoL in a series of 100 consecutive HNC patients treated with RT during in the definitive setting and, additionally, to identify patient-related, tumor-related, and dosimetric trismus-predictors.

4.5 Statistical considerations

Statistical considerations. Customary literature-supported statistical methods (e.g. logistic regression, Cox proportional hazards, Kaplan-Meier) will be employed to evaluate outcomes and associations among variables. The correlation between the variation in MIO measurements between pre-RT and 6-mos timepoint and baseline number of teeth and relevant cephalometric values was evaluated with a linear regression model. Demographic, pathologic, and treatment characteristics to be compared using Pearson's chi-square or Fischer's exact tests for categorical data and Mann-Whitney or Mood's Median tests for continuous variables. Survival rates between groups are to be generated using Kaplan-Meier product limit estimates with comparison of outcomes to be assessed using the log-rank test. To measure hazard ratios while adjusting for other factors, univariate and multivariate analysis are to be performed using Cox proportional hazard regression. For univariate and multivariate logistic regression analyses, odds ratios will be generated. Once collected and recorded in the appropriate de-identified format, data will be analyzed via standard statistical software (R-Studio, Python, SAS, SPSS, STATA).

5. Results of the Research

5.1 Characteristics of Study Accrual

The study involves two research centers: the AOU Città della Salute in Turin, Italy, and the Mother Teresa University Hospital Center in Tirana (MTUHC), Albania. The study began patient enrollment following the approval of the study protocol by the Ethical Committee of the University of Turin in *October 2022.*

At the time of the present analysis, a total of 38 patients met the study's inclusion criteria, with 23 participants (62%) enrolled from MTUHC in Tirana and 15 participants (38%) from AOU Città della Salute in Turin. Among the total study population, 73.7% were male and 26.3% were female.

The mean age was 62 years, with the largest proportion of patients (49%) falling into the 60-69 age group. Other age distributions included 22% in the 50-59 age range, 14% in the 70-79 group, 11% between 40-49 years, and a small minority of 3% aged 30-39 years. No patients under the age of 30 were enrolled in this study. The figures below visualize the Gender and Age Distribution:

Figure 3: Gender Distribution

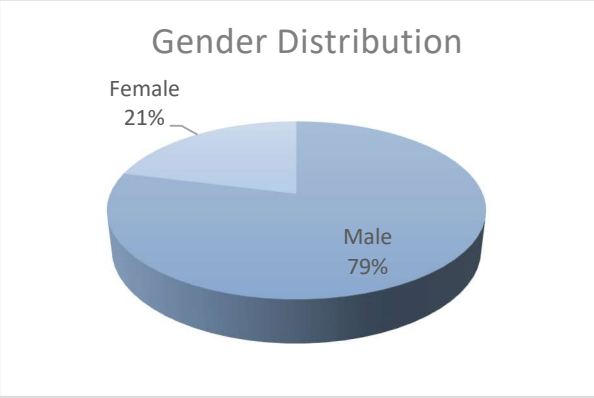
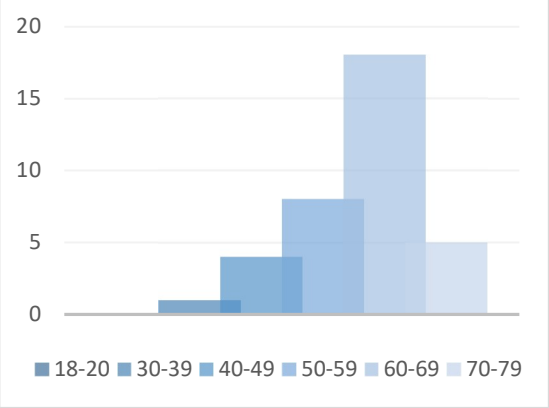


Figure 4: Age Distribution



The performance status of patients, as measured by the ECOG scale, showed that 58% of the cohort had a performance status of 0, indicating full activity with no restrictions, while 24% had a status of 1 (some restrictions but ambulatory). Only 13% of the patients

had a performance status of 2, indicating they were unable to work but could still engage in self-care.

As part of the clinical assessment, all patients were thoroughly evaluated regarding their lifestyle choices and the presence of additional non-communicable diseases. The analysis revealed that 24 patients (65%) were smokers, consuming more than 10 packs of cigarettes per year, while 14 patients (38%) reported alcohol consumption exceeding 2 units per day.

In terms of comorbidities**,** 8 patients (22%) were diagnosed with CV disease, 4 patients (11%) had diabetes, and 13 patients (35%) were affected by high blood pressure.

The detailed distribution of lifestyle factors and comorbidities is summarized in the table below:

Lifestyle And Co-Morbidities	YES	NO
Lifestyle (Cigarettes) (>10 Packs/Year)	24 (65%)	13 (35%)
LIFESTYLE (ALCOHOL) (>2 DRINK UNITS PER DAY)	14 (38%)	23 (62%)
CV DISEASES	8 (22%)	29 (78%)
DIABETES	4 (11%)	33 (89%)
HYPERTENSION	13 (35%)	24 (65%)

Note: CV: cardiovascular

Figure 5: Lifestyle Factors and Comorbidities

5.2 Tumor Characteristics and Comparative Analysis

The tumor characteristics of the patient cohort reflect a diverse range of head and neck cancer (HNC) characteristics, with notable distinctions in tumor histology, staging, and primary tumor sites. Registered data allows for both a descriptive and comparative analysis, highlighting the heterogeneity of the disease within the study population.

Histology of the Tumor. Among the 38 patients, the predominant histological diagnosis was Squamous Cell Carcinoma (SCC), consistent with global trends in head and neck

cancers. In this cohort, 95% (36 patients) of tumors were classified as SCC, while the remaining 5% (2 patients) were attributed to other less common histologies.

Primary Tumor Site Distribution. The primary tumor site analysis reveals a concentration of cases in the oropharynx, accounting for 57% (21 patients) of the cohort, followed by nasopharynx with 22% (8 patients), larynx with 8% (3 patients), and other anatomical sites in 14% (5 patients).

HPV and EBV Status. All patients underwent testing for Human Papillomavirus (HPV) and Epstein-Barr Virus (EBV). Results indicate that 32% of patients (12 individuals) were HPV-positive, while 17% (6 patients) were EBV-positive.

Tumor Laterality. Tumor laterality, or the side of the body where the tumor is located, is another key characteristic for the dosimetric analysis. In this cohort, 59% (22 patients) had tumors on the right side, 16% (6 patients) on the left side, and 19% (7 patients) presented with median-located tumors.

AJCC 8th Edition Staging. Staging, based on the American Joint Committee on Cancer (AJCC) 8th Edition, shows a significant number of patients with advanced-stage disease. 43% of the patients (16 individuals) were classified as Stage III, and 40% (14 patients) as Stage IV.Only 14% of the patients (5 individuals) were diagnosed with Stage II, and 1 patient presented with Stage I.

Grading of Tumors. Histopathological grading was available for the majority of patients, with the following distribution: 81% of tumors were categorized as Grade II (moderately differentiated), 11% were Grade III (poorly differentiated), and Grade I (well-differentiated) and Grade IV (undifferentiated) categorized 4% of patients for each. The Figure 6 provides a summary of the study population tumor characteristics:

Figure 6: Study Population Tumor Characteristics

	Histology	HPV Status	EBV Status	Primary Tumor Site	AJCC 8th Staging	Laterality
SCC	*33 (89.19%)*					
Other	*3 (8.11%)*					
Positive		*11 (29.73%)*	*6 (16.22%)*			
Negative		*26 (70.27%)*	*30 (81.08%)*			
Oropharynx				*20 (54.05%)*		
Nasopharynx				*8 (21.62%)*		
Larynx				*3 (8.11%)*		
Others				*5 (13.51%)*		
Stage I					*0 (0.00%)*	
Stage II					*5 (13.51%)*	
Stage III					*17 (45.95%)*	
Stage IV					*14 (37.84%)*	
Right						*22 (59.46%)*
Left						*6 (16.22%)*
Median						*8 (21.62%)*

SCC: Squamous Cell Carcinoma

AJCC: American Joint Committee on Cancer

5.3 Comparative Analysis of Tumor Characteristics

Comparison of Tumor Sites and Staging. The predominance of oropharyngeal tumors in this cohort is particularly notable when compared to nasopharyngeal and laryngeal cancers.

Oropharyngeal tumors presented with a high proportion of Stage III and IV cases, reflecting their aggressive nature and the potential for delayed detection.

Nasopharyngeal cancers also demonstrated a significant number of advanced-stage presentations.

Laryngeal cancers, while representing a smaller proportion of cases, also showed late-stage diagnosis,

HPV and EBV. A correlation between tumor site and viral status was observed within this cohort. Among patients with oropharyngeal cancer, 52.38% were HPV-positive. In contrast, 62.5% of nasopharyngeal cancer cases were EBV-positive.

5.4 Treatment characteristics

Treatment characteristics. The study employed three primary treatment modalities for the patient cohort: Definitive Radiotherapy (RT), Radiotherapy with Chemotherapy (RT+ChT), and Induction Chemotherapy followed by Radiotherapy (iChT+RT+/-ChT). Notably, none of the enrolled patients were treated with Definitive RT alone. Instead, the majority (81%) received combined RT+ChT, while the remaining 19% underwent iChT + RT(+/-ChT).

Regarding the treatment infrastructure, two centers provided therapy using different RT delivery and treatment planning systems. The Elekta Synergy Machine with the Monaco TPS was utilized for 61% of the patients at the Tirana center (61%), while the Tomotherapy (Radixact) with the Raystation system was used for the remaining 39% enrolled at the Turin center.

