Rating the methodological quality of Patient-Reported Outcome Measures for Radiotherapy Induced Xerostomia in Head and Neck Cancer

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Abstract

Radiotherapy-induced xerostomia (RIX) is the most commonly experienced late stage adverse effect of radiotherapy of head and neck malignancy. RIX can influence a patient's restoration of oral function, adversely affect their quality of life and possibly their prognosis. Knowledge of the severity of RIX is relevant as it can guide treatment. Measuring RIX can be done either objectively or subjectively. When measuring RIX subjectively, this is best performed with a patient-reported outcome measure (PROM). PROMs may be an effective tool in assessing xerostomia. However, to ensure that data captured by a PROM is trustworthy and can be used in reporting on the symptom with confidence, the PROM should have been appropriately validated. The aim is to identify high quality PROMs that measure RIX outcomes in order to be recommended for use on a population residing in England. After applying the COSMIN guidelines, this was performed by a systematic review that identified four RIX-specific PROMs (XQ, XI, GRIX and XeQoLS). All four PROMs were found to have methodological shortcomings in their validations. A qualitative study including focus group interviews, was performed to select the most suitable PROMs among the four PROMs, the XI and XeQoLS were then selected.

The XI and XeQoLS were tested for their validity and reliability on a sample of 75 RIX patients with HNC residing in England. Both PROMs had an acceptable overall score for internal consistency ($\alpha = 0.951$ and $\alpha = 0.839$ respectively). Structural validity; factor analysis, was below the acceptable score; XI (TLI= 0.632 and CFI=0.755 < 0.95) and XeQoLS (TLI= 0.838 CFI= 0.887< 0.95). Hypothesis testing score between both PROMs was a Spearman's correlation score of 0.74, this suggests an accordance with the tested hypothesis. Test-retest reliability was performed by calculating weighted kappa, scores for XI and XeQoLS (k = 0.484 and k = 0.473), these scores are considered good or fair scores (0.4 to 0.75). XI and XeQoLS questionnaires are therefore validly and reliably able to measure xerostomia outcomes in RIX patients with HNC residing in the England, based on their current construct. However there is a need for structural validity to be evaluated in a larger sample size.

Impact Statement

Despite the improvements to reducing delay of radiotherapy, radiotherapy-induced xerostomia (RIX) remains a common adverse effect of radiotherapy for head and neck malignancy. Loss of salivary gland function gives rise to a spectrum of symptoms that likely can reduce the quality of life of affected individuals and possibly delay or prevent the full recovery from the treatment of head and neck malignancy. To aid both present day clinical care and future research there is a need to accurately determine a patient's experience of the severity of dry mouth.

This work aimed at reporting on a high quality; in terms of validity and reliability, RIX-specific patient-reported outcome measure (PROM). After identifying four PROMs in a systematic review, all PROMs had discrepancies when assessed methodologically. Two PROMs out of four were then selected in a qualitative study and tested on RIX patients with HNC in England. Both were found to be valid and reliable, from a statistical standpoint, to measure RIX outcomes accurately. However structural validity for both PROMs, was found to be in need for further research.

It is hoped that this work sets a trend towards ensuring the methodological quality of an outcome measure is scrutinised prior to its use in clinical research and care. This approach will ensure that results of trials are meaningful when translated into everyday clinical care.

Declaration

I, Motaz Assas confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abbreviations

ADC	Apparent diffusion coefficient
AF-RT	Accelerated fractionation radiotherapy
AJCC	The American Joint Committee on Cancer
ATP	Adenosine 5′-triphosphate
CECT	Contrast-enhanced CT
CRT	Chemoradiotherapy
CI	Confidence interval
CT	Computed tomography
COSMIN	COnsensus-based Standards for the selection of health Measurement Instruments
CROMS	Clinician-reported outcome measures
CTCAE	Common Toxicity Criteria for adverse effect
DCE-PWI	Dynamic contrast-enhanced perfusion-weighted imaging
DW MRI	Diffusion-weighted MRI
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-H&N	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Head and Neck
FACT H&N	The Functional Assessment of Cancer Therapy general
FGI	Focus group interviews
FNAC	Ultrasonography with fine-needle aspiration cytology
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRIX	Groningen Radiotherapy-induced Xerostomia
Gy	Gray (unit of radiation)
HF-RT	Hyper-fractionation radiotherapy
HNC	Head and neck cancer
HNSCC	Squamous cell carcinomas in the head and neck

HPV	Human papilloma virus
HPV-HNSCC	Human papilloma virus related head and neck squamous cell carcinoma
HR-QoL	Health-Related Quality of Life
HR-PROM	Health-Related Patient-Reported Outcome measure
ICC	Interclass correlation coefficient
IMRT	Intensity-modulated radiation therapy
ISOQOL	The international society for Quality of Life Research
LENT- SOMA	Late Effects Normal Tissue Task Force Subjective Objective Management Analytic
MASCC	Multinational Association for Supportive Care in Cancer
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
NICE	The National Institute for Health and Care Excellence
OPSCC	Oropharyngeal squamous cell carcinoma
OR	Odds ratio
ORN	Osteoradionecrosis
OSCC	Oral squamous cell carcinoma
PBT	Proton beam therapy
PET/CT	Positron emission tomography
PET MRI	Positron emission tomography combined with MRI
PMD	potentially malignant disorder
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QoL	Quality of Life
QOL-RTI/H&N	Quality of Life Radiation Therapy Instrument Head and Neck Module
RT	Radiotherapy
RIT	Radiotherapy-induced trismus
RIX	Radiotherapy-induced xerostomia

RTOG	Radiation Therapy Oncology Group functional scale
SAC-MOT	The Scientific Advisory Committee of the Medical Outcomes Trust
SGT	Submandibular transfer
SGS	Salivary gland scintigraphy
SPECT	Single proton computed tomography
SCC	Squamous cell carncinoma
SUV	Standardised uptake value
TCGA	The Cancer Genome Atlas
TNM	Tumour nodule metastasis classification
TPF	5-fluorouracil
UADT	Upper aero-digestive tract
UICC	The Union Internationale Contre le Cancer
US	ultrasonography
UWQOL	University Washington quality of life Questionnaire
XeQoLS	the xerostomia quality of life scale
XI	Xerostomia Inventory
XQ	Xerostomia Questionnaire
VAS	Visual analogue scale
3D-CRT	Three-Dimensional Conformal Radiation Therapy
5FU	5-fluorouracil
^{18}F-FDG PET	^{18}F-fluorodeoxyglucose positron emission tomography

Chapter One

Literature Review

1   Head and Neck Cancer

1.2 Definition

Head and neck cancer (HNC) refers to a collective term describing all tumours affecting the upper aero-digestive tract (UADT), which includes more than 30 sites, such as oral, lip, nasal, pharyngeal, and laryngeal, salivary glands and para-nasal sinus cancers (Tobias and Hochhauser, 2014). The term excludes other diseases arising in the area, such as brain tumours (Ray-Chaudhuri et al., 2013). HNC can develop from different histopathological and anatomical sites within the head and neck region, however, squamous cell carcinomas of the head and neck (HNSCC) account for 85% to 90% of HNC (Tobias and Hochhauser, 2014).

1.3 Epidemiology

More than 880,000 cases of HNC are newly identified worldwide per annum, representing 4.9% of all cancers (Bray et al., 2018). In 2012, oral or lip cancer incidences and mortality rates ranked eighth and tenth most common cancer among men in under-developed and developing countries respectively (Ferlay et al., 2013, Ferlay et al., 2015). Even though both incidences and mortality rates for oral or lip cancer are less in developed countries (Ferlay et al., 2010, Torre et al., 2015, Ferlay et al., 2013, Mehanna et al., 2010a). Recent trends (2018) indicate incidences and mortality rates for oral or lip cancer are now the 18th and 16th most common cancer worldwide, respectively (Bray et al., 2018). There had been a steady decline in oral or lip cancer between 2002 (389,000 cases) and 2012 (300,373 cases). However, recent published numbers on cases of oral or lip cancer which might indicate an increase or an upwards trend (354864 cases) (Bray et al., 2018). Lip or oral cancer remain the most frequent HNC in the UK, probably reflecting trends in tobacco and alcohol use, followed by oropharyngeal and laryngeal cancer respectively (Ferlay et al., 2010, Bray et al., 2018, Ferlay et al., 2013, Tobias and Hochhauser, 2014).

Tables 1.1 and 1.2 indicate the estimated new cases, deaths and 5-year prevalence for cancer both worldwide and in the UK.

Table 1.1 Estimated new cases, deaths and 5-year prevalence for cancer worldwide[1]:

Cancer	New cases						Deaths						5-year prevalence	
	Number of cases	Male	Female	Rank	(%)	Cumulative risk	Number of cases	Male	female	Rank	(%)	Cumulative risk	Number	Prop.
Lip, oral cavity	354,864	246,420	108,444	18	2.07	0.46	177,384	119,693	57,691	16	1.99	0.23	913514	11.97
Larynx	177,422	154,977	22,445	23	1.28	0.25	94,771	81,806	12,965	20	1.06	0.13	488900	6.41
Nasopharynx	129,079	93,416	35,663	25	0.75	0.16	72,987	54,280	18,707	22	0.82	0.10	362219	4.75
Oropharynx	92,887	74,472	18,415	25	0.75	0.16	51,001	42,116	8,889	22	0.82	0.10	362219	4.75
Hypopharynx	80,608	67,496	13,112	27	0.47	0.11	34,984	29,415	5,569	27	0.39	0.05	119130	1.56
Salivary Glands	52,799	29,256	23,543	30	0.31	0.06	22,176	13,440	8,736	30	0.25	0.03	123460	1.62

[1]Incidence population-weighted average of the area-specific rates applied to the 2018 world population. Mortality population-weighted average of the area-specific rates applied to the 2018 world population. Prevalence Sum of area-specific prevalent cases BRAY, F., FERLAY, J., SOERJOMATARAM, I., SIEGEL, R. L., TORRE, L. A. & JEMAL, A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 0..

Table 1.2 Estimated new cases, deaths and 5-year prevalence in UK population[2]:

Cancer	New cases				Deaths				5-year prevalence	
	Number	Rank	(%)	Cumulative risk	Number	Rank	(%)	Cumulative risk	Number	Prop.
Lip, oral cavity	6087	19	1.42	0.60	1701	20	1.04	014	19987	30.02
Larynx	2482	26	0.58	0.24	906	24	0.55	0.07	8537	12.82
Nasopharynx	269	34	0.06	0.03	186	32	0.11	0.01	900	1.35
Oropharynx	3049	24	0.71	0.35	872	25	0.53	0.09	11008	16.54
Hypopharynx	782	33	0.18	0.08	337	30	0.21	0.03	1432	2.15
Salivary Glands	803	32	019	0.07	265	31	0.16	0.02	2193	3.29

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[2] Incidence and Mortality National rates projected to 2018 Prevalence computed using sex-; site- and age-specific incidence to 1-;3- and 5-year prevalence ratios from Nordic countries for the period (2000-2009), and scaled using human development index (HDI) ratios ibid.

1.4 Histopathology

About 90% of all HNCs arise from squamous cells, resulting in squamous cell carcinomas (SCC). The reminder arises from salivary glands, mesenchymal cells, neuroectodermal cells, lymphoid cells and other types (Harrison, 2014) (table 1.3).

A variety of different SCCs can arise in the head and neck including conventional SCC, papillary SCC, adenoid SCC, verrucous carcinoma, spindle cell squamous carcinoma, basal SCC, nasopharyngeal carcinoma, carcinoma cuniculatum , adenosquamous carcinoma acantholytic SCC, and lymphoepithelial SCC (Bice et al., 2015, El-Naggar, 2017, Ranganathan and Kavitha, 2019, Fritsch et al., 2014, Rytkonen et al., 2011, Kass et al., 2015, Sun et al., 2012, Muller, 2017).

The majority of squamous cell carcinomas do not arise de-novo but are the late consequences of cellular changes that are histopathologically collectively termed dysplasia (Porter et al., 2018). It can arise in association with a variety of potential oral mucosal diseases but is typically caused by tobacco and/or alcohol. Dysplasia is histopathologically graded into mild, moderate, severe, and carcinoma in-situ (CIS) (El-Naggar, 2017, Ranganathan and Kavitha, 2019). Each is suggested to carry a different chance of developing malignant invasive SCC. Mild or moderate dysplasia may reverse and not all dysplasias progress to carcinoma. Severe dysplasia and carcinoma in-situ without doubt will always irreversibly progress to SCC being succeeded by invasion of abnormal cells beyond the basal membrane (Harrison, 2014).

Table 1.3 WHO Classification of malignant tumours in the head and neck region

Tumour site	Classifications

Nasal Cavity, paranasal sinuses and skull base	• Carcinomas
	   ○ Keratinising squamous cell carcinoma
	   ○ Non-keratinising squamous cell carcinoma
	   ○ Spindle cell squamous cell carcinoma
	   ○ Lymphoepithelial carcinoma
	   ○ Sinonasal undifferentiated carcinoma
	   ○ Neuroendocrine carcinomas
	   ○ Adenocarcinomas
	• Malignant soft tissue tumours
	   ○ Fibrosarcoma
	   ○ Undifferentiated pleomorphic sarcoma
	   ○ Leiomyosarcoma
	   ○ Rhabdomyosarcoma, NOS
	   ○ Embryonal rhabdomyosarcoma
	   ○ Pleomorphic rhabdomyosarcoma, adult type
	   ○ Spindle cell rhabdomyosarcoma
	   ○ Angiosarcoma
	   ○ Malignant peripheral nerve sheath tumour
	   ○ Biphenotypic sinonasal sarcoma
	   ○ Synovial sarcoma

Nasopharynx	• Carcinomas
	   ○ Nasopharyngeal carcinomas
	      ▪ Non-keratinising squamous cell carcinoma
	      ▪ Keratinising squamous cell carcinoma
	      ▪ Basaloid squamous cell carcinoma
	   ○ Nasopharyngeal papillary adenocarcinoma

Hypopharynx, larynx, trachea and parapharyngeal space	• Malignant surface epithelial tumours
	   ○ Conventional squamous cell carcinoma
	   ○ Verrucous squamous cell carcinoma
	   ○ Basaloid squamous cell carcinoma
	   ○ Papillary squamous cell carcinoma
	   ○ Spindle cell squamous cell carcinoma
	   ○ Adenosquamous carcinoma
	   ○ Lymphoepithelial carcinoma

	• Precursor lesions
	  ○ Dysplasia (low grade, high grade)
	  ○ Squamous cell papilloma
	  ○ Squamous cell papillomatosis

Oral cavity and mobile tongue	• Epithelial tumours and lesions
	  ○ Squamous cell carcinoma
	  ○ Oral epithelial dysplasia (Low grade/High grade)
	  ○ Proliferative verrucous leukoplakia
	• Papillomas
	  ○ Squamous cell papilloma
	  ○ Condyloma acuminatum
	  ○ Verruca vulgaris
	  ○ Multifocal epithelial hyperplasia
	• Oral mucosal melanoma

Oropharynx (base of tongue, tonsils, adenoids)	• Squamous cell carcinoma
	  ○ Squamous cell carcinoma, HPV-positive
	  ○ Squamous cell carcinoma, HPV-negative