Figure 7: Study Population Treatment Characteristics

MODALITY OF TREATMENT (RT/ RT+ChT/ IChT+RT+/- ChT)	
1=RT	0%
2=RTCHT	81%
3=ICHT+RT(+/-CHT)	19%
MACHINES	
- **Elekta Synergy**	61%
- **Tomotherapy Radixact**	39%

TREATMENT PLANNING SYSTEM	
- **Monaco**	61%
- **Raystation**	39%
DOSE PRESCRIPTIONS:	
1=70 Gy PTV 1/63 Gy PTV 2/57 Gy PTV 3	64%
2=70 Gy PTV 1/63 Gy PTV 2/54.25 Gy PTV 3	19%
3= Other	17%

PTV1: High risk Planning target volume

PTV2: Intermediate risk Planning target volume

PTV3: Low risk Planning target volume

Dose prescriptions were as follow: i) 64% of patients received a prescription of 70 Gy to PTV 1, 63 Gy to PTV 2, and 57 Gy to PTV; ii) 19% received 70 Gy to PTV 1, 63 Gy to PTV 2, and 54.25 Gy to PTV 3**,** while 17% followed different dose protocols as required by their treatment plan.

A standardized delineation model was established to ensure consistent treatment planning between centers. This model, based on the atlas by Hague et al. [342]**,** emphasized key structures involved in masticatory function, including the Masseter (Left & Right)**,** Temporal (Left & Right)**,** Medial Pterygoid (Left & Right)**,** and Lateral Pterygoid (Left & Right) muscles.

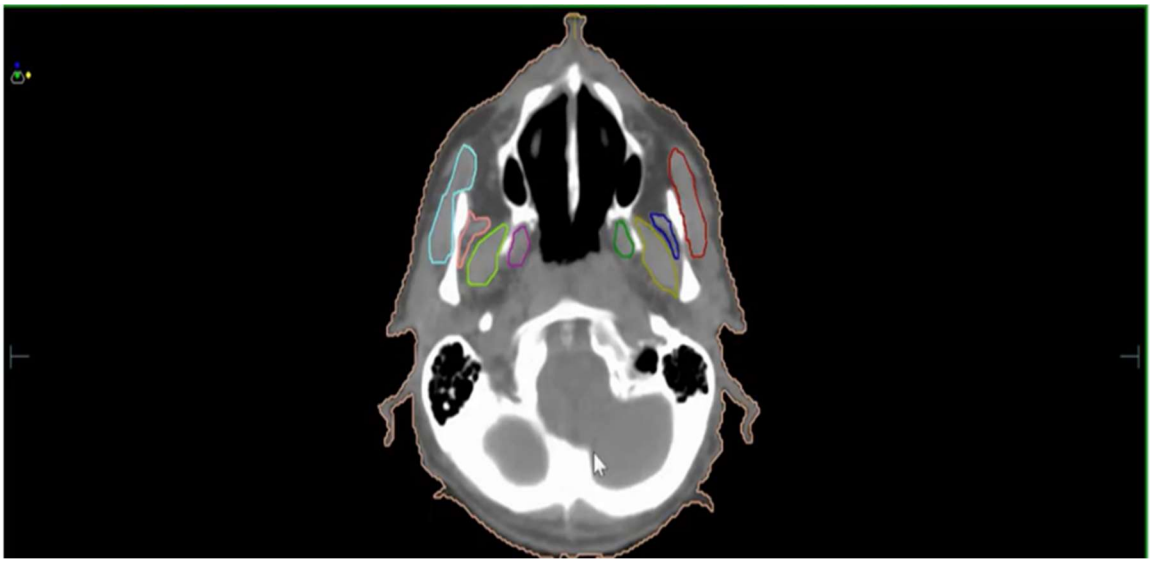


Figure 8: Delineation Model

Notes: Right Masseter: Light Blue; Left Masseter: Red; Right Temporal: Light Brown; Left Temporal: Blue; Right Lateral Pterygoid: Light Green; Left Lateral Pterygoid: Yellow; Right Medial Pterygoid: Purple; Left Median Pterygoid: Green.

The Planning Target Volume (PTV) 70 Gy was recorded for each patient, with volumes ranging from a minimum of 64.7 cc to a maximum of 517 cc. The median PTV 70 Gy volume across all patients was 166.8 cc**,** with a standard deviation of 109.82 cc**.**

When stratified by tumor site, the Nasopharynx had the highest median PTV 70 Gy at 225.07 cc (SD = 128.92). Tumors in the Larynx and Oropharynx had median volumes of 168.24 cc (SD = 32.80) and 160.7 cc (SD = 27.79), respectively.

Figure 9: Median PTV 70Gy (cc) by Tumors Site

Tumor site	***PTV 70Gy (cc) Median***	***Standard Deviation***
Larynx	168.24	32.80
Nasopharynx	225.07	128.92
Oropharynx	160.675	27.79

5.5 Maximal Interincisal Opening (MIO): Trismus Identification and Follow-Up

The Maximal Interincisal Opening (MIO) measurement (Figure 9) constitutes a fundamental component of this research, aiming to detect and longitudinally monitor trismus development in patients undergoing radiation therapy. To establish a robust baseline, MIO assessments were mandatorily performed on all participants prior to initiating radiation therapy. These evaluations were systematically conducted by radiation oncologists at both collaborating centers, ensuring methodological consistency. The TheraBite Motion Scale (Atos Medical AB) was utilized for these measurements, selected for its accuracy and reliability in quantifying the maximal interincisal opening, thereby

facilitating precise tracking of trismus progression throughout the treatment and follow-up phases.

Figure 10: MIO Measurement Tool and Patient No. 24 (signed consent for photography)

At the present timepoint, the MIO main analysis focused on the cluster that reached the 6-months post-RT follow-up (74% of the enrolled patients).

Baseline MIO assessments identified trismus in 8 individuals, constituting 22% of the study cohort, each presenting with an MIO ≤35 mm. By the end of RT, 2 out of 8 baseline trismus had a MIO increase. Analyzing the causes, it was identified that the improvement of pre-RT Trismus occurred due to disease-response (given the masticatory muscles infiltration at diagnosis).

Throughout the course of the study, an additional 13 occurrences of trismus were identified post-RT, representing 41% of the total accrual. The temporal distribution of these new cases was as follows: 3 cases were noted immediately at the end of RT, 1 case at 1 month post-RT, 3 cases at 3 months, 1 case at 6 months, 3 cases at 9 months, and 2 cases at 12 months post-RT. The proportion of participants reaching the 9- and 12-month follow-up periods was 68% and 46% of participants, respectively.

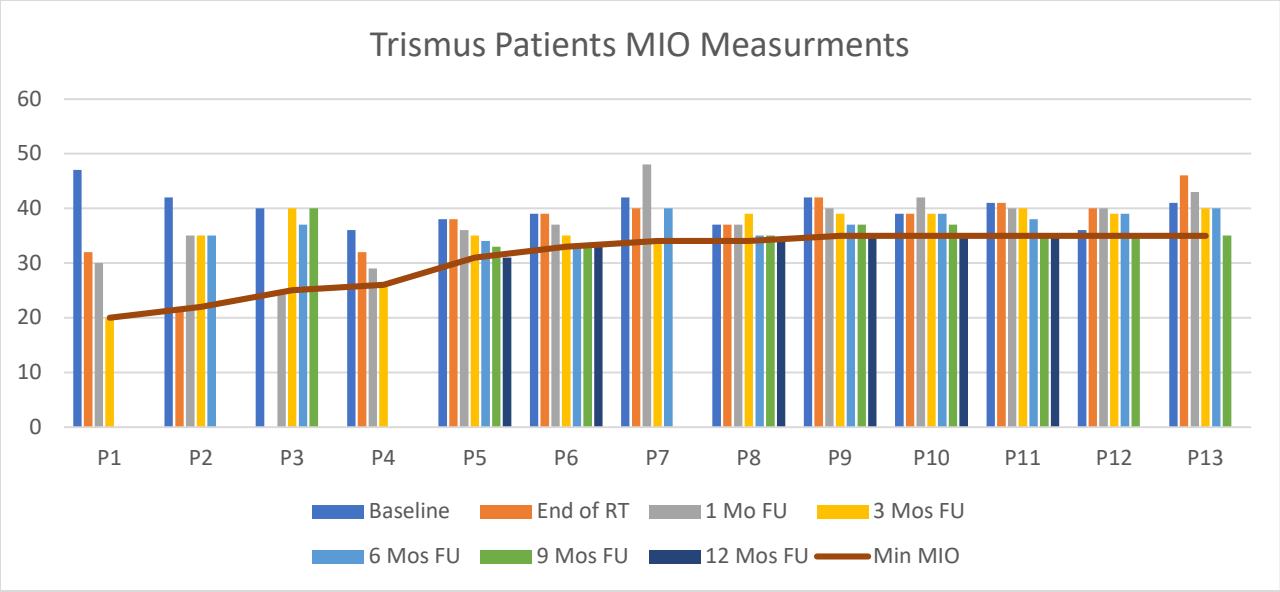


Figure 11: MIO-based post-RT trismus patients: measurements and trends

Figure 11 illustrates the heterogeneous varying trajectories of trismus severity post-RT, with some patients experiencing improvements and others showing declines or stability in MIO measurements.

Among the 13 MIO-based post-RT trismus cases, sites were as follow: 11 were Oropharynx, 1 Nasopharynx and 1 Larynx cancer.
At present, 28 patients have reached the 6-month post-RT evaluation. For this part of the analysis, variables were considered from T0 (baseline, before the beginning of RT), T1 (1 month after the end of RT), and T2 (6 months after the end of RT).

Figure 12 table shows the mean values of Maximum Interincisal Opening (MIO) at T0, T1, and T2. Analysis of variance did not show a significant difference in MIO between T0, T1, and T2, even though mean MIO values progressively decreased with time elapsed since the end of RT. Likewise, the ratio of patients with an MIO smaller than 35 mm, which is considered the threshold for trismus, did not show significant changes between T0, T1, and T2.