Neck and lymph nodes	• Tumours of unknown origin
	  ○ Carcinoma of unknown primary
	  ○ Merkel cell carcinoma
	  ○ Heterotopia-associated carcinoma

Salivary glands	• Malignant tumours
	  ○ Mucoepidermoid carcinoma
	  ○ Adenoid cystic carcinoma
	  ○ Acinic cell carcinoma
	  ○ Polymorphous adenocarcinoma
	  ○ Clear cell carcinoma
	  ○ Basal cell adenocarcinoma
	  ○ Intraductal carcinoma
	  ○ Adenocarcinoma, NOS
	  ○ Salivary duct carcinoma
	  ○ Myoepithelial carcinoma
	  ○ Epthithelial-myoepithelial carcinoma
	  ○ Carcinoma ex pleomorphic adenoma
	  ○ Secretory carcinoma
	  ○ Sebaceous adenocarcinoma
	  ○ Carcinosarcoma
	  ○ Poorly differentiated carcinoma

	▪ Undifferentiated carcinoma
	▪ Large cell neuroendocrine carcinoma
	▪ Small cell neuroendocrine carcinoma
	  ○ Lymphoepithelial carcinoma
	  ○ Squamous cell carcinoma
	  ○ Oncocystic carcinoma
	  ○ Uncertain malignant potential
	    ▪ Sialoblastoma

Odontogenic and maxillofacial bone tumours	• Odontogenic carcinomas
	  ○ Ameloblastic carcinoma
	  ○ Primary intraosseous carcinoma, NOS
	  ○ Sclerosing odontogenic carcinoma
	  ○ Clear cell odontogenic carcinoma
	  ○ Ghost cell odontogenic carcinoma
	• Odontogenic carcinosarcoma
	• Odontogenic sarcomas
	• Malignant maxillofacial bone and cartilage tumours
	  ○ Chondrosarcoma
	    ▪ Chondrasarcoma (grade 1, grade 2/3)
	    ▪ Mesenchymal chondrosarcoma
	    ▪ Osteosarcoma, NOS
	      • Low-grade central osteosarcoma
	      • Chondraoblastic osteosarcoma
	      • Parosteal osteosarcoma
	      • Periosteal osteosarcoma

Tumours of the ear	• Tumours of the external auditory canal
	  ○ Squamous cell carcinoma
	  ○ Adenocarcinoma
	  ○ Ceruminous adenocarcinoma
	  ○ Adenoid cystic carcinoma
	  ○ Mucoepidermoid carcinoma
	  ○ Ceruminous adenoma
	• Tumours of the middle and inner ear
	  ○ Squamous cell carcinoma
	  ○ Aggressive papillary tumour

1.5 Risk factors

HNC arising from squamous cells are almost always caused by lifestyle factors; particularly alcohol, tobacco products and HPV. Appropriate review articles are available (Porter et al., 2018, Kumar et al., 2016, Ernani and Saba, 2015, Radoi and Luce, 2013) and the present text will focus upon key concepts of the aetiopathogenesis of oral squamous cell carcinoma (OSCC).

Tobacco use

Tobacco use is widely known to expose users to carcinogenic agents. Whether smoked or chewed, tobacco use is considered a risk factor for developing many cancers, particularly HNC (Lubin et al., 2007, Radoi and Luce, 2013, Jethwa and Khariwala, 2017, Du et al., 2019). The link between tobacco smoking and oral cancer appearance has been determined epidemiologically in the past (Gupta et al., 1995). Key carcinogenic agents in tobacco smoke are the aromatic hydrocarbon benz-pyrene and the tobacco-specificnitrosamines (TSNs) specifically 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN). Studies performed on animals has shown that NNK and NNN in the tobacco products cause tumours in the oral cavity and elsewhere when their metabolites chemically bond to deoxyribonucleic acid (DNA), creating DNA adducts and disturbing normal genetic sequencing. When these carcinogens are metabolised, oxygenation by P450 enzymes and conjugation by glutathione-S-transferase (GST) occurs and these enzymes are believed to cause a genetic predisposition to tobacco-induced HNC (Warnakulasuriya et al., 1999, Scully et al., 2000). A pooled International Head and Neck Cancer Epidemiology consortium (INHANCE) analysis of 19,660 HNC cases and 25,566 controls, studied the relative risk of smoking cigarettes and HNC incidences found that there is no harmless level of cigarette smoking- as even at a level of three cigarettes a day showed as much as a 50% increase in the risk of developing HNC. The analysis also reported an association between amount of tobacco and duration of the habit, the greater the amount (e.g. number of cigarettes per day) and the longer the use of the habit- the higher the risk (Berthiller et al., 2015). Another

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INHANCE pooled analysis from 17 European and American case-control studies (11,221 cases and 16,168 controls) including 2993 oral cavity cancer cases, found the risk of developing oral cancer in individuals who only smoked was approximately 25% more compared with controls (Hashibe et al., 2009). Moreover, A Taiwanese "population-based" screening program of oral cancer was carried out in Taiwan from 2004-2017 (51% of the population) has found that individuals using tobacco products; namely tobacco smoking and betel quid chewing, were at greater risk of presenting with oral leukoplakia or developing other variants of oral cancer compared with the rest (2.7 folds) (Chuang et al., 2017).

Smokeless tobacco refers to all tobacco products that are either placed orally or nasally, it comes in many varieties and concoctions depending on location and local preference. In recent years, with the increasing prices of cigarettes and widespread misbelief that smokeless tobacco carries less harmful effects on oral health has increased the number of smokeless tobacco users (Mallery et al., 2014). One popular type of smokeless tobacco is betel quid chewing; also referred to as pan or paan, which typically contains betel leaf (leaf of Piper betel vine), areca nut, slaked lime, and tobacco. Other ingredients are often added based on cultural or country preferences, namely spices such as cardamom, cloves, lime, or aniseed to the quid in India and turmeric in Thailand, among more diverse subtypes and variations (Kumar et al., 2016). Studies have described lime, in particular, when mixed with the tobacco when preparing betel-nut quid, can carry a greater oncogenic potential as a result of lime alkalinisation increasing cytotoxic and genotoxic changes in the oral mucosa (Hukkanen et al., 2005). Moreover, when this mixed is chewed, a by-product called reactive oxygen species (ROS) os releases in the oral mucosa which play a critical role in chemical carcinogenesis (Franke et al., 2015, Hukkanen et al., 2005, Jeng et al., 2001). Studies done on oral mucosal fibroblasts in vitro showed some essential betel quid ingredients are genotoxic, cytotoxic, and also stimulate cell proliferation, especially showing reactive oxygen species (ROS), methylating agents, and reactive metabolic intermediates from betel quid which induces various kinds of DNA damage (Hecht, 2003). Moreover, a conceptual model of smokeless-tobacco-associated

carcinogenesis suggested that carcinogens present in smokeless tobacco products are ingested and the carcinogens metabolically activated. This causes the formation of DNA adducts and subsequent mutations in K-ras, p53, among other genes resulting in uncontrolled cell growth (Schwab, 2008). Other mechanisms such as activation of Akt and protein kinase A lead to reduced apoptosis and increased angiogenesis and cellular transformation. Apart from TSNAs, other compounds present in smokeless tobacco products such as polycyclic aromatic hydrocarbons and areca nut may also contribute to causation of cancer in smokeless tobacco users (Stanfill et al., 2011). Published studies have demonstrated high risk estimates of cancer occurrence in smokeless tobacco users (Sinha et al., 2018, Siddiqi et al., 2015, Stanfill et al., 2011, Mallery et al., 2014, Hecht, 2003). A meta-analysis of the global burden of all cause and cause specific mortality due to smokeless tobacco use, including prevalence data for 199 countries or 350 million users worldwide, found that smokeless tobacco was significantly associated with all mortality outcomes. The strongest association was found for UADT cancer (2.17; 1.47–3.22). The number of deaths that might be attributed to smokeless tobacco, due to all causes, was 652 494 (234 008–1 081 437), contact aetiology might play a critical role (Gupta et al., 2018). The bigger burden of this estimate (88%) is proportioned to Southern East Asia, studies on Europe showed no statistical significance in the association between all-cause mortality and smokeless tobacco (Sinha et al., 2018). Smokeless tobacco may be the single largest risk factor for intervention in the prevention of about 650 000 deaths, which is about 10% of all deaths that can be attributed to all forms of tobacco use, worldwide (Gupta et al., 2018).

Alcohol consumption

Alcohol consumption is also a well-known common risk factor for HNC. Systemic effects of alcohol mainly occurs from hepatic damage in alcoholic addiction, also liver cirrhosis and other diseases, i.e. cardiomyopathy, stroke, and dementia, apart from inhibiting the detoxification of carcinogenic compounds (Ogden and Wight, 1998, Lubin et al., 2009). Studies have identified carcinogens in alcohol, such as N-nitroso compounds, mycotoxins, urethane, inorganic

arsenic, among others. One major metabolite of alcohol, acetaldehyde is thought to cause DNA damage in mammal cells (Salaspuro, 2003, Tsuruta et al., 2020). Moreover, tobacco smokers can have seven times more salivary acetaldehyde than non-smokers when consuming alcohol (0.8/kg bodyweight of ethanol) (Salaspuro and Salaspuro, 2004). Acetaldehyde is a highly toxic and mutagenic agent and a local and topical carcinogen (Salaspuro, 2003). It occurs in the mouth as a result of the oxidation of alcohol orally by alcohol dehydrogenases (ADHs) and oral microflora (Seitz and Oneta, 1998).

Acetaldehyde is mainly transformed by the enzyme alcohol dehydrogenase (ADH) and then oxidized to acetate through aldehyde dehydrogenase (ALDH), it then interferes with the DNA synthesis and repair, as well as inducing sister chromatid exchanges and specific gene mutations (Tsuruta et al., 2020). Acetaldehyde also inhibits the enzyme 6-methylguanitransferase, responsible for repairing injuries caused by alkylating agents, inhibiting this enzyme could promote tumour formation. Genetic polymorphisms have been reported in the two enzymes, ADH and ALDH, which have been related to the increased risk of alcohol-related cancers (Hashibe et al., 2006). In addition, it is suggested that alcohol could increase the permeability of the oral mucosa and create an alteration in its "morphology" by epithelial atrophy, causing carcinogens to penetrate the oral mucosa easily (IARC, 2010). This resembles the effects of lime when added in betel-nut (Mallery et al., 2014).

Many studies have explored alcohol and its association with HNC, a pooled INHANCE consortium analysis, including 10,244 HNC case subjects and 15,227 controls, analysed data on alcohol drinkers in never users of tobacco and cigarette smoking in never drinkers, in order to explore the association between each factor and the risk of developing HNC. The study found that among never drinkers, cigarette smoking was associated with an increased risk of HNC (OR for ever versus never smoking = 2.13, 95% CI = 1.52- 2.98) with a clear dose-response relationships for frequency, duration, and number of pack-years of cigarette smoking. In never users of tobacco, alcohol consumption was associated with an elevated risk of HNC specifically when alcohol is consumed at high frequency (OR for three or more drinks

per day versus never drinking = 2.04, 95% CI = 1.29 – 3.21), this is found to be associated exclusively with oropharyngeal, hypo-pharyngeal and laryngeal cancers (Hashibe et al., 2007). Another pooled INHANCE consortium analysis that included 9,107 cases of HNC and 14,219 controls, found an increased relative risk to HNC in alcohol drinkers compared with non-drinkers, probably caused by direct contact aetiology. The dose-response relation for beer and liquor consumers were generally similar, whereas wine, had a weak association and only would compare in high intake amounts (>30 standard drinks per week) (Purdue et al., 2009). One study has however suggested that red wine includes ingredients that are anti-carcinogenic, such as Resveratrol (Aggarwal et al., 2004). One pooled INHANCE analysis (4759 HNC patients) evaluating pre-diagnosis lifestyle habits, tobacco smoking and alcohol consumption, are associated with the overall survival (OS) and HNC-specific survival in HNC patients, using the Cox proportional hazard ratios (HRs), found that five-year OS was 51.4% for all HNC sites combined (50.3% for oral cancer), alcohol drinking status and intensity were prognostic factor for both OS (current drinkers HR = 1.73, 95% CI 1.16-2.58) and HNC-specific survival (current drinkers HR = 2.11, 95% CI 1.22-3.66) (Giraldi et al., 2017).

When combining alcohol consumption with smoking cigarettes, which also contains high levels of acetaldehyde, this may result in an additive or multiplicative effect which could explain the drastic increase of HNC risk and the smoking/alcohol consumption synergy (Stick and Rosin, 1983, Helander and Lindahl-Kiessling, 1991, Choi and Kahyo, 1991, Ernani and Saba, 2015). A pooled INHANCE consortium analysis, using the population attributable risks (PAR) method to quantify the excess HNC burden, has found a "greater" than multiplicative joint effect between tobacco and alcohol consumption observed for head and neck cancer risk (PAR = 2.15, 95%CI=1.53–3.04). The PAR for tobacco or alcohol was 72% (95%CI=61%–79%) for head and neck cancer, of which 4% was due to alcohol alone, 33% was due tobacco alone and 35% was due to tobacco and alcohol combined. These findings suggest that a joint effect between tobacco and alcohol consumption is greater than multiplicative on HNC risk (Hashibe et al., 2009).

Potentially malignant disorders (PMDs)

As indicated previously oral SCC is usually preceded by histopathologically-evident dysplasia, that clinically can manifest as, or within, potentially malignant disorders (Porter et al., 2018).

Leukoplakia, erythroplakia, erythroleukoplakia, oral lichen planus (OLP) and oral sub mucous fibrosis (OSMF) are the most common of these clinically apparent PMDs. Those unrelated to lichen planus and/or OSMF manifest as indurated white or red patches (Warnakulasuriya, 2019). The term leukoplakia describes a white patch or plaque that cannot be "rubbed off". It is regarded as a 'diagnosis of exclusion', being uncharacterised as any other disease, neither clinically nor pathologically (van der Waal, 2015). Leukoplakia can be homogenous in appearance or non-homogenous. Homogenously, it appears in a uniform pattern of reaction throughout the lesion, with a uniform white patch with shallow ridges in the epithelium. Non-homogenously, it appears either: 1) speckled with mixed white and red appearance on the surface though predominantly white or 2) nodular with small polypoid outgrowths which are rounded red or white outgrowths; or 3) verrucous with a wrinkled or corrugated surface appearance (van der Waal, 2015). It tends to appear on the floor of the mouth, lateral aspects of the tongue, gingiva and on the lower lip (Amagasa et al., 2006). Leukoplakias arising in these sites are thought to carry the highest potential of progression to malignancy (Bewley and Farwell, 2017, Dionne et al., 2015). Erythroplakia refers clinically to an undistinguished; neither clinically nor pathologically, " fiery" red patch, similar to leukoplakia in its regard as an exclusionist diagnosis (Ganesh et al., 2018). Although erythroplakias are more prone to turn malignant than leukoplakias, turning dysplastic more often in comparison with leukoplakias (Müller, 2018, Chen et al., 2017). Both lesions are thought to be caused by/strongly associated with alcohol consumption, tobacco smoking or betel nut chewing (Ganesh et al., 2018). OLP is a chronic autoimmune inflammatory disorder, occurring when T lymphocytes gather underneath the epithelial layer of the oral mucosa, increasing the differentiation rate of squamous epithelial stratification (Fitzpatrick et al., 2014), this inevitably causes hyperkeratosis and erythema with or without ulceration (Epstein et al., 2003). Although OLP

is prone to turn malignant, the transformation rate is believed to be low (Müller, 2018, Yardimci et al., 2014). OSMF is a chronic disorder characterised pathogenically by an increased cross-linking of collagen through up-regulation of (lysyl) oxidase activity. Fibrosis, or the building up of collagen, results from the effects of areca nut, which increases collagen production (e.g., stimulated by arecoline, an alkaloid) and decreases collagen degradation (Yang et al., 2007, Bari et al., 2017).