Figure 12: Mean values of Maximum Interincisal Opening (MIO)

	T0 (baseline)	T1 (1-month)	T2 (6-months)	p-value
MIO	41 ± 8.7	40 ± 8.9	38.9 ± 7.2	0.471†
MIO<35mm	8 (21%)	8 (25%)	7 (25%)	0.912‡
N	37	32	28	-

† ANOVA (one-way)
‡ Fisher's exact test
MIO: maximum inter-incisal opening
MIO<35mm: number of patients (percentage of the total) with less than 35 mm of maximum interincisal opening
N: number of patients

RT doses received from the four muscles implicated in masticatory function were meticulously recorded and analyzed. Visual data depicting the median mean dose (Dmean) absorbed by the masticatory muscles of patients newly diagnosed with trismus highlights a pronounced exposure in both the medial and lateral pterygoid muscles.

The median Dmean values absorbed by each muscle resulted as follow: i) Left Masseter received 2830.4 cGy, ii) Right Masseter received 2938.0 cGy, iii) Left Temporal received 577.7 cGy, iv) Right Temporal received 624.5 cGy, v) Left Medial Pterygoid received 5790.0 cGy, vi) Right Medial Pterygoid received 6467.1 cGy, vii) Left Lateral Pterygoid received 2093.5 cGy, and viii) Right Lateral Pterygoid received 2571.2 cGy.

5.6 Impact of Trismus on Quality of Life: An In-Depth Evaluation

5.6.1 The EORTC QLQ - H&N35 Questionnaire Q32

At baseline, 51% of patients reported no jaw pain (score of 1), 27% reported slight pain (score of 2), 16% experienced moderate pain (score of 3), and 3% reported severe pain (score of 4). The median score at baseline was 1, indicating that most patients experienced no or minimal jaw pain initially,

By the end of radiation therapy (RT), the percentage of patients reporting no pain decreased by 10%, and those reporting slight pain decreased by 3%. Conversely, those reporting moderate pain increased by 8%.

1 month post-RT a 6% increase in patients reporting slight pain; and decreases in moderate and severe pain by 5% and 3%, respectively, were observed

This trend of improvement in jaw pain continued at the three-month follow-up, with an 11% decrease in patients experiencing moderate pain, balanced by increases of 2% and 5% in patients reporting no pain and slight pain, respectively.

At the six-month follow-up, a significant decrease in patients reporting no pain (19%) was noted, where there was an increase in patients reporting slight and moderate pain by 5% and 7%, respectively.

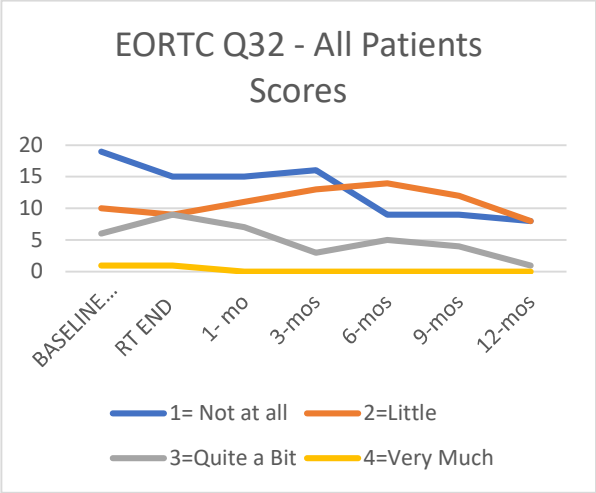


Figure 13: EORTC HN35 Q32 - All Patients Scores

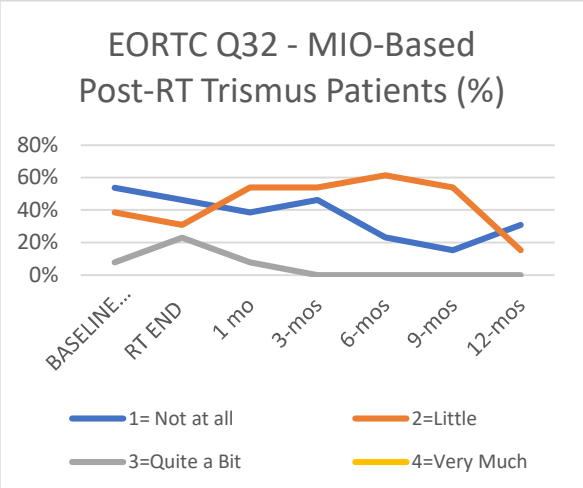


Figure 14: EORTC HN35 Q32 – MIO-Based Post-RT Trismus Patients Scores (%)

5.6.2 The EORTC QLQ - H&N35 Questionnaire, Q40

At baseline, the majority, 59% (22 patients), reported no difficulty (score of 1). About 22% (8 patients) perceived a slight problem (score of 2), and 11% (4 patients) indicated a moderate problem (score of 3), while only 2 patients experienced significant difficulties (score of 4).

Immediately post-radiation therapy (RT end), a significant shift in patient experiences was observed. The proportion of patients reporting no difficulty dropped by 29% to a lower

number of patients reporting no issues, concurrent with a simultaneous 16% increase in those experiencing slight difficulties (score of 2) and an 8% increase in those reporting moderate difficulties (score of 3).

1 month post-RT, there was a notable improvement with an 11% increase in patients reporting no problem. Conversely, there was a reduction of 6% and 5% in patients reporting slight and moderate difficulties, respectively.

By the 3-months follow-up, the most significant changes were observed in the increase of 11% in patients reporting slight problems and an equivalent decrease in those experiencing moderate problems.

At the 6-months follow-up, the number of patients reporting no problems decreased again by 8%, while those experiencing slight problems also decreased by 11%. Those reporting moderate problems increased by 5%, and the standard deviation slightly increased to 0.48, reflecting a modest increase in variability.

By the 9 and 12-months follow-ups, the data suggested further stabilization in the patient's ability to open their mouths wide. At 12 months, most responses were either no difficulty or slight difficulty.

Regarding MIO-based post-RT trismus patients, 62% (8 individuals) reported no difficulties in OMW, 31% (4 individuals) experienced slight problems, and a single patient (representing 8% of the total) reported significant difficulties.

At RT end, the proportion of patients reporting no difficulties in OMW significantly decreased to 31%. This trend persisted up to the 6-month follow-up. Correspondingly, the percentage of patients experiencing slight problems in OMW increased, with 46% reporting this issue at the RT end, which further rose to 54% by the 6-month mark. Remarkably, by the 6-month follow-up, no patients reported moderate or severe problems. The figures below show the trend of EORTC Q40 scores at different time points from the baseline to 12 months.

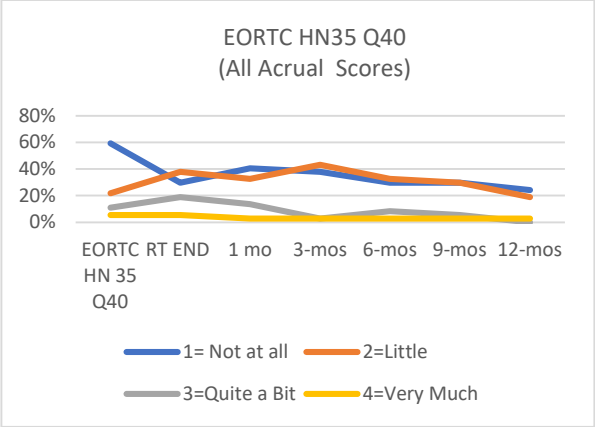


Figure 15: EORTC HN35 Q40 All Accrual Score (%)

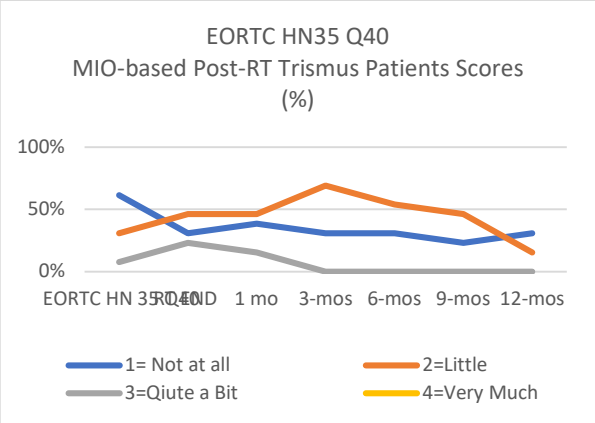


Figure 16: EORTC HN35 Q40 – MIO-Based Post-RT Trismus Patients Scores (%)

5.6.3 CTCAE 5.0 Toxicity Report on RT Induced Trismus

CTCAE 5.0 Toxicity Report on RT Induced Trismus. The Trismus Toxicity Report revealed a moderate overall toxicity in the study population following the conclusion of radiation therapy. At baseline, 30% of the patients (11 individuals) were classified as Grade 1, indicating a decreased range of motion (ROM) without impaired eating ability. A slightly higher 32% (12 individuals) were at Grade 2, experiencing a decreased ROM that necessitated modifications in diet such as small bites, soft foods, or purees. In more severe cases, 14% (5 individuals) scored Grade 3, where decreased ROM significantly hindered their ability to eat or hydrate orally. Additionally, 16% of the cohort (6 patients) reported no signs or symptoms of toxicity from radiation therapy.

Follow-up data one-month post-treatment revealed notable changes. Specifically, 11% of patients (5 individuals) who initially scored 2 at baseline improved to report no symptoms of toxicity. Conversely, 3 patients deteriorated, moving from a Grade 1 to Grade 2 status. Additionally, a small improvement was observed where 5% of the cohort shifted from Grade 3 to Grade 2. Consequently, at this one-month mark, 41% of the patients (15 individuals) were scored at Grade 2, indicating a persistent need for dietary adaptations, while 27% exhibited no symptoms of toxicity.