Many studies have investigated the malignancy link with these lesions' increasing risk of HNC (Dionne et al., 2015, Parashar, 2011, Hsue et al., 2007, Porter et al., 2018, Ranganathan and Kavitha, 2019, Walsh et al., 2013), these lesions' malignant transformation rates are shown in table 1.4.

Table 1.4 malignant transformation rate of potentially malignant diseases

PMDs	Malignant transformation rate (%)
Oral Lichen Planus	0.5-2.6
Oral submucous fibrosis	2-8
Erythroplakia	0.11
Leukoplakia	2.60

(Amagasa et al., 2006, Parashar, 2011, Ganesh et al., 2018, Yardimci et al., 2014)

A globally pooled study on oral leukoplakia prevalence, using inverse weighting and random effect methods, estimated the global prevalence of leukoplakia to be 1.49% to 2.6%, as well as a significantly higher prevalence among adult males (Bewley and Farwell, 2017). A meta-analysis evaluating malignant potential of OLP and malignant transformation into OSCC, by calculating the pooled proportion (PP), pooled data from 57 studies (19,676 HNC patients) and reported an overall PP of 1.1% (95% CI: 0.9%, 1.4%). Smokers, alcoholics and HCV-infected patients had higher incidence of malignant transformation (Aghbari et al., 2017). A case-control study on 921 HNC patients and 806 controls from China, studying the malignant link between PMDs and HNC, reported that patients with a history of OSMF had the most greater odds of developing HNC (OR = 24.24, 95% CI: 7.39–79.52), followed by oral leukoplakia (OR = 4.05, 95% CI: 2.44–6.71) (Li et al., 2015). A follow-up study, between 1991

and 2001, on Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders in Taiwan, reported that 44 patients with PMDs progressed to oral cancer arising from the patients' PMD lesions (OSMF, verrucous hyperplasia and OLP along with others) with an overall transformation rate of 3.02% on a mean follow-up time of 42.64 months. 8 of 166 patients with dysplastic lesions and 15 of 423 patients with hyperkeratotic/epithelial hyperplasia have turned malignant (Hsue et al., 2007).

Human papillomavirus

Human papilloma virus (HPV) is known to give rise to oropharyngeal SCC. HPV has more than 100 subtypes, distinctively of high-risk or low-risk, shown in table 1.5. High-risk oncogenic HPV DNA types 16 and 18 are archetypical in HPV spread and genesis. However, HPV16 has been, in particular, suggested to be the leading cause of HPV-HNSCC, in more than 90% of incidences (Husain and Neyaz, 2017, Singhi et al., 2010, Sturgis and Cinciripini, 2007, Münger and Howley, 2002). HPV-HNSCC arises most likely in the base of the tongue and palatine tonsils, followed by the oral cavity, larynx, and sinonasal mucosa (Syrjanen et al., 2017, Ghittoni et al., 2015, Stelow et al., 2010). In the past decade, these sites have been increasingly diagnosed with HPV-related HNSCC, whereas other HNC sites have marked a decrease in detection, suggesting an ongoing epidemical rise in HPV-related HNSCCs (Sturgis and Cinciripini, 2007, Radoi and Luce, 2013, Marur et al., 2010). HPV-related oropharyngeal cancer is perceived to be the cancer with the fastest growing incidence in the UK (Prue et al., 2018).

Table 1.5 Mucosal HPV types (genus alpha) and main associated diseases.

	HPV type	**Disease (% attributed cases)**
mucosal high-risk	HPV-16	- Cervical squamous cell carcinoma (~50) - Cervical adenocarcinoma (~35) - Oropharyngeal cancer (~25)
	HPV-18	- Cervical squamous cell carcinoma (~20) - Cervical adenocarcinoma (~35) - Oropharyngeal cancer (~1-3)

mucosal low-risk	HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59	• Cervical squamous cell carcinoma (~30) • Minority of oropharyngeal cancers
	HPV-6, 11	• Benign genital lesions • Respiratory papillomatosis
	HPV-13, 32	• Oral focal epithelial hyperplasia

(Ghittoni et al., 2015)

HPV infects the head and neck region as a result of oro-genital sexual activities (Gillison and Lowy, 2004, Munoz et al., 2003), approximately 20% to 25% of SCCs of the UADT are related to HPV infection (Marur et al., 2010). A study in the US on HPV prevalence nationally reported the overall HPV infection prevalence to be approximately 3.5% in individuals aged 20-69 years, with men having higher prevalence than women, also smokers and individuals with multiple sexual partners (≥5) were reported to have the most significant prevalence at 14.9% (D'Souza et al., 2017). An HPV prevalence study in the UK, measuring HPV seropositivity in individuals with oropharyngeal cancer, reported a 72.5% prevalence of HPV-16 in 1,583 study participants (Ness et al., 2018). HPV vaccination is greatly preventative of viral spread (Prue et al., 2018). The national HPV immunisation program in England was introduced in 2008, a study into its impact on 15459 HPV DNA specimens collected from 16-24 year-old women found that HPV 16/18, responsible for oral HPV, have decreased between 2010/2011 and 2016 from 8.2% to 1.6% in 16-18 year-olds and from 14% to 1.6% in 19-21 year-olds. The study also found the HPV 16/18 vaccine reduced chances of spread in this group by 82% (95% CI, 20.8%-66.8%) (Mesher et al., 2018). Possible outcomes on HPV positive and HPV negative are detailed below in Table 1.6.

Table 1.6 Possible outcomes of Human Papilloma Virus-HNC Positive HNCs versus Human Papilloma Virus-HNC Negative HNCs

variable	HPV +	HPV -
Age	Younger cohorts	Older cohorts
Gender	3:1 men	3:1 men
Risk factors	Direct contact to HPV+ host bodily fluids	Associated with tobacco or alcohol use/abuse
anatomical site	Oropharynx (base of tongue; tonsil)	All mucosal sites of the UADT
Histology	Non-keratinising carcinoma predominantly composed of basal cells	Keratinising squamous cell carcinoma
incidence	Increasing	Decreasing
Prognosis	Improved	Unchanging
Tumour stage at presentation	Tx, T1-2	Variable

(Marur et al., 2010)

In a multinational randomised trial, which included 801 patients with HPV related oropharyngeal squamous cell carcinoma (OPSCC) in Western Europe, Eastern Europe and Asia, looking specifically at the prevalence of OPSCC, reported that 37% of Western Europeans with OPSCC were HPV positive, compared to 6% of Eastern Europeans and 2% of Asians. These findings suggest that geographic disposition might be a risk factor in HPV related oropharyngeal cancer and that western Europe might be on the verge of an HPV epidemic (Mehanna et al., 2016). Another prospective study on 75 oropharyngeal cancer patients, found that HPV positive patients had a better prognosis and treatment outcome, compared to HPV negative patients in the study (Sedaghat et al., 2009). A systematic review into HPV's association with HNC, which looked into 5,046 HNSCC cancer specimens in 60 studies, found an overall HPV prevalence of 25.9% in HNC. It also found HPV prevalence in oropharyngeal SCCs to be the highest (35.6%) among all associated sites, attributing for 86.7% of HPV-positive cases (Kreimer et al., 2005). Another study on 53 samples of basal HNSCCs, similarly found 34% of the samples were associated with HPV16, comprising 76%

of oropharyngeal basal SCCs and 6% of basal SCCs from other sites (Begum and Westra, 2008).

Age

As might be expected, tobacco and/or alcohol related HNC is more likely in older from younger adults. A meta-analysis pooled from the INHANCE consortium found that smoking and alcohol consumption effects are more prominent in older than young adults (< 45 years). The increased risk of HNC in older persons possible simply reflects the extended period of exposure to risk factors. Of note, a family history of HNC seems to drive the age of development of HNC downwards (Toporcov et al., 2015).

Genetic disease

There are many reports of the genetic and (epi-genetic) changes that can within the tumours however there are few instances where an individual inherits the susceptibility of inability to metabolize carcinogens or procarcinogens and/or an impaired ability to repair the DNA damage (Kumar et al., 2016, Porter et al., 2018).

Certain genetic disorders might cause the development of HNCs. Fanconi anemia (FA) is a rare familial autosomal recessive disorder characterised by a mutation in one of 20 implicate genes, this mutation causes chromosomal instability and DNA repair flaws (Savage and Dufour, 2017). FA carries an increased risk of developing malignancies in the head and neck; especially OSCC (Alter, 2003), as well as progressive bone marrow failure and congenital anomalies (Velleuer et al., 2017, Savage and Dufour, 2017). A prospective study on 754 patients from the International Fanconi Anemia Registry, looking into the FA incidence of HNSCC and two-year overall, relapse-free and disease-specific survival, reported that 19 patients (3%) had HNSCC, which is a higher incidence rate than what is observed in the general population (standardized incidence ratio, 500; 95% confidence interval, 300-781) (P<.001). Also, the study noticed a significant increase in morbidity and mortality in FA patients treated with radiotherapy or chemotherapy (Kutler et al., 2003). Moreover, a study analysing more than 1300 cases of FA, reported that the estimated "cumulative probability" of developing

solid tumours in FA patients was 76% by the age of 45 years (Alter, 2003). It is believed that FA patients are 600-fold increased risk of developing solid tumours (Alter et al., 2018, Savage and Dufour, 2017). Dyskeratosis congenital (DC) is a genetic prototypic telomere biology disorder, marked by a wide spectrum of mucocutanous attributes, high risk of haematological illnesses, developing HNSCC, bone marrow failure among other health problems .(Ballew and Savage, 2013). A recent 15-year follow up study, including 197 DC patients reported that 11% of DC had developed "solid tumours" by age 50, the ratio of observed to expected cancers (O/E) was 4.2-fold higher than the general population (Alter et al., 2018).

Other factors

A poor state of oral health is thought to be contributing factor in HNC, as well as dietary intake, sexual habits (i.e. HPV) and low economic-status. Recent studies strongly suggest a relative risk association between such factors and the development of HNC (Guha et al., 2007, Divaris et al., 2010, Toporcov et al., 2015).

A case-control study conducted in the metropolitan area of São Paulo, Brazil on 309 HNC patients and 468 controls, studied the risk of developing HNC in schooling, oral health status and hygiene practices, tobacco use and alcohol consumption. The study found oral health and oral hygiene to have a significant attribute to HNC development. Patients who reported gingival bleeding upon brushing; indicative of periodontal disease, had a higher risk of oral cancer, as well as those who reported never having a dental check-up against those who attended at least once a year (OR=2.5 95% CI: 1.3-4.8). Also, those reporting never brushing their teeth were at higher risk than those who brushed three times a day (OR=2.6, 95% CI: 1.1-5.9). That association, however, lost statistical significance upon adjustments. Subjects who used alcohol containing mouthwashes more than once a day did show a statistically significant 3–fold increase in the risk of oral cancer compared to those who never used them (Marques et al., 2008). However, it is not clear whether those who were high-risk had other associated risks (i.e. poor oral hygiene), it is also unclear whether this increased risk is related to the ethanol component of mouthwashes or other responsible components in it.

Conversely, a case-control study matching age, race and gender, the oral health of the population, tooth loss and tooth mobility, mouthwash use, and frequency of dental visits on 1,289 HNSCC patients and 1,361 controls could not detect an association between oral health and HNSCC development risk except for a "modest" association between periodontal disease and HNSCC (OR= 1.33, 95% CI: 1.07-1.65) while the study found that routine dental visits were associated with a 30% risk reduction (OR= 0.68, 95% CI: 0.53-0.87) (Divaris et al., 2010).

Another case-control study in Poland on 122 HNC patients and 124 control subjects, investigated whether low economic-status, diet, dental care and sexual habits, among others, can be factors for developing HNC. The study reported that living in a less urbanised area was related to a higher risk of oral cancer, when compared with living in the capital city of Warsaw (OR=5.2 95% CI: 2.23–12.15). That could indicate that rural populations are at higher HNC risk resulting from lower access to healthcare or healthcare monitoring, early detection, healthcare education and guidance. High fruit intake was found in the study to be associated with significantly decreased risk (OR = 0.4, 95% CI: 0.7-0.95) and the most significant inverse association was for fruit juices and citrus fruits ($P < 0.01$). The study also reported, regardless of the smoking and alcohol intake status, poor oral health (defined by poor dentition, low frequency of dental check-ups and low frequency of teeth brushing) as a "strong" risk factor. The number of missing teeth scored (OR=9.8, 95% CI: 2.26–42.84), the frequency of dental check-ups were found to influence the risk HNC to almost 12 folds (OR=11.9 95% CI: 3.33–42.51) and frequency of tooth brushing showed over 3 folds (OR=3.2, 95% CI: 1.23–8.54) (Lissowska et al., 2003).

A pool analysis study from INHANCE consortium, with 22 case–control studies (14,520 cases and 22,737 controls studied the association between diet and HNC. The study reported an inverse association observed for higher-frequency intake of fruit (OR = 0.52, 95% CI: 0.43–0.62, $P < 0.01$) and vegetables (OR = 0.66, 95% CI: 0.49–0.90, $P = 0.01$). Intake of red meat (OR = 1.40, 95% CI: 1.13–1.74, $P = 0.13$) and processed meat (OR = 1.37, 95% CI: 1.14–1.65, $P < 0.01$) was positively associated with HNC risk. Higher dietary pattern scores,

reflecting high fruit/vegetable and low red meat intake, were associated with reduced HNC risk (per score increment OR = 0.90, 95% CI: 0.84–0.97) (Chuang et al., 2012).

A two multi-centre case-control study comprising 924 cases of HNSCC and 928 controls in central Europe and 2,286 cases and 1,824 controls in Latin America, studying the relation between poor oral health and the risk of developing HNSCC, reported that poor oral health in central Europe subjects scored (OR = 2.89, 95% CI: 1.74, 4.81) whereas in Latin America (OR = 1.89, 95% CI: 1.47, 2.42). Also, Latin American subjects that did not brush scored a significant (OR = 2.36 95% CI: 1.28-4.36), the study also suggested daily alcohol containing mouthwash use was risk factors for head and neck cancer in Latin America (OR = 3.40, 95% CI: 1.96-5.89). Results from this study suggest that poor oral health (as indicated by the poor periodontal condition of the mouth and missing teeth) and daily alcohol containing mouthwash use may be independent causes of cancers of HNC (Guha et al., 2007).

1.6 Clinical presentation

Head and neck cancers can significantly alter the function of the mouth, pharynx and/or larynx. Chewing, swallowing, speech or smell can each be affected, as can the facial aesthetics (Mehanna et al., 2010a). A clinically identifiable premalignant lesion often precedes the development of HNSCC. Ulcers might be an indicator of the presence of an early formation of cancer in an area of the head and neck however not in all cancers (Li et al., 2015).

Early-stage squamous cell carcinoma often presents as a white patch (leukoplakia), red patch (erythroplakia), or a mixed red and white lesion (erythroleukoplakia), which might, if left undetected, turn malignant. A HNSCC lesion might present clinically as a depressed, ulcerated surface with a raised and rolled border (Neville and Day, 2002). Later-stage symptoms could include: tumour growth, bleeding, teeth mobility, pain, dysphagia, dysarthria (Warnakulasuriya, 2019). Since HNCs arise around neurological and lymphatic anatomies, it is expected that some HNC patients might have HNC-associated pain, lymphadenopathy or neuropathy due to the spread of primary tumour (Aiken, 2006), it is suggested that 80% of HNC patients develop concomitant pain (Dios and Lestón, 2010). Even though pain is the

common symptom in nearly a third of the HNC patients at presentation, it is not a reliable indicator as to whether a particular lesion may be malignant. Larger, late stage carcinomas will often be painful, but many early oral cancers will be asymptomatic or may be associated with only minor discomfort (Neville and Day, 2002, Haddad and Shin, 2008, Ernani and Saba, 2015).

There is a wide spectrum of possible signs and/or symptoms that, in turn, can be used as diagnostic guides to early referral of affected individuals (Table 1.7). The National Institute of Health and Care Excellence (NICE) has also suggested a "2 weeks referral" recommendation regarding certain signs and symptoms of HNC (Excellence, 2015).

Table 1.7 NICE recommendations for HNC referral guidelines

cancers	Type of referral	Signs
Laryngeal	Suspected cancer pathway referral, if a patient is 45 years old or more.	▪ Persistent unexplained hoarseness ▪ An unexplained lump in the neck.
Oral	Suspected cancer pathway referral	▪ Unexplained ulceration in the oral cavity lasting for more than three weeks ▪ A persistent and unexplained lump in the neck.
	Urgent referral for assessment	▪ A lump on the lip or in the oral cavity or ▪ A red or red and white patch in the oral cavity consistent with erythroplakia or erythroleukoplakia.
	Suspected cancer pathway referral by the dentist for oral cancer in people when assessed by a dentist	▪ a lump on the lip or in the oral cavity consistent with oral cancer or ▪ a red or red and white patch in the oral cavity consistent with erythroplakia or erythroleukoplakia
Thyroid	Suspected cancer pathway referral	▪ Unexplained thyroid lump

(Excellence, 2015)

1.7 Management

Head and neck cancer is an invasive disease, with life-altering results causing the loss of functions or senses and possible physical disfigurement. Therefore the need for a comprehensive treatment plan is pivotal. A HNC treatment plan usually always include an

accurate medical history, clinical examination, correct tumour staging, the use of suitable investigatory methods, a treatment of choice that eradicates the tumour, restores function and produces minimum treatment side effects as much as possible. Moreover, the treatment plan should cater to patient wishes and needs, whether in choosing the treatment pathway or their input on the plan in total (Harrison, 2014).

The management of patients with HNC includes a multi-disciplinary team (MDT) approach (Excellence, 2004). The MDT includes surgeons, radiotherapists, oncologists, dental surgeons, plastic surgeons, dietitians, speech therapists, specialist nurses and rehabilitation specialists. The MDT list of duties includes investigating the disease, identifying the tumour stage, marking the therapeutic strategy accordingly, managing the disease, executing the treatment, controlling the adverse effects, rehabilitation and patient support.

Investigation

Pre-therapeutic 'work-up' for HNC usually requires clinical evaluation, pan-endoscopy with biopsy and cross-sectional imaging. Cross-sectional imaging is indicated to provide accurate staging at the time of diagnosis. It also includes a variety of imaging modalities, such as conventional photography, plain radiography, computed tomography (CT); contrast-enhanced CT (CECT), magnetic resonance imaging (MRI), ultrasonography (US) with or without fine-needle aspiration cytology (FNAC), positron emission tomography (PET/CT) or positron emission tomography combined with MRI (PET MRI); which is suggested to be the most efficient investigatory method for HNC. Pre-therapy work-up generally includes a combination of these techniques that are developed upon the search of the likely disease and the patients' health and wishes (de Bree et al., 2000, Argiris et al., 2008).

Recent studies have reported the benefit of complementary imaging techniques and parametric biomarkers when used with imaging tools, such as ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), diffusion-weighted MRI (DW MRI) and dynamic contrast-enhanced perfusion-weighted imaging (DCE-PWI). ^{18}F-FDG PET/CT is used in clinical staging of tumours, assessing primary tumours, reoccurrence, nodal metastasis,

detecting unknown primary tumours and in radiation treatment planning (Ong, 2008, Becker and Zaidi, 2014, Al-Ibraheem A., 2009, Spick et al., 2016).

FDG PET/CT, in terms of tumour staging modality, covers most of the body within a single scan, providing information on the primary tumour, nodal and distant metastases and expose possible unknown primary tumours. FDG PET/CT measures increased cellular glucose metabolism as expressed by the standardised uptake value (SUV), this increase might suggest an increase in cell proliferation, corresponding to tumour necrosis (Jacob et al., 2001, Argiris et al., 2008). A literature survey on the use of 18F-FDG PET in HNC compared to CT reported that PET has a higher sensitivity (87% versus 62%) and specificity (89% versus 73%) for staging cancer (Grkovski et al., 2015).

Also, DW MRI and DCE-PWI are of some clinical benefit in assessing the functional aspects of HNSCC (Ng et al., 2014). DWI is a rapid MRI technique that allows quantification of the diffusion of water molecules in tissues using the apparent diffusion coefficient (ADC), ADC values account for cellular perforation, which could decrease in value in case of micro-necrosis, resulting in lower cellular density. That is suggested to help indicate the presence of malignancy (Thoeny et al., 2012). However, some studies have shown conflicting results, highlighting the ADC's inability to predict patient prognosis (Kim et al., 2009, Chawla et al., 2013).

Performing a chest radiograph or CT scan of the thorax is also recommended, since the lungs are a major site for HNC metastases, and a principle presence of secondary cancer or metastases in the chest area might have a significant implication on the survival rate of patients with HNC (Ong et al., 1999).

Clinical staging

The American Joint Committee on Cancer (AJCC) tumour nodule metastasis classification (TNM) (Edge, 2010) (Table 1.8) and the Union Internationale Contre le Cancer (UICC) for standard TNM (Gospodarowicz et al., 2010) (Table 1.9), are two of the most widely accepted

classification systems, they classify (T) primary tumour size, (N) lymph node spread and (M)

metastasis presence.

Table 1.8 AJCC Classification of the lip and oral cavity cancer

	Primary tumour (T)
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤2 cm in greatest dimension
T2	Tumour >2 cm but ≤4 cm in greatest dimension
T3	Tumour >4 cm in greatest dimension
T4	(Lip) Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose
T4a	Moderately advanced local disease* (Oral cavity) Tumour invades adjacent structures only [e.g. through cortical bone (mandible or maxilla) into deep (extrinsic) muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face]
T4b	Very advanced local disease* Tumour invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
	Regional lymph nodes (N)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension
	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension
N2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension
	Distant metastasis (M)
M0	No distant metastasis
M1	Distant metastasis
	*Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4.

(Edge, 2010, Tobias and Hochhauser, 2014, Ernani and Saba, 2015)

Table 1.9 UICC Staging of nodes and metastases in head and neck cancers (except thyroid gland)

A. International Consortium:	
T1	UICC 7th T1 or less in greatest dimension, maximum depth of invasion <5 mm
T2	UICC 7th T1, maximum depth of invasion ≥5 mm
T3	UICC 7th T2, maximum depth of invasion ≥10 mm
T4	UICC 7th T3-T4, maximum depth of invasion ≥10 mm
B. 8th edition UICC (TNM 8)	
T1	2 cm or less in greatest dimension, maximum depth of invasion DOI <5 mm
T2	2 cm or less in greatest dimension, maximum depth of invasion ≥5 mm, or tumour >2 cm and 4 cm or more in greatest dimension, maximum depth of invasion <10 mm
T3	Any tumour maximum depth of invasion ≥10 mm or tumour >4 cm in greatest dimension
T4a	Invades through cortical bone, or maxillary sinus, or invades the skin
T4b	Invades masticator space, pterygoid plates or skull base, or encases the internal carotid artery
C. 7th edition UICC (TNM 7):	
T1	2 cm or less in greatest dimension
T2	Tumour >2 cm and 4 cm or more in greatest dimension
T3	Tumour >4 cm in greatest dimension
T4a	Invades bone, or maxillary sinus, or invades skin, into deep extrinsic muscles of the tongue
T4b	Invades masticator space, pterygoid plates or skull base, or encases the internal carotid artery

(Vuity et al., 2018, Gospodarowicz et al., 2010)

Treatment

The treatment options for HNC include: surgery, chemotherapy, radiotherapy or combined therapy. The treatment choice depends upon the site, the stage or extent of the tumour, health status of the patients; co-morbidities, and patient preference (Baijal et al., 2012). Early stages of HNC (stage I or stage II) are usually managed with surgery or radiotherapy. Surgery is favoured more due to the benefit of sparing patients the late toxic effects other therapies. However, in the hypo-pharynx, mesopharynx or oropharynx SCC, radiotherapy is often favoured for its higher cure and low morbidity rates (Nakamura et al., 2006).

Furthermore, late stages of HNC (stage III or VI) are managed typically with a multimodality approach that incorporates surgery, radiotherapy and chemotherapy. Maintaining highest survival rates and patients' quality of life influences clinicians' choice of treatment, therefore using a cohort-valid tool able to measure or help predict these rates can be highly beneficial to clinicians treating HNC patients as well as researchers testing new interventions (D'Antonio et al., 1996, Deshpande et al., 2011, Fang et al., 2004).

Surgery

Surgery is considered to be the standard treatment for HNSCC. However, at times, when seeking a preservative approach in treating HNC, the surgical approach might not be the most suited. Therefore the recent surgical advances are all in favour of a conservative approach to HNC surgery, such as the microsurgery free tissue transfer, which has substantially improved functional outcomes for HNC patients in need of advanced surgical sectioning (Argiris et al., 2008). In small and accessible cancers (oral, larynx and pharynx), microsurgery is suggested to have a better preservational and functional outcome than radiotherapy (Myers et al., 1994). Neck dissection is usually carried out in concurrence with HNC surgery (called therapeutic neck dissection) to manage nodular involvement. Bilateral (or contralateral) elective neck dissection is also performed when managing N0, per golden standard, however this preventative measure has been debatable for many decades (D'Cruz et al., 2015), but is supported by low survival and recurrence rates (Knopf et al., 2020, Singh et al., 2013). Elective

neck dissection is also performed following chemo-radiotherapy if metastasis is suspected (Pfister et al., 2006).

Although surgical interventions are considered to have a better overall outcome in some types of HNC, such as oral cancer, it still has its complications, such as dysphagia, dysarthria, aspiration and airway compromise (Mehanna et al., 2010b).

<u>Systemic therapy (chemotherapy)</u>

Chemotherapy in the past was used in palliative stages but has been introduced later in the management of patients with advanced HNC. While HNC patients are usually treated surgically alone or with radiotherapy, a chance of harbouring low loco-regional control and develop adverse treatment effects might occur. Chemotherapy is thought to express better organ preservation and improve survival rates (Lamont and Vokes, 2001, Pignon et al., 2009). Systemic therapy includes induction (sequential) chemotherapy, concurrent chemotherapy or anti-tumour drugs. Induction chemotherapy regimen includes the administration of docetaxel, cisplatin, and 5-fluorouracil (TPF) administration. Induction chemotherapy is thought to have favourable outcomes among patients with locally advanced HNSCC, mainly of oropharyngeal origin (Hutcheson et al., 2014). Whereas Concomitant chemoradiotherapy (CRT) holds the promise of efficiently eliminating the loco-regional tumour burden while also providing systemic ant-tumour activity. Unlike induction chemotherapy, it can directly impact the activity of radiation therapy and bypassing tumour radio-sensitivity (Cohen et al., 2004).

HNC has been found to histopathologically show an enhanced expression and activity of the epidermal growth factor receptor (EGFR). The main EGFR downstream signalling pathways involved in HNSCC are RAS/RAF/MEK/ERK, PI3-K/AKT, STAT, PLC/PKC, EGFR nuclear signalling and the Src pathways. There are two identified ways to inhibit EGFR signalling are suggested to be inhibited by either block ligand-binding induced receptor activation or abrogating downstream signalling (Schmitz et al., 2014). Cetuximab is an epidermal growth factor receptor monoclonal antibody, suggested to have an anti-tumour activity effect and inhibits DNA double strand-break repair which plays a pivotal role in resisting radiotherapy

and DNA damage-inducing chemotherapeutic agents by preventing the nuclear import of EGFR (Chen and Nirodi, 2007).

Radiotherapy

Radiotherapy (RT) can be a primary HNC treatment or adjuvant therapy. Conventional RT can help control tumour growth and result in high cure rates, especially when treating hypo-pharyngeal, hypoglossal or sublingual tumours.

Types of radiotherapy

The radiotherapeutic management of HNC has had an extensive change due to significant advances in diagnostic radiation imagery and radiation delivery techniques. Cross-sectional imaging, combined with CT parametric scans, are used to draw tumour manifestations in three dimensions. Also, from the conventional radiotherapy technique, a new technique has emerged, intensity-modulated radiation therapy (IMRT). IMRT delivers radiotherapy to patients with precise location accuracy and dose sufficiency, aiming at minimising radiation towards healthy surrounding tissues or organs, a major advantage over conventional radiotherapy, importantly, IMRT is considered the first non-surgical tissue saving development (Nutting et al., 2009, Mehanna et al., 2010b). Also, proton beam therapy (PBT) is suggested to have the advantage of avoiding surrounding sensitive organs when providing radiation to tumours, such as the brain or the spinal cord, unlike conventional techniques. Still, proton therapy has not been validated nor proven to be beneficial and is more costly than other therapies (Mehanna et al., 2010b, Ding et al., 2005).

Radiotherapy fractionations

When radiotherapy is the primary therapy, it is given in daily fractions of 2.0 Gy x 5 days/week with a maximum of 70 Gy within seven weeks. On the other hand, when provided as adjuvant therapy RT is given in a dose of 60 Gy prescribed to improve loco-regional control in case of extra-capsular extension presence (Peters et al., 1993). RT can also be given post-therapy and should be delivered without delay, to prevent repopulation of cancer cells (Suwinski et al., 2003).

Two fractions have been proposed to aid in delivering RT with no delay and reduce toxic effects, hyper-fractionation (HF-RT) and accelerated fractionation (AF-RT). Hyper-fractionation delivers 2-3 fractions per day, and each fraction carries a low dose of radiation (1.1-1.2 Gy), this is designed to improve fraction effect and lower chronic toxic effects of fractionation. In accelerated fractionation, high doses are delivered once daily (1.6-1.8 Gy) in a short time compared with hyper-fractionation, serving the same purpose (Bernier, 2005).