By the second follow-up, no significant changes were observed in the symptoms of Trismus Toxicity. However, by the 6-month follow-up, the dynamics shifted notably: the proportion of patients reporting no symptoms decreased by over 50% (from 22% to 11%), while those scoring Grade 3 doubled from 8% to 16%.

Hereby, the 13 MIO-based post-RT trismus patients are analyzed regarding CTCAE trismus toxicity item incidence and trend:

Toxicity levels were reported from 0 (no symptoms or signs) to 2 (decreased range of motion requiring small bites, soft foods, or purees). At baseline, the majority, 54%, reported mild decreased ROM (score 1), and 38% experienced more severe limitations requiring dietary modifications (score 2).

Over the subsequent follow-up periods, the data revealed a progressive shift in the severity of symptoms:

- 1 month post-RT: The proportion of patients reporting score 1 decreased to 31%, while those reporting more severe symptoms (score 2) increased to 54%. This period showed an initial worsening in trismus symptoms among patients.
- 3 months post-RT: Symptoms further intensified for some, with 62% now reporting score 2. The percentage of patients reporting mild symptoms (score 1) stabilized at 31%.
- 6 months post-RT: There was a slight decrease in the severity of symptoms with 46% reporting score 2, and the proportion of patients at score 1 remained consistent at 31%.
- 9 months post-RT: The severity of symptoms showed a notable variation with fewer patients (46%) reporting score 2 and an increase in milder cases (score 1) to 15%.
- 12 months post-RT: The data demonstrated a stabilization, with 23% of patients reporting mild to moderate symptoms (scores 1 and 2).

Throughout the study period, the baseline toxicity profile established that initially, 8% of patients did not report any symptoms of trismus, a figure that remained constant.

The Figures below shows the variation of CTCAE 5.0 RT Induced Toxicity Level scoring at different timepoints starting from Baseline (End of RT) to 6 months FU.

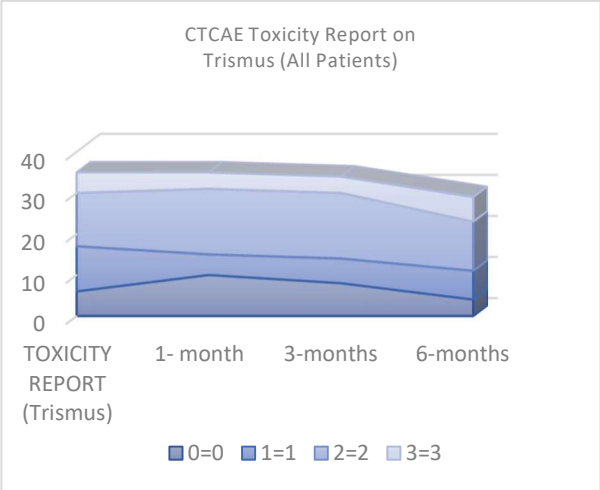


Figure 17 CTCAE 5.0 Toxicity Level - Trismus (All Patients)

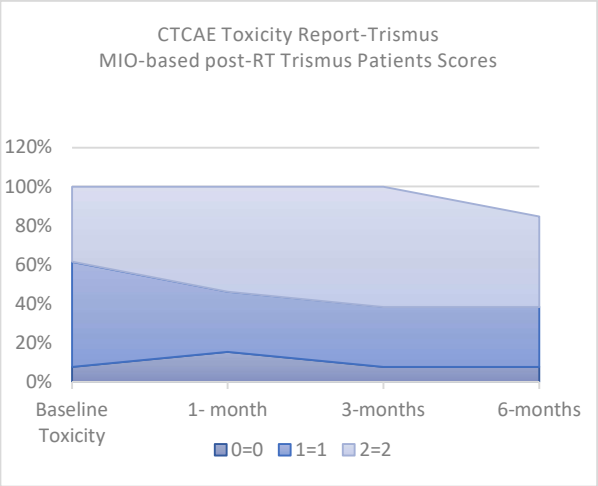


Figure 18: CTCAE 5.0 Toxicity Level Trismus - MIO-Based Post-RT Trismus Patients Scores (%).

5.6.4 CTCAE 5.0 Toxicity Report on RT Induced Oral Mucositis

CTCAE 5.0 Toxicity Report on RT Induced Oral Mucositis. At the conclusion of radiation therapy, the toxicity levels were characterized as follows:

- Grade 0: 8% of patients (3 individuals) showed no signs of oral mucositis.
- Grade 1: 16% of patients (6 individuals) experienced asymptomatic or mild symptoms, not requiring intervention.
- Grade 2: 49% of patients (18 individuals) reported moderate pain or ulceration that did not interfere with oral intake, though a modified diet was indicated.
- Grade 3: 16% of patients (6 individuals) suffered from severe pain that interfered significantly with oral intake.
- Grade 4: One patient experienced life-threatening consequences.

No patients experienced death (Grade 5) because of oral mucositis.

The incidence of Grade 3 mucositis progressively decreased from 16% at baseline to 8% at 6 months, while Grade 2 mucositis showed a fluctuation before returning to initial levels (35% at 1 and 6 months), peaking at 42% at 3 months.

Grade 1 mucositis decreased significantly, from 14% at 1 month to 5% at 6 months.

Notably, the proportion of patients with no mucositis symptoms (Grade 0) increased significantly from 8% at baseline to 24% at 6 months, reflecting a substantial improvement in a subset of the cohort.

MIO-based post-RT trismus patients resulted with different pattern of oral mucositis scores. At the baseline (End of RT) most of them, 77% (10) experienced acute toxicity scoring 2 (moderate pain or ulcer that does not interfere with oral intake, modified feeding indicated) and 15% (2) scored 3 (Severe pain; interfering with oral intake). Only one patient did not experience Oral Mucositis Toxicity at the baseline classifying with the extra score 0. None of the Trismus patients scored 1 (asymptomatic or mild symptoms) or 5 (death because of Oral Mucositis Toxicity).

The patients scoring 2 at the baseline reduced by 31% (4) in the 1 Month FU in favor to 15% (2) patients increase in the number of patients scoring 1 and 15% (2) of those classified at the score 0. The patients experiencing grade 3 also increased from 2 to 3 patients at the Month 1 FU.

At 3 months FU patients scoring 2 increases again by 16% and patients scoring 3 reduced by 15%.

At 6 months FU the Oral Mucositis toxicity level registered in MIO-based post-RT trismus patients was as follows: 23% (4) scored 0, 54% (8) scored 2. Only one patient scored 3 and none of the patients scored 1.

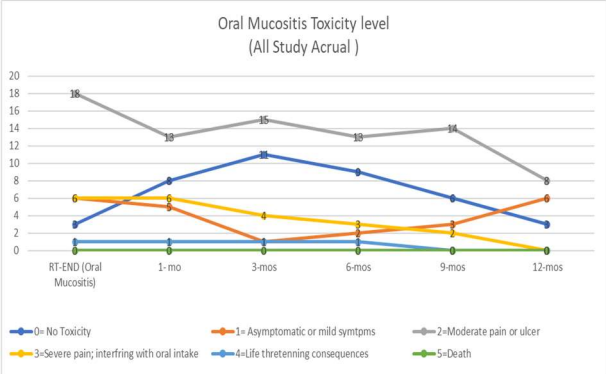


Figure 19: CTCAE 5.0 Toxicity Level - Oral Mucositis All Study Accrual

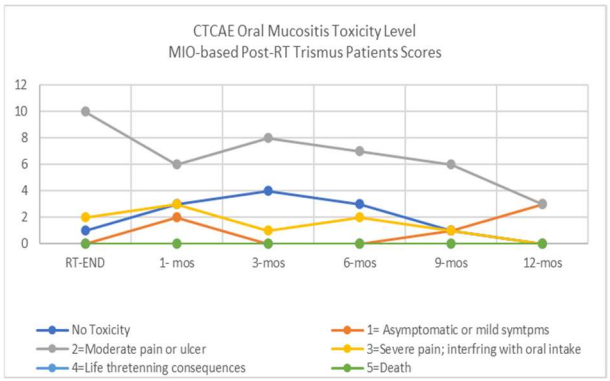


Figure 20: CTCAE 5.0 Toxicity Level - Oral Mucositis– MIO Based Post-RT Trismus Patients scores

5.6.5 CTCAE 5.0 Toxicity Report on RT Induced Dry Mouth

At the baseline most of the patients 41% (15) scored 2 experiencing moderate symptoms, oral intake alterations and diet limited to purees. The rest of the patient 44% (18) split equally between score 1 (Asymptomatic, thick Saliva, and no significant dietary alterations) and score 3 (Inability to adequately aliment and hydrate; tube feeding).

The 1st month scoring patterns did not change much at the 1st month FU except score 2, which dropped by 1 patient. At the third month FU 30% of patients experienced the most severe level of dry mouth toxicity, score 3.

At the 6-months FU scoring changed in favor to score 2 with 38% of the patients classified under this score, followed by 19% of patients scoring 3, and 16% scoring 1.

Dry mouth toxicity scoring patterns for the MIO-based post RT trismus patients included a baseline where 46% (6) scored 1 (Asymptomatic - thick Saliva, significant dietary alterations), 38% (5) scored 2 (Moderate symptoms; Oral intake alterations- diet limited to purees) and 15% scored 3 (Inability to aliment and hydrate adequately - tube feeding).

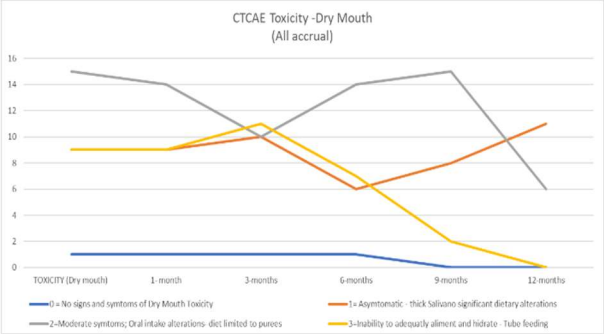


Figure 21: CTCAE 5.0 Toxicity Level - Dry Mouth - All Accrual

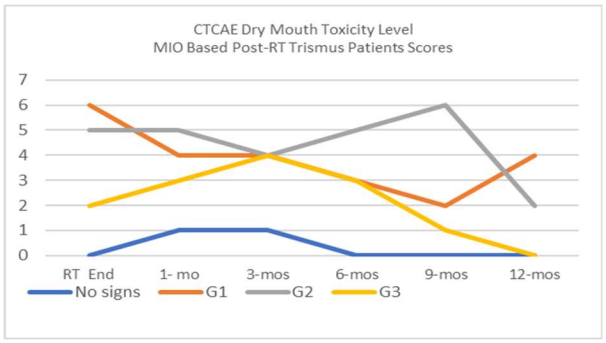


Figure 22: CTCAE 5.0 Toxicity Level - Dry Mouth (MIO-Based Post-RT Trismus Patients Scores)

5.6.5 CTCAE 5.0 Toxicity Report on RT Induced Dermatitis

Immediately after RT, 43% of the study population registered grade 2 dermatitis toxicity level (Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema), 30 % grade 1 (Faint erythema or dry desquamation, moderate to brisk erythema). 19% grade 3 (Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion). None of the patients experienced grade 4 or 5 corresponding to (Life-threatening consequences, skin necrosis or ulceration of full-thickness dermis, spontaneous bleeding from involved site;) and (Death), respectively.

At the 1st Month FU was observed an amelioration /reduction by 5% of the patients scoring grade 3 and by 11% of the patients scoring 2 while emerged an additional group of 14% (5) with no signs or symptoms of Dermatitis toxicity qualified under 0.

At the 3 months FU was observed a further reduction of the patients scoring 1 by 13%, which went in favor of the extra group 0, with no signs or symptoms of toxicity, which reached 27% of the study population.

At 6-months FU the major variation is in the number of patients scoring 2, with 11%.

The group of MIO-based post-RT trismus patients showed the following dermatitis toxicity patterns: At RT end, there was a distribution of 31% for both score 1 and score 2, while

38% for score 3. At the 1 month FU patients scoring 1 and 2 increased respectively at 38%, while score 3 reduced by 23%. At the 3 Month FU 23% of patients scored 1, 31% scored 2 and 15% scored 3, while at the 6 months FU there was an equal distribution of 23% for each scoring level.

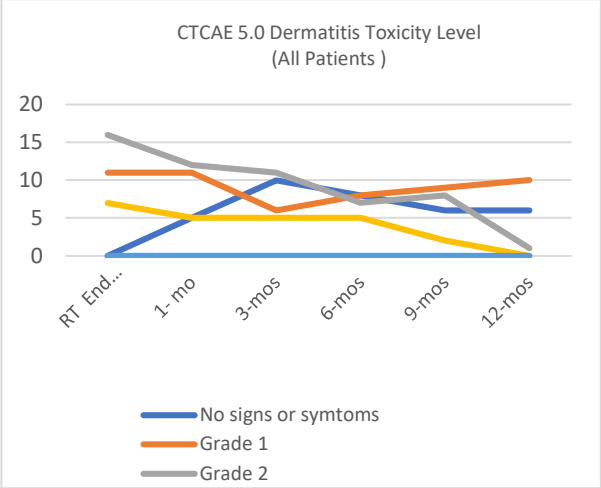


Figure 23: CTCAE 5.0 Toxicity Level Dermatitis (All Patients)

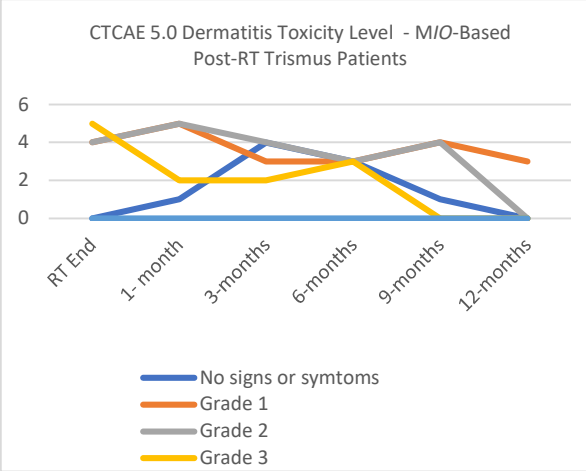


Figure 24: CTCAE 5.0 Toxicity Level Dermatitis (MIO-Based Post-RT Trismus Patients Scores)

5.6.6 CTCAE 5.0 Toxicity Report on RT Induced Dysphagia

Immediately after RT, the majority of patients (37%) scored grade 2 (Symptomatic and altered eating/swallowing), followed by 27% scoring grade 3 (Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated), 13.5% scoring grade 1 (Symptomatic, able to eat regular diet). 11 % of the study population experienced no symptoms or signs of dysphagia. Only 1 patient experienced grade 4 dysphagia (Life-threatening consequences; urgent intervention indicated) and none of the patients experienced grade 5 of dysphagia.

At 1 month FU was observed a slight decrease of the number of patients scoring grade 2 and 3, respectively by 3% and 5% in favor of the number of patients scoring 1, who increased by 4% and those not experiencing any sign and symptoms, by 3%.

At 3 months FU the number of patients experiencing grade 1 dysphagia reduced by 6%, the number of patients experiencing grade 2 by 8%, while the number of patients experiencing grade 3 dysphagia increased by 5%. The no symptoms group also increased by 5%.

At the 6-months FU it was observed a decrease by 8% of the patients experiencing grade 3 dysphagia and a decrease by 5% of those experiencing grade 1. There was an increase of 3% of the patients experiencing grade 2 while the group experiencing no signs remained unchanged.

Regarding the MIO-based post RT trismus patients, at RT end the 46% (6) experienced grade 2 dysphagia, 38% (5) grade 3 and 8% (5) grade 1 of this adverse event. None of the patients scored severe grades of Dysphagia (4 and 5). 1 patient had no sign or symptoms of this RT adverse event.

At the 1 Month FU, the number of patients scoring grade 2 reduced by 15% while the patients experiencing grade 1 and those with no dysphagia signs or symptoms increased by 7% respectively.

At 3 months FU 54% were experiencing grade 3 dysphagia, 31% grade 2. The patients with no dysphagia signs or symptoms had also an increase of 7% at this timepoint. None of the trismus patients was experiencing grade 1 dysphagia or severe grade 4 and 5 dysphagia 3 months after RT.

At the 6 months FU 38% (5) were experiencing grade 3 dysphagia, 23% grade 2 and 8% grade 1. 15 % of the trismus patients had no signs of symptoms of dysphagia at the 6-month FU.

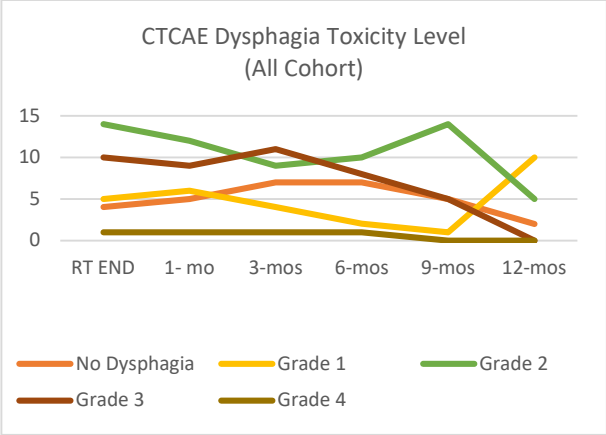


Figure 25: CTCAE 5.0 Toxicity Level Dysphagia (All Cohort)

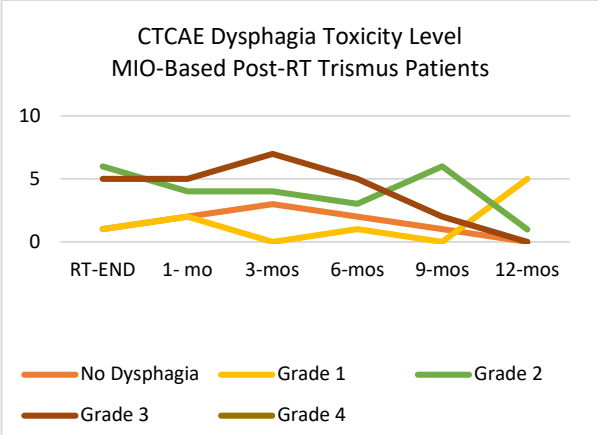


Figure 26: CTCAE 5.0 Toxicity Level Dysphagia (MIO-Based Post-RT Trismus Patients Scores)

5.7 Dosimetric findings

We identified potential constraints for MIO-based trismus related to the LP, particularly V40 and V60. Indeed, across all time points analyzed (1 month, 3 months, and 6 months), V40 and V60 of the LP bilaterally exhibited a p-value < 0.05. Additionally, we found a statistically significant difference for V27 of the left LP at 6 months and for the right LP at 1 month and 3 months.

An interesting observation relates to the tumor site. Despite 57% of patients having oropharyngeal cancer and 20% nasopharyngeal cancer, no statistically significant difference was observed based on tumor location. Similarly, laterality did not influence the results, as LP V40 and V60 were found to be significant bilaterally.

Patients treated with Linac-based techniques exhibit more acute toxicity related to trismus, developing it earlier than those treated with Tomohelical.

Further investigation is ongoing to validate these preliminary dosimetric findings.

5.8 Dental Assessment

Dental Assessment Data from 37 enrolled patients was analyzed. At initial evaluation, the median number of teeth of 20 (25^{th} percentile=4; 75^{th} percentile=26). For the purposes of this study, a tooth was defined as a fixed masticatory unit, be it a natural tooth, a crown supported by a natural root, a crown supported by an implant, or the pontic element of a fixed bridge. 18% (7 patients) had some kind of fixed prosthodontic rehabilitation in both the upper and lower arches, while 24% (9 patients) had some fixed prosthodontic rehabilitation in the upper arch; 18% (7 patients) had partial or total removable dentures.