The role of radiotherapy in Head and Neck Cancer and possible adverse effects

Adverse effects in radiotherapy to the head and neck are common, it can be of carcinogenic; teratogenic or mutagenic nature. The adverse effects can be of short or long term, such as mucositis, trismus, osteoradionecrosis and xerostomia, summarised in Table 1.10. These effects depend on the cancer site, type of malignancy, frequency of exposure to radiotherapy and whether it was used as primary therapy of treatment or in combination with other therapies (Deasy et al., 2010, Bourhis et al., 2005). Adverse effects in the oral cavity and the oropharynx are common. These sites have a high mucosal cellular turnover rate, a complex microflora, plus the susceptibility to trauma by normal function. It is believed that more than 90% of HNC patients receiving radiotherapy will develop oral complications (Herrstedt, 2000). The multidisciplinary approach to HNC is designed to minimise, or even eliminate, any short or long adverse effects of radiation while treating HNC. Specific therapeutic application techniques are adapted to create less adverse effects; IMRT, PBT, salivary gland sparing and concomitant chemo agents (cisplatin, and 5-fluorouracil, Cetuximab) (Epstein et al., 2012).

Table 1.10 adverse effect of radiation to the head and neck[3]

Short term	Long term
• Radiotherapy induced xerostomia • Excessive mucus production • Mucositis • Radiation dermatitis • Sialadenitis • Salivary gland dysfunction and hypo-secretion • Other infections*	• Radiotherapy induced xerostomia • Dysphagia • Limited mouth opening • Dental caries • HNC muscles fibrosis • Osteoradionecrosis of the mandible • Soft-tissue necrosis • Muscular/cutaneous fibrosis • Maturational disturbances • Ageusia • Dysgeusia • Trismus • Other infections*

Radiotherapy induced mucositis

An acute reaction for radiotherapy, the term mucositis describes the inflammation of the oral mucosa as a result of exposure to a chemical or radial irritant. Beginning as erythema that turns into ulceration, mucositis is thought to result from the radiation-induced mitosis of basal keratinocytes, which permits the loss of squamous epithelial cells. An increased rate of cellular production counters this loss. However, still, cellular regeneration often cannot maintain a linear rate of cellular regeneration against the number of mitotic cells. That results in denudation of the mucosa (Sciubba and Goldenberg, 2006).

Mucositis occurs in up to 60% of HNC patients receiving primary radiotherapy and in mostly all patients after HF-RT or AF-RT regimens and in combined therapies (Elting et al., 2007). Mucositis usually begins to manifest within 2 to 3 weeks of the start of radiotherapy. Initial symptoms are typically mild discomfort with the development of mucosal erythema. By week 5, frank erythema, ulceration, and pseudo-membrane formation are usually present. These

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[3]   could include infections by viral, bacterial and fungal agents. RAY-CHAUDHURI, A., SHAH, K. & PORTER, R. J. 2013. The oral management of patients who have received radiotherapy to the head and neck region. *Br Dent J,* 214**,** 387-393, SCIUBBA, J. J. & GOLDENBERG, D. 2006. Oral complications of radiotherapy. *The Lancet Oncology,* 7**,** 175-183.

are associated with general oral pain and odynophagia affecting the oral function, such as chewing or speech. After the delivery of radiotherapy, symptoms start to gradually decrease, with ulcerations dramatically improving within 4 to 6 weeks (Epstein et al., 2012).

Management for mucositis focuses on prevention and treatment. Preventive measures include the use of 3D radiotherapy with midline radiation blocks, plus the use of IMRT to reduce mucosal injury. The Mucositis Study Section of the Multinational Association for Supportive Care in Cancer (MASCC) recommends the use of Benzydamine as a preventive agent against mucositis in patients receiving moderate doses of radiotherapy (Rubenstein et al., 2004). Treatments for mucositis, on the other hand, include the use of lubricants, pain management regimens and mucosal coating drugs (Scully et al., 2003).

Radiotherapy induced trismus

Trismus occurs from the inflammation of the pterygo-masseteric sling, pterygoid muscle, and the mandible or masseter muscle. Radiotherapy-induced trismus (RIT) develops as a result of re-irradiation or surgery plus radiotherapy treatment modality (Sciubba and Goldenberg, 2006). One of the prominent signs of RIT is fibrosis of the masticatory muscles, and this causes degenerative problems in the temporomandibular joint. RIT could result in a significant reduction in oral function; chewing, articulation or jaw movement. These changes could affect patients ability to maintain a healthy diet or proper oral hygiene (Wang et al., 2005).

In the prevention and management of RIT, it is focal that radiation doses are delivered accurately and with little TMJ involvement as possible. Physicians should be able to detect early signs of RIT and refer the patient to passive and active jaw physiotherapy (Germano et al., 2015).

Osteoradionecrosis

Osteoradionecrosis (ORN) is an uncommon adverse effect of radiotherapy. It is caused by chronic endothelial cell damage, which results in tissue hypo-vascularity, hypoxia, osteocyte-necrosis and marrow fibrosis. ORN appears in the oral cavity as a bony exposure,

accompanied by a foul taste and smell and suppuration. ORN might also cause pain, orofacial fistulas, exposed necrotic bone and mandible pathologic fracture (Hancock et al., 2003). Risk factors for ORN include radiotherapy, oral surgery, short time elapse between extractions and radiotherapy, dental and periodontal disease, the association of the tumour with bone and the high-dose volume of the horizontal ramus of the irradiated mandible. Comorbidities that may increase the risk of ORN include diabetes and collagen vascular disease, tobacco use, alcohol consumption and poor nutrition (Glanzmann and Gratz, 1995, Gomez et al., 2011). Preventing ORN includes managing the comorbid factors, improve oral hygiene, decreasing the presence of infectious agents (chlorhexidine rinses and systemic antibiotics), improving patients' diet, pain and dental management (Epstein et al., 1987, Wong et al., 1997).

Radiotherapy induced xerostomia

Definition

The term 'Xerostomia' describes the subjective sensation of dry mouth by the patient or the 'feeling' of having insufficient amounts of saliva. Saliva is about 90% produced by the major salivary glands; the parotid, the submandibular and the sublingual glands, while the minor salivary glands only contribute to saliva secretion (Jensen et al., 2010). Radiotherapy-induced xerostomia (RIX) is the subjective feeling of dry mouth by HNC patients following radiotherapy treatment to the head and neck area. Xerostomia can arise due to many causes, but RIX is known to develop exclusively in patients receiving radiotherapy to the head and neck, due to the effect radiation has on the salivary gland and saliva production.

Salivary glands structure, role of saliva and aetiologies

The parotid gland secretes serous proteinaceous fluid, accounting for around 25-30% of salivary output, the submandibular gland also secretes serous fluid, however it secretes a more mucinous fluid constituting up to 70% of all saliva secretion, the sublingual gland secretes the least at around 5% (Humphrey and Williamson, 2001). The amount of saliva a healthy individual produced daily is 1.5L. Salivary flow differs from stimulated to unstimulated flow. Stimulated flow is mainly produced by the parotid gland, whereas the submandibular

glands primarily produce unstimulated flow. The precursors of salivary flow are the cell surface receptors, which either triggers the secretion of aqueous low amylase saliva (parasympathetic stimulation) or high viscous protein and rich amylase saliva (sympathetic stimulation).

Aqueous saliva is secreted from the submandibular gland when acetylcholine binds to M3 muscarinic receptors resulting in downstream activation of inositol-1, 4, 5-trisphosphate, which releases calcium from its intracellular stores, triggering aqueous and low amylase saliva release from salivary acinar cells.

Viscous saliva is secreted from the parotid gland when β2 adrenergic activates protein kinase A, along with the AMP pathway, resulting in the exocytosis of secretory granules giving a viscous saliva, which is rich in organic and inorganic components and high in amylase (Konings et al., 2005, Bhide et al., 2009).

Saliva has many critical roles in the oral cavity, including the regulation of pH levels in the oral cavity acting as a buffer, countering dental plaque formation, aiding with indigestion and digestion, helping with respiration, helping with the remineralisation cycle of dental surfaces and providing an antibacterial effect. The lack of saliva in the mouth can compromise all oral functions and deteriorate oral health (Pinna et al., 2015).

As the salivary glands are positioned relatively superficially and are highly radiosensitive, the radio-damage is likely to occur if the glands are within the area treated with radiotherapy for HNC (Pinna et al., 2015, Shannon et al., 1978, Bhide et al., 2009). The threshold of salivary glandular resistance to radiation is suggested to be around 26 Gy, any doses surpassing this is believed to render an irreversible decrease in salivary output (Deasy et al., 2010, Eisbruch et al., 1999, Ship et al., 1997).

Two mechanisms have been suggested to be responsible for salivary gland hypofunction, either cellular plasma membrane damage, or loss of functioning acinar cells due to cell loss or death by radiation (Konings et al., 2005). Salivary function declines rapidly following the concomitant radiotherapy. This decline commences about one week after radiation starts, with

a decreased salivary function of up to 90%, and a non-significant improvement for up to at least a year after treatment with conventional radiotherapy (Shannon et al., 1978, Mossman, 1983, Ship et al., 1997). The salivary output may and may not return over time, with only one study observing a 32% increase flow rate at five years compared with 12 months post Radiotherapy (Braam et al., 2005). The return of salivary function can vary considerably between individuals (Franzén et al., 1992). Moreover, this particular issue is highlighted as probably the most concern patients report, salivary output regain can therefore have a direct impact on patients' whole recovery, especially since no significant recovery has been observed (Montgomery-Cranny et al., 2014, Kałużny et al., 2014, Kakoei et al., 2012). Of note, acinar cell damage may also be worsened by concomitant use of some chemotherapeutic agents such as 5-fluorouracil (5FU) or methotrexate (Mallick et al., 2015). This might contribute negatively on saliva recovery (Konings et al., 2005).

RIX is perceived to be a common adverse effect, with many HNC patients having moderate or severe symptoms (Dirix et al., 2006). RIX starts with an acute onset followed by long-standing features. The acute phase starts within a week or two post-treatment, for up to 6-12 months, followed by the chronic onset, observable after 120 days (6months) and lasting for more than five years or lifelong. RIX clinical presentation is summarised in Table 1.11.

Xerostomia can be responsible for causing or aggravating other adverse effects of radiotherapy in HNC since many oral functions rely significantly on a sustained salivary presence. Taste, for example, is reliant on saliva to aid in mastication and taste expression by adding solubility to indigested foods (McLaughlin and Mahon, 2014). Altered (dysgusia) or loss of taste (ageusia) can affect patients' appetite, can either lead to anorexia or post-treatment weight gain inevitably delaying their recovery (McLaughlin and Mahon, 2014). Mucositis is another radiotherapy acute toxic effect that is suggested to be affected by salivary hypo-function post-radiotherapy, due to the absence of the protective proteins found in saliva, this might permit the bacterial "colonization" of ulcerated epithelium, and this is thought to contribute to a more severe form of mucositis (Eisbruch et al., 2003a).

Table 1.11 Clinical presentation of RIX and causes [4]

Clinical presentation	Cause
• Mucositis • Difficulties with chewing • Dysarthria • Mucosal burning sensation and discomfort • Dysgeusia • Sensitivity to acidic or spicy foods • Ageusia • Dysphagia	Loss of salivary lubrication effect and mucosal tolerability
• Dental caries	Demineralisation due to absence of saliva
• Accelerated dental caries • Fissuring of the tongue and lips • Halitosis	Absence of washing mechanism of saliva
• Oral pseudomembranous candidiasis • Angular cheilitis • Acute supporative sialadenitis	Absence of salivary antimicrobial factors
• Loss of appetite • Weight loss	Mucosal pain and/or malnutrition

Radiotherapy induced salivary gland dysfunction is can also greatly affect oral and pharyngeal function and often never entirely resolve. Hence unsurprisingly RIX can significantly lessen the Quality of Life (QoL) of patients affected, xerostomia is thought to be one of the major causes of poor QoL (Dirix et al., 2006, Jellema et al., 2007). Furthermore RIX is considered to be the most common late adverse effect or radiotherapy in HNC (Bjordal et al., 1994, Cooper et al., 1995).

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[4] BRUCE, S. D. 2004. Radiation-Induced Xerostomia : How Dry Is Your Patient? *Clinical journal of oncology nursing,* 8**,** 61-67, RAY-CHAUDHURI, A., SHAH, K. & PORTER, R. J. 2013. The oral management of patients who have received radiotherapy to the head and neck region. *Br Dent J,* 214**,** 387-393, EPSTEIN, J. B., THARIAT, J., BENSADOUN, R.-J., BARASCH, A., MURPHY, B. A., KOLNICK, L., POPPLEWELL, L. & MAGHAMI, E. 2012. Oral complications of cancer and cancer therapy. *CA: A Cancer Journal for Clinicians,* 62**,** 400-422.

The health-related QoL (HR-QoL) fall of the acute phase of RT-induced salivary gland damage may be short termed and reversible, but if RIX develops in the chronic phase, there is the possibility for lifelong reduction in QoL (Chambers et al., 2004, Jensen et al., 2010).

There are studies on the association between persistent RT-salivary hypo-function and patients' quality of life (table 1.12), these studies showcase that the impact of xerostomia on QoL may vary with time (Jellema et al., 2007), so that when the patients QoL falls, there may be a little improvement over one to five years, represented in various measure scales including ones on xerostomia (Abendstein et al., 2005). Moreover, the size of the initial tumour (T classification), clinical-stage, radiation dose or use of combined chemotherapy may perhaps unsurprisingly, also influence QoL (Dirix et al., 2008). However, while specific xerostomia-related items can improve over time, they do not seem to return to baseline levels (Pinna et al., 2015). In one study 41% of patients complained of moderate or severe xerostomia at five year follow-up after RT. Five years after RT, the mean cumulated parotid flow ratio returned to baseline in some patients, 20% of patients had a salivary flow ratio below 25% of the baseline score. The loss of the dry mouth 'feeling' was significantly correlated with an improvement in parotid flow ratio (Braam et al., 2007). A correlation between parotid mean dose and fraction reduction of stimulated saliva was reported by Chao et al., even suggesting a rate of 4% per Gy of mean parotid dose (Chao et al., 2001). This relation was noted in another study (Eisbruch et al., 2001), but this is yet to be verified.