The mean overbite, defined as the overlap between upper and lower central incisor teeth, whether natural or prosthetic, was 0.9 mm ± 1.8 mm. Overbite could not be recorded in edentulous patients who did not receive prosthodontic rehabilitation.

70% (26 patients) did not show any mandibular deviation during mouth opening, whereas 22% (8 patients) showed right-sided deviation and 8% (3 patients) showed left-sided deviation.

32% (12 patients) reported bruxism, defined as teeth clenching and/or teeth grinding: 1 patient reported daytime bruxism, 6 reported nighttime bruxism, and 5 reported both daytime and nighttime bruxism.

46% of patients (17 patients) had temporomandibular joint sounds during opening (e.g., clicking or grating), and 35% of patients (13 patients) reported masticatory muscles' tenderness during palpation.

Recurrent headache was reported by 32% (12 patients).

After dental screening prior to the beginning of radiotherapy (RT), 54% (20 patients) needed preventative tooth extraction; the median number of teeth needing extraction per patient was 3 (Q1=1.5; Q3=3.5). After pre-RT tooth extractions, included patients had a median of 18 teeth (Q1=2; Q3=23); 22% (8 patients) were fully edentulous; 59% (22 patients) had less than 20 remaining teeth.

Cephalometric tracings were obtained from the lateral cephalograms of 28 patients: 64% (18 patients) showed a mesodivergent cranial structure, 11% (3 patients) showed a

hypodivergent cranial structure, and 25% (7 patients) showed a hypodivergent cranial structure.

Figure 27 below shows the results of linear regression analysis between the mean T0/T2 variation in MIO (mean ± standard deviation = -1.75 mm ± 4.3 mm) and, respectively, the number of teeth before the beginning of RT, the cephalometric value indicating intermaxillary divergence (SpP^GoGn; mean ± standard deviation = 21.6° ± 6.1°) and the cephalometric value indicating mandibular posterior rotation (SpP^CoOr; mean ± standard deviation = 1.6° ± 3.7°). Neither the number of teeth before the beginning of RT nor intermaxillary divergence were found to be associated with the T0/T2 MIO variation. On the other hand, mandibular posterior rotation was found to be significantly associated with the T0/T2 MIO variation (p=0.01), with a regression coefficient of 0.64.

Figure 27: Results of Linear Regression Analysis between T0-T2 variations.

	p-value	MIO T0/T2 Regression coefficient
N teeth RT §	0.32	-0.07
SpP^GoGn †	0.99	0
SpP^CoOr ‡	0.01**	0.64

§ linear regression model (dependent variable=MIO T0/T2; independent variable=N teeth RT
† linear regression model (dependent variable=MIO T0/T2; independent variable=SpP^GoGn
‡ linear regression model (dependent variable=MIO T0/T2; independent variable=SpP^CoOr
N teeth RT: number of teeth at the beginning of radiotherapy
SpP^GoGn: cephalometric value indicating craniofacial vertical divergence
SpP^CoOr: cephalometric value indicating mandibular posterior rotation

Figure 28 shows the results of comparing the percentage of patients with more or less than 20 teeth before the beginning of RT with the presence or absence of temporomandibular joint (TMJ) sounds, pain at palpation of the masseter and/or lateral pterygoid muscles, opening deviation of the mandible, history of recurrent headaches and history of bruxism. No association was found between the presence of more or less than 20 teeth and any of these variables.

Figure 28:Comparative Results of Dental Assessment Parameters

	Baseline presence of:					
	TMJ sounds	**Pain at palpation masseter**	**Pain at palpation lateral pterygoid**	**Opening deviation of the mandible**	**History of recurrent headaches**	**History of bruxism**
<20 teeth	7 (25%)	6 (21%)	6 (21%)	2 (7%)	5 (17%)	5 (17%)
>20 teeth	9 (32%)	5 (17%)	5 (17%)	4 (14%)	5 (17%)	5 (17%)
p-value†	0.13	1	1	0.35	0.69	0.69

† Fisher's exact test

The percentages indicated in the table refer to a total of 28 patients included in the analysis.

5. Discussion

5.1 Literature Review

Trismus is a potentially critical morbidity following curative-intended radiotherapy in head and neck cancer patients. In our study, 22% of patients had baseline trismus, and an additional 41% developed trismus post-radiotherapy up to 12 months. The literature highlights wide-ranging trismus incidence rates following radiotherapy for head and neck cancer, with figures ranging from 38% to 79% depending on study design, population, and measurement methods [2,3,115,116,122,155,156, 365]. While patients with a history of surgery are more likely to have trismus already prior to adjuvant RT [10] due to surgical scarring (see paragraphs 2.5.1.4.1.1.1; 2.5.1.4.2.1; 2.5.1.4.2.5; 2.6.3.1.1), in the definitive setting evidence regarding this side effect underpinnings remains to be fully defined, particularly in terms of dosimetric parameters. Due to the extreme anatomical complexity and large number of organs-at-risk (OARs) to spare, radiation delivery for this district is challenging and notoriously burdened by considerable side effects [14]. Modern radiotherapy, namely image-guided intensity-modulated RT (IG-IMRT) and volumetric arc therapy (VMAT) have profoundly impacted the therapeutic index in HNC treatment improving patients' toxicity profile and tolerance [15,16,17].

Proper contouring of the trismus-related structures is critical to investigate dosimetric predictors. A new atlas for contouring masticatory muscles during RT planning for HNC has been recently published by Hague et al (Hague et al., 2019). The atlas included: medial and lateral pterygoids (MP, LP), masseter (M) and temporalis (T) muscles, and the TMJs Hague et al., 2019 [342]. Rao et al. [12] investigated the dose-volume factors in mastication muscles that are implicated as possible causes of trismus in patients following treatment with IMRT (70 Gy, median dose) and concurrent chemotherapy (predominantly cisplatin) for HNC [12]. The study included squamous cell cancers of the oropharynx, nasopharynx, hypopharynx or larynx (N = 421). Trismus was assessed using Common Terminology Criteria for Adverse Events 4.0 (CTCAE 4.0). Bi-lateral M, T, LP and MP muscles were delineated on axial computed tomography (CT) treatment planning

images, and dose-volume parameters were extracted to investigate univariate and multimetric correlations. Forty-six patients (10.9%) were observed to have chronic trismus of grade 1 or greater. From analysis of baseline patient characteristics, toxicity correlated with primary site and patient age. From dose-volume analysis, the steepest dose thresholds and highest correlations were seen for mean dose to ipsilateral M (Spearman's rank correlation coefficient Rs = 0.25) and MP (Rs = 0.23) muscles. Lyman-Kutcher-Burman modeling showed highest correlations for the same muscles. The best correlation for multimetric logistic regression modeling was with V68Gy to the ipsilateral MP (Rs = 0.29). The authors stated that this parameter could pose a competing treatment planning limitation for tumor coverage, considering the potential proximity of pharyngeal tumors to the immediately located ipsilateral MP [12]. A cross-sectional dosimetric analysis was performed by Kamal et al. [336]. to ascertain the dose–toxicity relationship for the prevalence of self-reported trismus in long-term survivors after IMRT for oropharyngeal carcinoma [336]. Self-reported mouth opening was ascertained prospectively via a cross-sectional survey of oropharyngeal carcinoma survivors using the intraoral finger test. RT dose–volume histograms (DVHs) were generated for the following masticatory regions of interest: MP, LP, and M muscles, which were designated as ipsilateral or contralateral to the primary tumor. Trismus was defined as self-reported mouth opening of <3 finger-widths. Recursive partitioning analysis (RPA) was performed to identify the dose–volume thresholds associated with late trismus. At a median follow-up time of 72 months, 29% of the survey respondents reported late trismus. Multivariate analysis demonstrated a significant association between late trismus and the following clinical variables: tonsillar primary site, advanced T stage, or higher total RT dose. RPA showed DVH-derived ipsilateral LP mean dose of 61 Gy and volume receiving 27 Gy of at least 98.6% were independently associated with late trismus. The association between the ipsilateral LP dosimetric parameters and the prevalence of late trismus was maintained after adjustment for clinical variables. The authors correctly stated that a potential study limitation was the risk of misclassification of trismus as the prevalence and severity of trismus reported by the patients were solely subjective. Indeed, a more accurate stratification of trismus would have required an objective measurement of the maximum inter-incisal opening (MIO), as well as physician/dental assessment (Kamal et al., 2020).

Our preliminary analysis, based on a limited number of patients, cannot confirm the constraints previously established by Kamal regarding V27 of the ILP and Dmean <61 Gy for the ILP [336].