Table 1.12 studies of the QoL of patients with radiotherapy-induced xerostomia (RIX)

Study	Sample size	Outcome measures	Method	Results
(Messmer et al., 2011)	42 HNC patients	Self-developed questionnaire for xerostomia	Recorded at 41 and 90 months after radiotherapy	After radiotherapy xerostomia had no significant changes for over five years.
(Langendijk et al., 2008)	425 HNC patients	EORTC--QLQ-C30 & RTOG scales	Recorded 6, 12, 18, and 24 months after completion of radiotherapy	Radiation-induced xerostomia had a significant negative impact on various health-related quality of life measures.
(Eisbruch et al., 2001)	84 HNC patients	Xerostomia Questionnaire (XQ)	Recorded before radiotherapy and periodically up to two years post-RT, Salivary flow measured (major salivary glands)	IMRT or organ-sparing radiotherapy positively impacted xerostomia on patients in the long term. QoL was not affected
(Braam et al., 2007)	44 HNC patients	EORTC--QLQ-C30 & EORTC--QLQ-H&N35	Recorded after radiotherapy treatment, with intervals of 6 weeks, 6 months, 12 months, and at least 3.5 years post-treatment. Parotid salivary flow was also determined after the X time points.	Most QoL items compared with baseline decreased. A gradual improvement over five years post-RT follow-up.
(Dirix et al., 2008)	75 HNC patients	Xerostomia score, quality of life survey, and visual analogue scale	Recorded at six months after treatment	The majority of patients (93%) reported a dry mouth sensation, with 65% having moderate to severe xerostomia (grade 2 to 3)
(Abendstein et al., 2005)	357 HNC patients	EORTC--QLQ-C30 & EORTC--QLQ-H&N35	Recorded at the time of diagnosis of HNC, then five times during the first year post-RT and at five years of radiotherapy	A decrease in patient QoL was noted in the first year and remained low over the 5 year post-RT timeframe.
(Jellema et al., 2007)	288 HNC patients stage (I-IV)	$RTOG_{xerostomia}$ plus EORTC-QLQ-C30	Recorded 6 monthly between 6 to 24 months post-RT	The results suggested that the impact of xerostomia on QoL was increasing with time, even with a relative decrease in the RTOG score over time
(Kakoei et al., 2012)	63 HNC patients	Xerostomia Questionnaire (XQ)	Recorded at 0, 2, 4, and 6 Weeks post-RT and at six months. Unstimulated flow was also determine	QoL significantly decreased with time (P=0.0001), Xerostomia severity increased over time (P=0.0001)

As RIX can give rise to local diseases, adverse effects on oropharyngeal function and lessen both oral and general QoL, there is a need to lessen the risk of RIX developing and therapies that will shorten the duration, or lessen the severity of the few symptoms and complications of this potentially adverse-effect inducing therapy. Preventive measures or techniques, before and while performing radiotherapy in HNC, are recommended to inhibit radiotherapy adverse effects. Although post-treatment management is equally crucial to elevate and promote symptom relief (Kałużny et al., 2014). Some patients might receive pharmacological stimulation of saliva production to counter the effects of RIX; such as pilocarpine or Cevimeline, while others use non-pharmacological stimulators; such as topical applications (i.e. citrus applications or saliva substitutes), acupuncture or certain regimens or techniques aimed at improving the oral hygiene and habits (Eisbruch et al., 2003b, Montgomery-Cranny et al., 2014, Pinna et al., 2015).

Preventive measures

Several preventive measures for RIX have been proposed, anticholinergic agents, cytoprotectives and radiation delivery techniques to lessen the risk of radiotherapy damage of structures close to the focus of therapy. Submandibular transfer to a radio-free sites is another, albeit, uncommon and complex preventative strategy (Seikaly et al., 2001, Wu et al., 2015).

Pre-treatment pilocarpine

The cholinergic muscarinic agonist agent, pilocarpine can stimulate salivary flow in patients with lacrimal or salivary hypo-function of different causes. Pilocarpine can be systemically administered, 5-10 mg daily. Pilocarpine has been suggested to have a positive effect on hypo-salivation in patients with RIX (Hamlar et al., 1996). It is unclear, however, if pilocarpine should be given before, during or after radiotherapy and salivary hypo-function development to increase salivary function. Pilocarpine is contra-indicated for patients with uncontrolled asthma, uncontrolled chronic obstructive pulmonary disease, uncontrolled cardiorenal disease, acute iritis, pregnancy, breast-feeding. It is thought to have significant side effects

such as sweating, headaches, urinary frequency, vasodilatation hyperhidrosis (Greenspan and Daniels, 1987, Davies Andrew and Thompson, 2015, Pimentel et al., 2014).

A prospective and double-blinded study during radiotherapy for HNC, found that pilocarpine administered during the time of radiotherapy lowered the incidence of xerostomia (Pimentel et al., 2014), however, the sample (5) was very small. A larger study of 58 patients receiving bilateral radiotherapy to the head and neck found that pilocarpine 5mg given five times daily did not improve salivary flow or decrease the symptoms of xerostomia at five weeks post-RT in patients (Gornitsky et al., 2004).

A study of 170 patients with RIX, found that pilocarpine prior to radiotherapy did not lessen the frequency or severity of xerostomia (Burlage et al., 2008). A Phase III placebo-controlled trial of oral pilocarpine in 130 patients undergoing radiotherapy for HNC then assessed QoL, (the McMaster University questionnaire and the RTOG scale)found that pilocarpine 5 mg three times daily administered Day 1 of RT until one month after treatment did not prevent RIX or positively influence QoL (Warde et al., 2002).

Amifostine

Amifostine is a cytoprotectant that has been proposed to prevent or lessen RT-induced salivary gland damage (Giatromanolaki et al., 2002).

A phase III trial on 330 randomised patients showed positive support for the use of amifostine, with a significant decrease in xerostomia symptoms following administration of the drug while receiving radiotherapy. However, adverse effects have been reported in this study, including vomiting, hypotension, nausea and allergic reactions (Brizel et al., 2000).

56 HNC patients were included in randomized phase III trial on the efficacy of amifostine, when given with or without chemo-radiotherapy, using carboplatin (CRT +/-Amifostine). Twenty-five patients were in the CRT+A group and 25 patients in the CRT-A group. 250 mg amifostine was given to participants daily before each radiotherapy session determined by the acute toxicity according to the Common Toxicity Criteria for adverse effect (CTCAE v.3.0). The study did report some reduction in the acute phase of xerostomia in patients receiving

amifostine compared to the controlled group, (acute xerostomia CRT-A SD. = 22; CRT +A SD. = 19) especially in weeks 2 and 4 of the study (p = 0.002, p = 0.0021). However, apart from acute xerostomia, the differences between both treatment groups did not reach statistical significance, and the study failed to show radio-protective effects on other healthy tissues (Vacha et al., 2003). A systematic review and meta-analysis of 14 randomised controlled trials, including 1451 patients, comparing the use of radiotherapy vs radiotherapy plus amifostine for cancer treatment, reported that amifostine significantly reduces the side effects of radiation therapy (Sasse et al., 2006).

Low dose radiation

As discussed previously the degree of salivary gland hypofunction is directly related to the radiation dose. Decreasing radiation doses to major salivary glands in RT (less than 25 Gy) has been thus suggested to lessen the risk or severity of salivary gland dysfunction (Deasy et al., 2010). Radiation doses of above 50 Gy are usually administered in HNC, which can cause significant effects to the salivary function (Porter et al., 2004). However, its impact on the salivary glands is also influenced by the administering technique, the duration of the treatment and the dosage.

Intensity-modulated radiotherapy (IMRT)

IMRT lessens the radiation dosage of tissues adjacent to the primary focus of RT and effects of radiotherapy on patients, with no marked effect on local control and survival rates, and is believed to be the most sufficient and less impactful on patients' QoL and their glandular function (Jabbari et al., 2005, Nutting et al., 2009, Huang et al., 2010). Eighteen patients receiving IMRT for HNC had scintigraphy of the parotid gland performed before and after therapy to examine any anatomical changes in the gland. The study suggests possible protection to parotid glands against adverse effects of radiotherapy and reduction in incidence and severity of xerostomia (Munter et al., 2004). A prospective study comparing 71 HNC patients treated with IMRT and 122 HNC patients treated with Three-Dimensional Conformal Radiation Therapy (3D-CRT), in terms of mean dose, patients' radiotherapy adverse effects,

including xerostomia, reported that the use of IMRT resulted in a decrease in the mean dose received by the parotid glands only (27 Gy vs 43 Gy (P < 0.001)). Also, at six months after baseline, 41% of patients treated with IMRT reported moderate or severe xerostomia (29 of 71) compared with 67% of patients treated with 3D-CRT (82 of 122) (OR=0.27 95% CI: 0.13–0.54; p < 0.001) (Vergeer et al., 2009). 3D-CRT uses a 3-deminsional image to target the tumour, whereas IMRT manipulates photons and proton beams to target tumours, both these techniques are meant to accurately target tumours and bypass healthy tissues as much as possible (Hall and Wuu, 2003).

However, a prospective study on 41 patients receiving either IMRT or 3DCRT, compared whether IMRT would have a significant impact on preventing xerostomia and studying the results of 6 months post-radiotherapy subjectively and objectively, reported that radiation techniques (IMRT or 3DCRT) did not influence the functional outcome of salivary glands (Chao et al., 2001). Nonetheless, IMRT uses two to three times more monitor units than 3D-CRT, by which total body dose increases due to increased radiation leakage. These factors can cause the prevalence of radiation-induced malignancies to double compared to 3D conformal radiotherapy. Hence, IMRT is discouraged in situations where it fails to offer significant advantages while delivering radical radiotherapy, or that glandular transfer is utilised to reduce this effect (Bhide et al., 2012, Hall and Wuu, 2003).

Submandibular transfer (SGT)

It has been previously proposed that the transfer of the submandibular gland of the side of RT into the submental space may spare it from radiation exposure, and hence lessen the severity of RIX (Seikaly et al., 2001, Deasy et al., 2010).

A phase II study, to determine the reproducibility of a submandibular salivary gland transfer surgical technique for the prevention of RIX reported that 74% of HNC patients (n=44) did not develop xerostomia (Jha et al., 2012). The study did not report on any controls included. A study compared between the administration of pilocarpine and SGT in the preventing RIX included 69 HNC patients. Assessing their speech, swallowing outcomes, and QoL at pre-

treatment, and one month, six months, and 12 months after the pre-treatment assessment, results showed that patients who received the SGT procedure had better swallowing outcomes and QoL scores than patients who received pilocarpine (Rieger et al., 2012).

Thirty-eight patients with oropharyngeal carcinoma were included in a longitudinal case-control study, studying the benefit of SGT. The submandibular salivary flow rate recovered by six months after radiotherapy in the SGT group (n=24), whereas the flow rate declined drastically after radiotherapy and remained at a low level in the longer term in the control group (n=14) who had not received SGT. Two years after radiotherapy, 92.3% of patients in the SGT group had no or minimal xerostomia, and the QoL, in the SGT group, was always greater than that in the control group from 3 months post-radiotherapy (Zhang et al., 2012). A systematic review and meta-analysis of 7 trials and 369 participants in glandular transfer studies has suggested that there is good evidence that SGT can prevent RIX (Wu et al., 2015). Nevertheless, this is an expensive, invasive and costly therapeutic strategy.

Management measures

A Cochran systematic review of three studies comparing 293 patients treated with systemic pilocarpine hydrochloride for RIX, reported this agent to be more effective than placebo in improving RIX symptoms (41-51%). However, adverse side-effects can arise in about 15% of patients given pilocarpine (excessive sweating, salivating and urination, among others), such that the authors concluded that there is limited evidence to support the use of parasympathetic agonist drugs, such as pilocarpine, for the treatment of RIX. although the side effects generated by the drug outweighed by its dose-dependent benefit (Davies Andrew and Thompson, 2015).

In contrast, a meta-analysis and systematic review of the efficacy and safety of pilocarpine for RIX in HNC patients (n = 752) found that pilocarpine performed better than the placebo in terms of the patients' subjective reports. The study also reported adverse effects of the drug, mainly excessive sweating, to a mild or moderate extent, the fixed-effects model of sweating

combined odds ratio was reported to be 3.71 (95% CI, 2.34-5.86; P < .00001) compared with the placebo (Cheng et al., 2015).

Cevimeline, a Quinuclidine derivative of acetylcholine, is a cholinergic agent with muscarinic agonist activity prominently affecting the M1 and M3 receptors prevalent in exocrine glands (and not M2 in cardiac tissue and M4 in lung tissue). It has been suggested to have a positive effect on saliva stimulation in patients with xerostomia of Sjögren's syndrome (Chambers et al., 2007a).

A study of two double-blinded trials, assessing Cevimeline's safety and efficacy against a placebo, had 570 patients. It reported that the first trial had more Cevimeline-treated subjects than placebo recipients expressing improved dryness (Cevimeline 47.4% vs placebo=33.3% p = 0.0162), while the second trial reported no significant difference between groups in the final global evaluation, and the placebo response rate was 47.6%. Patients who had received Cevimeline had a greater increase a considerable increase in unstimulated salivary flow than placebo recipients. Cevimeline was generally well tolerated. The study also recommended a Cevimeline dose of 30–45 mg three times a day (Chambers et al., 2007b).

An open-label and long term safety study of Cevimeline 45 mg twice daily for 1 year for RIX, in 255 HNC patients, found that 59.2% of patients reported having some clinical benefit from RIX while using the drug. Although 68.6% of patients reported mild to moderate side-effects from using Cevimeline. The study suggested that 45 mg of Cevimeline could help improve oral dryness in HNC patients (Chambers et al., 2007a).

Electrostimulation

With its less adverse side-effects both locally and systemically, electrostimulation was proposed as treatment for xerostomia "regardless of the aetiology", by applying electronic rods, charging impulses to the corresponding nervous areas in order to stimulate the nervous system and inducing a "normal physiological" reflex that would promote normal salivation by the salivary glands (Weiss et al., 1986).

A multicentre and randomised trial looked into the efficacy and safety of an intraoral electrostimulation device for 114 xerostomia patients (14 RIX patients) in stage I (double-blind, crossover stage designed to compare the effects of the electrically active device with the sham device) each used for 1 month, stage II was a 3-month open-label stage designed to assess the long-term effects of the active device. Against a sham device, the intraoral device performed better for patient-reported xerostomia severity ($P < 0.002$), xerostomia frequency ($P < 0.05$), quality of life impairment ($P < 0.01$), and swallowing difficulty ($P < 0.02$). At the end of stage II an improved statistical significance was further noticed, patient-reported xerostomia severity ($P < 0.0001$), xerostomia frequency ($P < 0.0001$), oral discomfort ($P < 0.001$), speech difficulty ($P < 0.02$), sleeping difficulty ($P < 0.001$), and resting salivary flow rate ($P < 0.01$). The study concluded that the device has shown benefit with the symptom if worn for long periods, and has been showing promise from baseline to the end of the trial (Strietzel et al., 2011).

Acupuncture

Acupuncture treatment for RIX has been suggested to help increase circulation to the parotid glands and might induce vital tissue regeneration within salivary glands (Sagar, 2008).

A study of 70 patients with xerostomia, including 38 RIX patients, received 24 acupuncture therapy sessions and had their whole saliva stimulated/unstimulated flow rate (SFR) measured before treatment and after six months up to 3 years. The results showed a significant improvement in stimulated salivary flow rate in patients after 24 sessions of acupuncture, which occurred after six months, and suggested that the later sessions extending to up to three years could help maintain the improvement (Blom and Lundeberg, 2000). A Cochrane review into non-pharmacological treatments for xerostomia; which included five studies (total of 153 participants with RIX), compared acupuncture with placebo acupuncture and concluded that there is "low-quality" evidence that acupuncture differs from placebo acupuncture in treating xerostomia. Acupuncture was reported to have midland short-lasting advert effects. (Furness et al., 2013).