Morimoto et al. developed a normal tissue complication probability (NTCP) model for trismus in HNC patients treated with RT [338]. Prospective measurements of MIO were performed at baseline and 6 months after definitive RT in 132 HNC patients. The primary endpoint of this study was defined when a patient fulfilled both of the following criteria: 1) MIO at 6 months after RT ≤35 mm and 2) MIO at 6 months after RT ≤80% of baseline MIO. Eleven clinical factors and a wide range of dosimetric factors (mean dose, maximum dose, V5, V10, V20, and V40) in twelve OARs were chosen as candidate prognostic variables. Thirty out of 132 patients (23%) developed the primary endpoint. Multivariate logistic regression analysis revealed that the mean dose to the contralateral mandible joint (p=0.001) and baseline MIO (p=0.027) were independent prognostic factors. The authors stated that this prediction model may help identify patients at high risk of developing trismus and, thus, who may benefit from preventive exercise programs (early, during, or directly after treatment) [338]

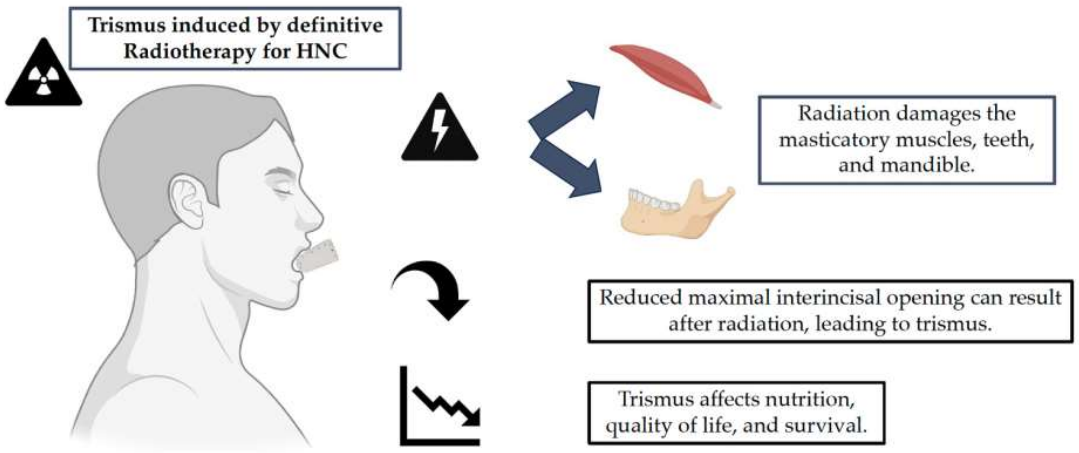


Figure 29: Trismus Induced by Definitive Radiotherapy for HNC, (Spahiu et al. 2024).

Massaccesi et al. [13] aimed at developing a prediction model for trismus (maximal interincisal distance equal to or less than 35 mm) based on a multivariable analysis of

dosimetric and clinical factors [13]. The MIO of HNC patients who underwent RT (with radical intent in 53.8% of cases) ± concurrent chemotherapy was prospectively measured (using a slide caliper) prior to RT (baseline) and 6 months post-RT. In edentulous patients (not wearing a dental prosthesis), mouth opening was measured from the alveolar ridge. One hundred and four consecutive patients were included (mean age 63 years, range 25–87), 68 males and 36 females. In the univariate analysis, the MIO at baseline, as an independent variable, and several Vdoses of different masticatory structures were found to be significant. Additionally, using a bivariate model, a feature selection process was performed. Finally, the authors considered as best performing model the MIO at baseline and V42 at M muscles. The area under curve (AUC) of Receiver Operating Characteristic (ROC) curve value was 0.8255 (95% CI 0.74–0.9). The Hosmer and Lemeshow goodness-of-fit test, used to calibrate the model, was not significant. Among the study's potential limitations, the authors reported the absence of an evaluation of the patient's reported QoL, remarking on the importance of such an assessment [13]. Regarding fractionation, the prospective randomized ARTSCAN multicenter trial investigated the long-term prevalence of radiation-induced trismus in patients treated for HNC according to two different fractionation schedules, conventional and accelerated fractionation [337]. One hundred twenty-four patients agreed to a clinical Ear-Nose-Throat (ENT) examination 21–127 months (median 66 months) after beginning RT. The TheraBite range of motion scale was used to measure maximal interincisal distance. The dose–response relationship for structures important for mastication and the TMJ was investigated by NTCP modeling. No significant differences in patient-reported trismus or maximal interincisal distance were found between the two trial arms. The best dose–response fit to the endpoint data was found for the dose to the ipsilateral M. 93% of patients had been treated with three-dimensional conformal (3D-CRT) technique. Since there was a high prevalence of long-term trismus after 3D-CRT, the authors suggested that it would be valuable to determine whether using IMRT at a reduced dose on structures important for mastication would have decreased trismus [337].

Regarding dosimetric parameters, we noted potential constraints related to the LP, particularly V40 and V60. Indeed, across all time points analyzed (1 month, 3 months, and 6 months), V40 and V60 of the LP bilaterally exhibited a p-value < 0.05. Additionally,

we found a statistically significant difference for V27 of the left LP at 6 months and for the right LP at 1 month and 3 months.

An interesting observation relates to tumor site. Despite 57% of patients having oropharyngeal cancer and 20% nasopharyngeal cancer, no statistically significant difference was observed based on tumor location. Similarly, laterality did not influence the results, as LP V40 and V60 were found to be significant bilaterally.

Noteworthy, in our study patients treated with Linac-based techniques exhibit more acute toxicity related to trismus, developing it earlier than those treated with TomoHelical.

In HNC patients treated with heavy ions, although a highly localized energy deposition allows an increase in radiation doses to the tumor while minimizing irradiation of adjacent normal tissues, trismus may also occur. Indeed, Musha et al. [344], in a prospective observational study, assessed the trismus/carbon ion dose relationship using DVHs in 35 patients [344]. Trismus was evaluated in patients according to the CTCAE v 4.0. All patients were treated with 57.6 or 64 Gy (relative biological effectiveness, RBE) in 16 fractions; the median follow-up time was 57 months. Grade 2 trismus was observed in six patients. The median onset time was 12 months. In the DVH analysis, not only the high dose of radiation received by the M muscle but also the low to middle dose range received by the coronoid process seemed to be associated with the development of C-ion RT-induced trismus [344]. Of interest, pre-treatment impaired hematological parameters (such as anemia and low hemoglobin-to-platelet ratio) have been reported as predictive markers of higher radiation-induced trismus rates [345].

Summary of the main studies' clinical findings and dosimetry trismus predictors

Summary of main studies' clinical findings and dosimetric trismus predictors. *Abbreviations:* n,number; OPC, oropharyngeal cancer; NPC, nasopharyngeal cancer; OCC, oral cavity cancer; RT, radiotherapy; 3D-CRT, 3 dimensional conformal radiotherapy; VMAT, volumetric arc therapy; ART, Adjuvant RT; w,weeks; HR, high risk volume; IR, intermediate risk volume; LR, low risk volume; cChT, concurrent chemotherapy; ChT, chemotherapy; cCRT, concurrent chemoradiotherapy; CF, conventional fractionation; AF, accelerated fractionation; T, primary tumor; ND, neck dissection; M, masseter; ILP, ipsilateral lateral pterygoid; IMP, ipsilateral medial pterygoid; IMRT, intensity modulated radiotherapy; C-ion RT, carbon ion radiotherapy; RBE, relative biological effectiveness; frs, fractions.

Study	***Population***	***Treatment***	***Clinical findings/ Dosimetric predictors***
Kamal et al. (2020) *Cross-sectional survey study [336]*	n= 587 OPC patients.	• IMRT either alone or in combination with ChT. -The mean radiation dose was 68 Gy	• Keeping ILP V27Gy <98.6% and Dmean<61 Gy may reduce the prevalence of late trismus
Rao et al. (2016) *Retrospective study [12]*	n= 421 HNC including OPC, NPC, hypopharyngeal, and laryngeal cancer patients	• IMRT and cChT (predominantly cisplatin). • 70 Gy, median dose	• V68Gy to the IMP correlates with trismus; IMP V68Gy <10 cc is recommended.
Massaccesi et al. (2022) *Prospective*	n= 104 HNC including OCC, OPC, NPC, hypopharyngeal,	• VMAT (with radical intent in 53.8% of cases) ± cChT.	• MIO at baseline and V42Gy at M muscles identified

observational study [13]	laryngeal, and major salivary glands cancer patients	• Definitive RT doses: 70, 63 and 56 Gy were administered to the HR, IR and LR volumes in 35frs, respectively. • ART dose: 60–66 Gy in 30–33 frs administered to the tumor bed.	as the most performing model for predicting trismus risk.
Morimoto et al. (2019) *Retrospective study [338]*	n= 132 HNC including OCC, OPC, NPC, hypopharyngeal, and laryngeal cancer patients	CF n=54 (94% with 3D-CRT); AF n=70 (91% with 3D-CRT). • 15 patients underwent postRT T surgery, 47 ND, 8 ND+ T surgery.	• High prevalence of long-term trismus after 3D-CRT. • No differences related to fractionation. • Significant correlation between trismus and the absorbed dose to ipsilateral M
Musha et al. (2020) *Prospective study [334]*	n= 31 HNC including maxillary sinus, nasal cavity, parotid gland, OCC, pharyngeal, and external auditory canal cancer patients.	• C-ion RT; • 64 Gy RBE in 16 frs (29/31 patients).	• M (maximum doses) showed the most significant difference between the presence and absence of trismus. • The coronoid process suggested

	as a guideline for treatment planning

Figure 30: Summary of the main studies' clinical findings and dosimetry trismus predictors. Source: Spahiu et al. 2024