Other treatments

The use of salivary substitutes, mouthwashes, dentifrices, aloe Vera gel and other means of palliative care often suggested for the symptoms of RIX; increasing lubrication, wetting of the mucosa, help with indigestion and injury protection. Nocturnal discomfort, in particular, is proposed to be troublesome for RIX patients, xylitol patches, lozenges and ointments applied to the mucosa could help relief it (Dost and Farah, 2013, Eisbruch et al., 2003b, Nieuw Amerongen and Veerman, 2003).

A crossover trial comparing 4 compounds effect (aloe Vera gel, Carboxy-Methyl-Cellulose or CMC-based artificial saliva spray, rapeseed oil in a spray, and a mucin-based spray) on 120 participants with RIX, did not uncover any statistically significant differences between the compounds. However, all participants reported improvement in symptoms for all compounds compared to baseline (Momm et al., 2005).

Different patients have different expected outcomes, needs, attitudes and demands when it comes to the benefit of palliative means. Therefore it is advisable to ask patients to try different types of palliative means to figure the most suitable type (Dost and Farah, 2013). Moreover, these other means of management are disadvantaged by its short-lasting effect, allergy, tolerance, discomfort, application limitation and patient convenience (Epstein and Stevenson-Moore, 1992, Davies, 1997).

1.8 Measurement of Radiotherapy induced xerostomia

The demand for a reliable and accurate measure of xerostomia is ever-increasing, from the development of objective measurement techniques, clinician guided scores or the development of subjective patient-reported outcome measures. Without reliable and valid measures of any clinical disorder it is impossible to truly know the severity of a symptom and hence undertake research altered to cause or management, or to monitor the effects of any clinical intervention or better understand the condition and aid in the maintenance of the salivary function post-radiotherapy. a number of different objective and other measures of RIX have been proposed (Fox et al., 1987, Lipscomb et al., 2004, Wiklund, 2004, Lohr and Zebrack, 2009, Ringash et al., 2015). RIX can be assessed objectively by measuring salivary output or function using different methods. it can also be assessed subjectively using clinician or patient reported outcome measures (Ringash et al., 2015).

Objective measurement of xerostomia

Salivary flow rate

Salivary flow rate (SFR) assessment includes measuring it in an unstimulated or stimulated state. Unstimulated salivary flow measure might be considered more relevant to the cause of RIX than stimulated salivary flow rate, due to the salivary basal level protection of UADT by unstimulated flow than stimulated flow (Malouf et al., 2003).

It is usually always measured by sialometry, other means of objectively detecting changes in salivary presence are the modified Schirmer's test and the Saxon test, and these techniques are discussed in detail below.

Sialometry

Saliva collection can include the collections of stimulated saliva and unstimulated saliva, which is collected and measured for 5-10 min equivocal to 1 ml/min for a normal salivation or flow rate (Humphrey and Williamson, 2001). The collection is volumetrically based, either done by collecting spit in a pot,/draining or absorbing saliva by cotton rolls inserted into the mouth and placed in a pot and weighted against change in pot weight (Navazesh, 1993).

Furthermore, to selectively collect saliva from the parotid gland, the Stensen duct is catheterised, or a suction cup (Lashley cup) is applied to the duct, absorbing the exiting saliva and collecting it. The selective collection of saliva from the submandibular or sublingual glands follows the same techniques described, collecting it from the glands' canals orifices at the floor of the mouth. Stimulation can be used while collecting saliva, like chemical stimulation or mechanical stimulation. 2% citric acid, a chemical stimulant, is placed when needed on the dorsum of the tongue to induce salivation. Also, chewing is considered to be a mechanical saliva stimulant hence patients are instructed to chew before collection. This technique however is hardly reproducible or reliable, it is also uncomfortable to patients (Navazesh, 1993, Humphrey and Williamson, 2001).

After collection, the saliva weight, volume and flow rate (ml/min) are calculated, the standard salivary output is believed to be 0.1ml/min. However, salivary flow rate might be affected by technical difficulties; high sensitive collection methods, the need for a stimulate-free area for collection in unstimulated saliva collection and the patient's level of hydration (Navazesh, 1993, Eisbruch et al., 2003a, Dirix et al., 2006). With no significant clinical proof, a measure of ≤25% in salivary rate compared with the rate measured before radiotherapy is considered a borderline threshold (Roesink et al., 2001).

Saliva collected from the major salivary glands itself is not a true representative of whole saliva capable of being studied, it also will not include fluid from minor salivary glands (Navazesh, 1993, Eisbruch et al., 2003a). Also, the significant "inter-individual" variation in salivary output may prove to be trying to study when the healthy flow is expected to be generated (O'Connell, 2000).

Modified Schirmer's test

The Schirmer's test is used to test the degree of ocular dryness in Sjögren's syndrome patients, by placing a scaled paper strip and if more than 10 mm of moisture on the paper appear in under 5 minutes this is considered normal lacrimation. This has been modified and utilised as a mean of assessing xerostomia (Davis and Marks, 1986).

One study used two tongue depressors with a paper strip in-between, protruding 3mm at the end and placed at the opening of the parotid gland for five minutes (Davis and Marks, 1986). The second study placed a 1X17 cm paper strip in a polythene bag and put one end in the patient's mouth for five minutes (López-Jornet et al., 1996). The third study placed a Schirmer's test strip on the floor of the mouth of a controlled group of 20 xerostomia patients and 41 healthy individuals and measured changes at 1,2 and 3 minutes. The study reported the ability of the MST to differentiate between healthy controls and xerostomia patients' saliva levels (Chen et al., 2005).

Saxon test

The Saxon test is used to assess xerostomia, measuring the saliva produced by weighing a sponge before and after chewing. A study on 70 patients with xerostomia and 25 healthy controls, which were asked to chew on a folded sterile sponge for 2 minutes. The healthy control group produced a mean of ≤ 2.75 gm of saliva in 2 minutes. Twelve patients had a decreased saliva weight, with a significant difference, in comparison with controls ($P < 0.01$), an indication that proves the ability of the Saxton test to detect abnormalities (Kohler and Winter, 1985). Still, these techniques lack consensus on approach and validation.

<u>Salivary gland imaging</u>

Scintigraphy

Salivary gland scintigraphy (SGS) with [99M]Tc-pertechnetate, can be used to assess functional changes in glandular function at any stage of salivation (Van Acker et al., 2001, Kosuda et al., 1999). SGS is favourably performed using single proton computed tomography (SPECT), which supplies a spatial aspect to the images (Valdés Olmos et al., 1994, Dirix et al., 2006). However, scintigraphy is invasive, uncomfortable to the patient, carries a risk of allergic responses to the radionuclide medium and requires technical training and personnel, the potential for using radiomic assessments is therefore not optimal (Shah, 2002).

Ultrasonography

Ultrasonography (US), is used widely in the screening and monitoring of cancer, is considered to be an inexpensive, easy, non-invasive and non-radiation-induced imagery (Cheng et al., 2011, Kotecha et al., 2008). It has been used to describe superficial soft tissue of salivary glands and detect signs of cancer, Sjögren's syndrome, sialadenitis and sialolithiasis. US can showcase the anatomy of all major salivary glands, except for the deep lobe of the parotid gland (Kotecha et al., 2008, Gritzmann et al., 2003). Healthy salivary glands appear on a US scan as being homogenous, hyper-echoic and regular (Cheng et al., 2011, Bialek et al., 2006, Gritzmann et al., 2003). Following RT, salivary gland tissue can appear heterogeneous, hypo-echoic and irregular in shape (Imanimoghaddam et al., 2012).

The Nakagami parameter has been used in detecting changes in the breast and eyes (Caixinha et al., 2014, Liao et al., 2012). A study to investigate the feasibility of the Nakagami parameter on RIX included a group of twelve post-radiotherapy patients and 12 healthy individuals. Nakagami scales were applied to both groups. The results showed a significant difference between the normal scanned parotid glands of healthy individuals and the patients' scans, suggesting the application of the parameter in detecting physical effects of radiotherapy on salivary glands and the need for further investigation (Yang et al., 2014).

while US scans may provide information about the structure of salivary glands they do not give any indication of the actual function of glandular tissue (Ying et al., 2007). Furthermore, the characteristics with those of Sjögren's syndrome, which could cause a misdiagnosis, and the need for a trained operator to perform the scan (Kotecha et al., 2008, Cheng et al., 2011).

Subjective measurement of xerostomia

Subjective assessment of xerostomia includes patient-reported outcome measures (PROMs) and clinician-reported outcome measures (CROMS).

A Patient-reported outcome (PRO) is defined as "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response

by a clinician or anyone else" (Varma et al., 2010). A PRO is used concurrently with other objective outcomes in assessing biomarkers, morbidities, burden and survival in clinical trials (Beaver et al., 2018). PROMs are instruments that are used to measure PROs (Powers III et al., 2017). There is a firm belief that patient input on the projection of care is pivotal when deciding on the most suitable treatment, and any disregard to patients' expression, whether on the treatment choice or the declining quality of care or life, should not be overlooked (Meirovitz et al., 2006). PROMs that are used to measure RIX in the literature subjectively may either have been created for HNC patients with some items about xerostomia or disease-specific questionnaires structured to measure xerostomia that have been employed for RIX patients explicitly. Another instrument used in subjectively expressing patients' opinion on RIX is the Visual Analog Scale (VAS), which has been used in combination with other PROMs (Dirix et al., 2007). PROMs may measure the symptom's severity and treatment effect or measure the HR-QoL of patients (Shields et al., 2006).

In contrast to PROMs functional questionnaires, CROMs are a clinician's 'guide of patients' symptom interpretation. Several CROMs have been developed to measure xerostomia based on symptom expression and appearance per observer assessment. They include the Radiation Therapy Oncology Group functional scale (RTOG), the Common Toxicity Criteria for adverse effect (CTCAE), the European Organisation for Research and Treatment of Cancer (EORTC) and the Late Effects Normal Tissue Task Force Subjective Objective Management Analytic (LENT-SOMA). All of these instruments have xerostomia specific items to help interpret the effect of post-radiotherapy in HNC patients. However, they were not developed to solely measure xerostomia severity.

Patient-reported outcome measures (PROMs):

(HNC disease-specific) subjective measures

the concept of PROMs crosses over with that of QoL, as they each acknoledge the experience/opinion of the patients or affected individual. The World Health Organisation defines HR-QoL as "an individual's perception of their position in life in the context of the

culture and value systems in which they live and in relation to their goals, standards and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychosocial state, level of independence, social relationships, and their relationships to salient features of their environment." (WHO, 1993). Including all these aspects and adjusting it according to population specifics, linguistic interpretation and incorporating symptoms can prove challenging (Seikaly et al., 2001, Murphy et al., 2007).

Several HNC disease-specific PROMs have been created to measure the impact of HNC treatment on the quality of life of patients, seen in Table 1.13.

Table 1.13 Disease-specific QoL questionnaires for HNC

Instrument	reference	Description	Response
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- H&N 43 (EROTC-QLQ-H&N 43)*	(Singer et al., 2019)	73 items with scales on Pain, swallowing, senses, speech, social eating, social contact and intimate relations	mixed format with four-point Likert-like and yes/no response
Functional Assessment of Cancer Therapy General- (FACT H&N)	(D'Antonio et al., 1996)	27 items 11 domains functional wellbeing, emotional wellbeing, social/family wellbeing, physical wellbeing, and additional concerns specific to head and neck cancer	0 not at all to 5 very much
Head & Neck Radiotherapy Questionnaire (HNRQ)	(Browman et al., 1993)	22 items, interviewer conducted six domains skin, throat, oral stomatitis, digestion, energy and psychosocial	yes/no question followed by Likert-like scale
Quality of Life Radiation Therapy Instrument Head and Neck Module (QOL-RTI/H&N)	(Trotti et al., 1998)	14 items and Seven dimensions pain, appearance, speech, chewing and swallowing, mucous and saliva, taste and cough	0 for not at all to 10 very much
The University of Michigan Head and Neck Quality of Life Instrument (HNQOL)	(Marta and Saad, 2017)	20 items with four domains communication, pain, eating and swallowing, and emotional	Likert-like scale
University Washington Quality of LIfe Questionnaire (UWQOL)	(Boyapati et al., 2013)	Ten items with 4 written response questions on three dimensions physical functioning, physical symptoms and social functioning	range from 0 for worst to 100 for best
University of Liverpool Questionnaire for head and neck cancer	(Pace-Balzan et al., 2004)	Twenty-five items divided into 12 items assessing general issues related to oral function; 13 items deal with denture satisfaction.	rated on a 1–4 Likert scale ranging from never (1) to always (4)

* be used with the EORTC-C30   (Singer et al., 2019)

These instruments are designed to capture all related QoL dimensions, and some even include parameters of assessing xerostomia severity and its co-symptoms (Eisbruch et al., 2003a).

The EORTC QLQ-C30 is a disease-specific QoL instrument, while the EORTC QLQ-H&N43 is a newly validated HNC disease-specific QoL PROM. with regard to RCT related xerostomia, these instruments have been validated for use in the head and neck (Bjordal et al., 1999, Singer et al., 2019). However, they measure all symptoms related to HNC, and are generic, rendering them insensitive to the specificity of the symptom of RIX.

The Functional Assessment of Cancer Therapy general (FACT H&N) is used by adding symptom indexes (FHNSI) or "additional concerns" in order to cover the adverse effect affiliate information to the disturbances in function. The FACT H&N is validated for use on HNC patients (Yount et al., 2007, List et al., 1996, D'Antonio et al., 1996).

Quality of Life Radiation Therapy Instrument Head and Neck Module (QOL-RTI/H&N) does include subscales of saliva measures. They have been reported to be valid by Trotti et al. 1998, in a non-randomised study, including only 35 HNC patients (Trotti et al., 1998).

The University Washington Quality of life Questionnaire (UWQOL), had previous versions that did not have a saliva domain (versions 1.0 and 2.0). These versions were validated for consistency and reliability (Hassan and Weymuller, 1993, Weymuller Jr et al., 2001). The later versions (3.0 and 4.0) did include saliva scales, the latest version UW-QoL (version 4.0) has a saliva subscale that was employed by Roger and co-workers (2010) in a cross-sectional study comparing it with XeQoLS, reporting that it is "a suitable mean" of screening and could be used as an indicator for intervention (Rogers et al., 2010).

Disease-specific subjective measures

Xerostomia-specific PROMs are used to determine RIX for patients with HNC, either alone or in combination with objective assessment measures.

Visual Analog Scale (VAS)

The Visual Analog Scale (VAS) is widely utilised as subjective means of recording a patient's response to treatment or indeed their preserved severity of any symptom. Patients are asked to place a mark on a 100mm line that has two anchors, one having terms like "very difficult" or "very dry" to describe tolerance or symptom status scored at the other end, terms such as "easy" or "not dry at all" are used. The patient is then asked to mark their response on the scale. The attending clinician measures the distance on the scale between patient visits scoring it from 0-10 or 0-100. Many studies have used this scale to measure patient perceptions with regards to the severity of xerostomia (LeVeque et al., 1993, Pai et al., 2001, Taweechaisupapong et al., 2006, Cheng et al., 2011).