Trismus-related radiological findings, particularly in the case of functional imaging, may help clarify the underpinnings of the radiation induced damage. However, the magnetic resonance imaging (MRI) - based study of masticatory muscles has yet to receive much attention in the literature. Distinguishing post-radiation effects from denervation atrophy and tumor recurrence requires consideration of location, clinical findings, previous images, and timing of the changes, given the expected time course of evolution of post-radiation and denervation changes [339] In this regard, Al-Saleh et al. (2013) [339] conducted a systematic review. The included papers (Ariji et al., 2002; Bhatia et al., 2009; Chong et al., 2000; Pajari et al., 1996) [346, 347, 343, 348] focused on the MRI appearance of masticatory muscles following RT [339]. All included papers reported the MRI findings of the masticatory muscles at least 12 months after RT completion. Two papers reported outcomes based on retrospective clinical and imaging records [347, 343], whereas the remaining two were case reports [346, 348]. Also, muscle size changes were reported based on subjective comparison with the contralateral side. The quality of all included papers was considered poor, with a high risk of bias. Irradiated muscles have been observed to show a diffuse increase in T2 signal and post-gadolinium enhancement [339]. Thor et al. investigated the ability of textures from T1-weighted MRI scans post-contrast (T1wPost) to identify the critical muscle(s) for radiation-induced trismus [349]. The study included ten cases (trismus: ≥Grade 1) and ten controls treated with IMRT to 70 Gy. Trismus status and T1wPost were conducted within one-year post-RT. For the M, LP and MP, and T muscles, 24 textures were extracted (Grey Level Co-Occurrence (GLCM), Histogram, and Shape). Univariate logistic regression with Bootstrapping (1000 populations) was applied to compare the muscle mean dose (Dmean) and textures between cases and controls (ipsilateral muscles); candidate predictors were suggested by an average $p \leq 0.20$ across all Bootstrap populations. Dmean to M/LP/MP ($p=0.03/0.14/0.09$), one MP/T ($p=0.12/0.17$), and three M ($p=0.14–0.19$) textures were

candidate predictors. Three of these textures were GLCM- and two Histogram textures, with the former being generally higher and the latter lower for cases compared to controls. The Dmean to M and MP, and Haralick Correlation (GLCM) of MP presented with the best discriminative ability (area under the receiver-operating characteristic curve: 0.85, 0.77, and 0.78), and the correlation between Dmean and this texture was weak (Spearman's rank correlation coefficient: 0.26–0.27). This study demonstrated an image- and dose-based approach, rather than the widely used dose-based approach, to assess dose-response relationships and, more specifically, by quantifying intensities from T1-weighted MRI scans after gadolinium administration as a means to measure radiation-induced normal tissue injury. The findings pointed towards a multi-masticatory involvement for trismus, emphasizing the dose to the M and the MP, and the local relationship between the mean and the variance of the MRI intensity within the MP [349]. Various imaging modalities are available to investigate radiation-induced TMJ damage: plain and panoramic radiography, CT, ultrasonography, and MRI [350]. MRI is commonly used to evaluate TMJ because it provides superior contrast resolution and can acquire dynamic imaging to demonstrate the functionality of the joint [350]. With the high contrast sensitivity to tissue differences, including TMJ, MRI has now replaced CT and acts as the gold standard for diagnosing TMJ disorder [350]. In terms of QoL, while RT plus concomitant chemotherapy has become an accepted treatment modality in advanced HNC to achieve organ preservation, unfortunately, it is not synonymous with function preservation [340]. Patient-reported outcomes (PROs) instruments are becoming increasingly important because reliable measures of how the patients experience their symptoms can be considered equally important in clinical research as survival and mortality [341]. Patients with trismus experience restricted or painful mouth opening that may limit oral intake, impair speech, and worsen oral hygiene [336]. In the previously discussed ARTSCAN trial, trismus-related scores were assessed using the EORTC H&N35 QoL questionnaire [337]. Patients reported moderate to high scores regarding trismus, which increased from 3% at the start of RT to 25% at the long-term follow-up. Maximal interincisal distance correlated significantly with patient-reported scores of trismus [337]. In this regard further analysis of our study population comorbidities and lifestyle factors will be essential to comprehend QoL data and trends following treatment.

Johnson and Colleagues developed and validated a comprehensive, self-administered questionnaire for patients with limited ability to open their mouths [341]. The authors derived the Gothenburg Trismus Questionnaire (GTQ) from empirical evidence in the medical literature and interviews with medical experts and patients. The draft version was tested in a pilot study (n = 18). Patients with MIO of ≤35 mm were included. The study comprised patients with benign jaw-related conditions (n = 51), patients treated for HNC (n = 78), and an age- and gender-matched control group without trismus (n = 129). The GTQ instrument was well accepted by the patients, with satisfactory compliance and low rates of missing items. After item reduction, due to items not being conceptually relevant and/or low factor loadings, the GTQ demonstrated high internal consistency (Cronbach's alpha 0.72–0.90), good construct validity and known-group validity. Thus, this clinically relevant questionnaire has been recommended as a screening tool and an endpoint in intervention and jaw physiotherapy/rehabilitation studies [341]. Loh et al. [351] performed a systematic review to compare the subjective measure of trismus between different interventions to treat HNC, particularly those of the oropharynx [351]. Among the six studies reviewed, five showed a significantly worse outcome about the QoL questionnaire scores for RT or surgery and RT ± chemotherapy or chemoRT when compared to surgery alone. There was no consensus on which treatment modality had better outcomes overall [351].

Noteworthy, it is conceivable that patients' susceptibility to the development of post-RT trismus may be, at least in part, correlated with features of craniofacial structure, particularly those influencing the orientation of the masticatory muscles. Hyperdivergent, dolichofacial cranial structures (i.e., a cranial structure where the vertical dimension is dominant over the horizontal one, with a long, thin facial type) have been associated with reduced maxillary size, leading to a higher incidence of certain malocclusions, most notably posterior crossbite [353, 354, 355, 356, 357, 358, 359]. It has been postulated that the more oblique position of the masseter, medial pterygoid and buccinator muscles in hyperdivergent patients leads to an increased level of tension on the bones of the midface, and the maxilla in particular, limiting the extent of transverse growth of the palate [354, 360, 361]. On the other hand, hypodivergent, brachyfacial individuals have more vertically oriented masticatory muscles' insertions, leading to wider dental arches and

less dental crowding. The orientation of masticatory muscles' insertion is also correlated with the rotation of the mandible relative to the rest of the facial complex. It is, in other words, interesting to observe that masticatory muscles' insertion orientation and craniofacial structure are correlated, which translates to typical patterns of malocclusion and temporomandibular joint dysfunction [362]. In the context of the present study, it was very interesting to investigate the correlation between craniofacial structure and MIO progression after the beginning of RT. Two cephalometric measurements were identified as likely candidates for a positive association:

- I) intermaxillary divergence (SpP^GoGn), i.e., the angle formed between the maxillary and the mandibular planes, which is increased in hyper-divergent subjects;
- II) clockwise mandibular rotation (SpP^CoOr), i.e., a cephalometric angle that expresses the degree of mandibular posterior rotation relative to the position of the maxillary plane.

As some patients in this study were edentulous or had received prosthodontic rehabilitation prior to their enrolment, cephalometric measurements dependent on dental landmarks were not considered, to reduce the risk of bias. Preliminary data analysis showed no correlation between MIO reduction (pre-RT/6-month post-RT) and intermaxillary divergence, but a positive correlation ($p=0.01$, regression coefficient=0.64) between clockwise mandibular rotation and MIO reduction (pre-RT/6-month post-RT). This finding needs to be confirmed by subsequent analysis at the end of data collection for this study; at present, nevertheless, it appears that the higher the degree of mandibular posterior rotation relative to the maxillary bones, the more MIO tends to decrease after the beginning of RT.

Many treatment modalities for preventing or improving limited mouth opening have been proposed, such as programs using different jaw-stretching devices, mouth-opening exercises, or a combination of devices and exercises (6; 363). In 2015, Kamstra et al. [363] performed a systematic review regarding exercise therapy for trismus secondary to HNC. Two hundred-eleven articles were found, and 20 studies were included [364]. A significant variation in research methodology, stretching techniques, duration of stretch,

and repetition of exercises was found. The overall quality was moderate. Five of the eight preventive studies found that exercises during (chemo-) RT could not prevent a reduction in mouth opening. In 4 therapeutic case studies, mouth opening increased between 17 and 24 mm. In 8 other therapeutic studies, mouth opening increased between 13.6 and 21.9 mm. No exercise therapy was superior to the others (Kamstra et al., 2017). In 2020, Shao et al. published a systematic review and meta-analysis evaluating the effectiveness of exercise therapy combined with a jaw mobilizing device in preventing and treating cancer treatment-induced trismus (Shao et al., 2020). Six studies assessed MIO and found that exercise therapy adjuvant to the use of a jaw-mobilizing device significantly improved the MIO from 4.48 (95% CI = 0.20, 8.75) to 14.20 (95% CI = 10.73, 17.67) mm. Seven studies evaluating the preventive outcome of the incidence of trismus found no significant difference between standard usual care and exercise therapy adjuvant to using a jaw-mobilizing device (risk ratio = 1.20; 95% CI = 0.61, 2.34). The authors concluded that exercise therapy can lead to MIO improvement following the development of cancer treatment-induced trismus but does not prevent trismus in patients being treated for HNC (Shao et al., 2020). The minimum MIO observed in our population (at the present analysis, Figure 10) provides critical insight into the extent of functional impairment experienced by patients, highlighting the need for targeted interventions to mitigate the impact of RT on masticatory function *(see 2.5.1.4.1.1.2; 2.5.1.4.2.3; 2.5.1.4.2.6; 2.5.2.5.1; 2.5.3.2.1; 2.5.3.2.3; 2.5.3.3).*

6. Conclusions

Trismus is a detrimental radiation-induced side-effect, jeopardizing the QoL of HNC patients. Literature evidence regarding the biological underpinnings and the clinical/dosimetric predictors of trismus in HNC patients treated with definitive RT is still scant.

We realized this study thanks to an interdisciplinary collaboration involving particularly radiation oncologists and orthodontist specialists.

This allows us to collect specific clinical data (dental and cephalometric data) that will enable us to seek associations and correlations between dosimetric parameters and clinical predictors.

In this interim analysis, we highlight a potential role as a dosimetric predictor for trismus at six months for bilateral lateral pterygoid muscles.

Noteworthy, this multidisciplinary study highlighted a positive correlation between the cranial feature with clockwise mandibular posterior rotation and MIO reduction which could be considered a predisposition to trismus development requiring special care for these patients from the beginning of the radiotherapy.

Of course, given the nature of this interim analysis (accrual to be completed and short follow-up), the present data should be taken with caution.

Finally, tumor control should routinely take priority in the treatment planning process to avoid disease progression (see paragraphs: 2.5.1.5; 2.5.2.5.2; 2.5.2.5.4; 2.5.3.2; 2.5.3.3). Future prospective studies are eagerly awaited.

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