PROMs used to measure RIX

Available of PROMs that specifically assess RIX for HNC patients are summarised in Table 1.14. It has been principally employed to investigate xerostomia in relation to radiotherapy (Jabbari et al., 2005, Henson, 2001, Meirovitz et al., 2006, Parliament et al., 2004). Some focus on the severity of the symptom of RIX, while others measure the QoL of RIX in patients with HNC.

A study reported that xerostomia questionnaire (XQ) is valid for its use in HNC (Eisbruch et al., 2001). Thirty-eight patients who had received IMRT for HNC underwent xerostomia evaluations 6 to 24 months after completion of therapy, using three methods at each time point: (1) Grading by three observers using the RTOG/EORTC system; (2) the XQ and (3) major salivary gland flow measurements. The study reported a significant correlation between the XQ scores and non-stimulated ($P < 0.005$) and stimulated ($P < 0.005$) salivary flow rates, as well as with the percentages of the corresponding pre-therapy values ($P = 0.002$ and 0.038, respectively). The study reported no significant correlation between the RTOG/EORTC grades and the XQ scores. The observer-based grades underestimated the severity of xerostomia compared with the patient self-reported scores (Meirovitz et al., 2006).

Table 1.14 RIX -specific PROMs

Instrument	Reference	Construct	Description
Xerostomia Questionnaire (XQ)	(Eisbruch et al., 2001)	Severity	8 items including four items on dryness when eating or chewing
Xerostomia Inventory (XI)	(Thomson and Williams, 2000)	Severity	5 dimensions Likert type scoring: Total score, higher scores denote greater severity of symptoms.
Xerostomia-related Quality of Life scale (XeQoLS)	(Henson et al., 2001)	QoL	4 dimensions: physical, psychological, social, pain/discomfort One global score
Groningen Radiotherapy-induced Xerostomia (GRIX)	(Beetz et al., 2010)	QoL	Fourteen items, with four subscales xerostomia and sticky saliva during day and night, scaled linearly from 0 to100.

(Heutte et al., 2014)

In an earlier study by Henson et al. 2001, XeQoLS was found to correlate with stimulated and unstimulated saliva flow rates (Henson, 2001). Also, XeQoLS might be considered to have an elaborate structural development with the inclusion of salivary gland dysfunction attributes in its HR-QoL format (Malouf et al., 2003).

Clinician reported outcome measures (CROMs)

Functional questionnaires are performed by the clinician. the questionnaires provide subjective descriptions of functional aspects of a symptom and can graded by severity. These measures are also used to measure adverse effects or rate toxicity on healthy surrounding tissue. These measures can be used on their own, or in combination with other, subjective or objective measures. Functional measures include the RTOG grading system, CTCAE versions 3.0 and 4.0, and LENT-SOMA among others.

Radiation therapy oncology group (RTOG) toxicity grading system

The RTOG is designed to grade the level of radiation toxicity the tissue has sustained, in order to manage adverse effects of therapy accordingly. This observer toxicity grading system,

shown in Table 1.15, contributes to the whole multi-prospective study of RIX in HNC, as it assesses the degree of the effect of radiotherapy upon different organ tissues around the body. The RTOG scoring criteria, grading the toxic effect on 13 organs, such as the eyes, ears, mucosa, salivary glands, skin and more (Cox et al., 1995). Acute xerostomia (within three months of therapy commencement) is graded by symptom; the degree of dry mouth, thick saliva, and altered taste. Chronic xerostomia is divided according to the degree of mouth dryness and response to a stimulus.

Table 1.15   RTOG xerostomia Grading System

chronic (Beyond 90 days from the commencement of RT)
Grade 1: Slight dryness of the mouth; good response to stimulation
Grade 2: Moderate dryness of the mouth, poor response to stimulation
Grade 3: Complete dryness of the mouth; no response to stimulation
Grade 4: Fibrosis

(Eisbruch et al., 2003a, Cox et al., 1995).

Performance Status Scale for Head & Neck Cancer Patients (PSS-HN)

The PSS-HN was developed by the RTOG group to assess the functional activities in patients with HNC, based on the performance of functions in different HNC groups. It allows clinicians to score items on diet, speech and eating from 0–100, the higher the score, the better the performance (List et al., 1996).

Common Terminology Criteria for Adverse Events (CTCAE) system

The CTCAE system was created in response to the increased need for a standard and comprehensive system to record all aspects of the toxic effect of radiotherapy upon healthy tissue. The CTCAE 2.0 is focused only on the acute toxic effects of radiotherapy upon 22 organs (Trotti, 2000). The CTCAE v3.0 scoring system acknowledges both the early and late effects of toxicity and all the treatment modalities into the grading system; the scoring system is filled from the first radiotherapy session throughout the therapy period weekly (Trotti et al.,

2003). The CTCAE version 4.0 and version 5.0 (table 1.16) were later developed to tackle the issue of the increased objective labelling CTCAE v3.0 had, by emphasising subjective rather than objective factors (Health, 2009).

Table 1.16 The CTCAE version 5.0 for the late effect of xerostomia

Effect	Adverse effect	Grade				
		1	2	3	4	5
late	Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-

(Health, 2009)

Palazzi et al. studied the validity of the CTCAE v3.0 and suggested that is valid for assessing acute toxic effect of radiotherapy (Palazzi et al., 2008). However, these measures have not been vigorously tested for their reliability or validity in studying the toxic effect of radiotherapy in the treatment of patients with HNC.

Late Effect of Normal Tissue (LENT) Objective Subjective Management and Analytic (SOMA) system

LENT/SOMA includes both objective and subjective measures, aspects of management and type of analytic investigation (e.g. sialometry, CT, MRI). Also, this measure stages the severity of both acute and late toxic effects, which include radio-pathological and chemo-pathological items, with a 1-4 scoring system, it also describes the frequency of symptom effect (Rubin et al., 1995) (Table 1.17).

Table 1.17 Adverse radiation reactions of the salivary glands according to the LENT-SOMA scale.

Stage	1	2	3	4
Subjective Xerostomia	Occasional dryness	Partial but persistence dryness	Complete dryness, non-debilitating	Complete dryness, debilitating
Objective Saliva	Normal moisture	Scant saliva	Absence of moisture, sticky viscous saliva	Needs saliva substitute or water in order to eat sugarless candy or gum sialagogues
Management Xerostomia	-	Occasional saliva substitutes, sugarless candy or gum, sialagogues	Frequent saliva substitute or water sugarless candy or gum	needs saliva substitute or water in order to eat sugarless candy or gum
Analytic Flow/quality/ stimulation	76-95% of pre-treatment	51-75% of pre-treatment	26-50% of pre-treatment	0-25% of pre-treatment

(Pavy et al., 1995, Rubin et al., 1995)

The LENT/SOMA has been reported to better measure adverse reactions, in comparison with other functional measures (Denis et al., 2003) and considered as a standardised reporting method of late radiation morbidity (Hoeller et al., 2003). One study highlighted the reliability and feasibility of its late toxic effect measures (Ho et al., 2009). Another study recommended its subjective xerostomia score to be useful to predict salivation recovery after radiotherapy due to its strong association with dosimetry and ease of recording (Miah et al., 2013).

A study in which LENT–SOMA and EORTC QLQ-C30 patient questionnaires were prospectively completed by 220 HNC patients over 3 years, with 72 patients completing the EORTC QLQ-H&N35 questionnaires at 2 years post-radiotherapy, found that the LENT-SOMA patient questionnaire is both reliable and sensitive to differences between patients treated with different modalities, when compared with results obtained by EORTC questionnaires (Ho et al., 2010).

1.9 Limitations and shortcomings of current outcome measurements for radiotherapy-induced xerostomia

The available outcome measures both objective and subjective (PROMs and CROMs) for RIX are considered to be of limited value in view of their construct or their lack of explicitness when measuring RIX outcomes (Fox et al., 1987, Ringash and Bezjak, 2001, Gotay and Moore, 1992). In addition, validity studies have not been vigorously undertaken, in terms of methodology, hence their robustness and rigour may be questioned (Eisbruch et al., 2003a, Ringash et al., 2015). Therefore a comprehensive methodological assessment of validation studies concerning these measurement tools in critical in distinguishing which can be trusted and incorporated in clinical practice and research. Follows a description on the limitation for each method in detail:

Objective measurement

Objective assessments of RIX, such as salivary flow rate are flawed as there has been a weak correlation between the amount of saliva in the mouth and the "feeling" of xerostomia, leading some to suggest basing assessments on patient symptoms rather than objective tests (Visvanathan and Nix, 2010).

Subjective measurement

<u>Clinician-reported outcome measures</u>

Functional assessments are thought to be able to account for short and long term HNC symptoms (Ringash and Bezjak, 2001), however, not without disadvantages. In the RTOG scoring system, it is not stated with clarity whether a clinician or patient can rate them, and the response to a stimulus is not defined. Moreover, RTOG has not been thoroughly validated or tested for its internal consistency (Eisbruch et al., 2003a, Langendijk et al., 2008). Also, one of the main flaws of this scoring system is the lack of clear boundaries between the grades and the arbitrary assignment of relative salivary flow reduction to the different grades (Eisbruch et al., 2003a).

The present outcome measures, tested in the past for their validity, reliability and reproducibility for assessing HNC PROMs, are often noted by conflicting results (Rogers et al., 2007), since many conflicting studies have reported CROMs as unreliable or invaluable especially while measuring xerostomia (Eisbruch et al., 2003a, Jellema et al., 2007, Murphy et al., 2007).

<u>Patient-reported outcome measures</u>

PROMs are more expressive and elaborative, although they are regarded as being always "an over-estimation" of related symptom, which leads to the conclusion that a PROMs symptom over-estimation is more preventive than an objective assessment which could be "under-estimated", patients are not trained in explaining where and what symptoms might be or mean and can only express how dryness might 'feel' and therefore can cause and over-estimation or exaggeration of their symptoms. An over-estimation might counter an underestimation observed by CROMs measures for example when treating RIX (Meirovitz et al., 2006). PROMs are not without flaws. Currently available HNC disease-specific PROMs are innately too broad to be able to singularly measure symptoms related to RIX, which makes them unintentionally shallow or lacking an in-depth outlook when measuring RIX. The EORTC for instance has one item on RIX only (Snyder et al., 2012). Furthermore, the generality of the HNC-disease-specific PROMs makes them imperfect by nature and fail to reflect the real state of HNC related symptoms when studying them individually (Ringash and Bezjak, 2001). Many of these outcome measures where studied for their validity and reliability; EORTC QLQ-30&HN-35, FACT H&N, WUQOL and QoL-RTI/H&N (Cella et al., 1993, Trotti et al., 1998, Bjordal et al., 1999, Weymuller Jr et al., 2001, Yount et al., 2007), but some of these validations did not include validity information on the xerostomia-specific items within it.

Other disadvantages of current HNC disease-specific PROMs could be patient commitment and patient adaptation to adverse effects. A symptom-specific PROM could better detect and unveil subtle changes in symptoms that could overcome this limitation (Breetvelt IS, 1991, Murphy et al., 2007). One study, comparing the scores on the EORTC QLQ-C30 study for 65

untreated early-stage laryngeal cancer patients versus controls, focused on QoL and found no difference between the two groups (De Graeff et al., 1999). That could be related to the insensitivity of HNC PROMs and the inability to detect specific symptoms specifically.

It is arguable that the first challenge for assessing RIX is choosing the right outcome measure (Murphy et al., 2007). Current HNC PROMs, if chosen incorrectly, could deter the outcome of the measurement profoundly. There are generic and disease-specific PROMs, the generic ones may be able to detect the main health domains and allow direct comparisons with a healthy population, although it would lack in sensitivity to the subtle changes in the disease which a disease-specific PROM may be able to detect more accurately.

Xerostomia-specific PROMs are thought to be more suited to measure RIX in HNC better than HNC disease-specific PROMs. Many of the current xerostomia-specific PROMs have been validated on HNC patients and are suggested to be more able to measure RIX in HNC patients (Meirovitz et al., 2006). However, these validations are non-adherent to a robust methodological approach to validity and therefore should be assessed for their validity method in order to be used with confidence. Moreover, a disease-specific PROM might be overly focused on the disease that it misses domains that affect patients that are unrelated to the disease measured (Lohr and Zebrack, 2009). These shortcomings were addressed in the international society for Quality of Life Research (ISOQOL) "User's Guide for Implementing Patient-Reported Outcomes Assessment in Clinical Practice" that highlights the positives, negatives and requirements for each type of options for PROMs. This user guide aims at minimising measurement error and ensuring an appropriate selection of a PROM for the appropriate patients, an appropriate administrating method and scoring, an appropriate reporting as well as developing strategies for responding to issues identified by the PROMs (Snyder et al., 2012).

The VAS scale presents a high risk of error, as well as its lack of attention to patient adaption to symptoms, which could deviate VAS scores considerably (LeVeque et al., 1993) VAS scale

was only validated in a group of 36 HNC patients with RIX (Pai et al., 2001), which is relatively a small sample size.

1.12 Aim of this study

At the present time, a high-quality, statistically robust and rigorous PROM for RIX is non-existent. Many of the current validation studies on PROMs for RIX lack an appropriate methodology, execution and format. Some studies have adapted a rather non-methodological approach to instrument validation, based on proposed criteria for methodological assessments, while others have incorporated inappropriate tests to study specific property measures (Terwee et al., 2018, Prinsen et al., 2018). These supposed validated PROMs have been extensively used in studies of RIX in patients with HNC. These instruments should be, therefore, re-assessed and re-validated with methodological rigour. Some assessment measures have been developed and proposed, to study the validity of PROMs in a methodological and comprehensive format, such as the COSMIN checklist, to assess PROMs instruments measuring radiotherapy-induced xerostomia in patients with HNC.

No RIX PROM has been validated on a population residing in London, UK, therefore we aim to validate the most suitable RIX PROM, via application of the COSMIN standard, on a population residing in London, UK.

Aims and objectives:

- Assess the psychometric properties of current validated RIX PROMs in by performing a systematic review using the COSMIN guideline.
- Validating the most suitable RIX PROM on RIX patients residing in London, UK.

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1.11 Methodological assessment of current RIX patient reported outcome measurements using the COSMIN standard

According to the National Institute for Health Research (NIHR), between 2018 and 2019 there were 6,106 clinical trials conducted in England, with 67,652 peoples participating in cancer research. These clinical trials are meant to test new drugs or treatments, surgical techniques, medical devices or aids and all sort of new and uniquely novel approaches that researchers hope would improve patients' lives and ease their way towards the path of recovery. Albeit is it enough for an intervention to perform its intended objective safely for it to be recommended?

Patient prospectives are becoming essential to conclusions in clinical trials, many regulatory bodies are recommending the coupling of PROMs with other clinical means of measure, in order to capture the added value recognised by PROMs. PROMs are suggested to be the best method of collecting patients' opinion and prospectives on interventions (Vodicka et al., 2015, Ringash et al., 2015, Wiklund, 2004).

However, before using PROMs, the validation of the PROMs should be assessed, in terms of methodological quality, in order to accept the data a PROM gathers with confidence. Hence the aim is to conduct the first COSMIN systematic review for Radiotherapy-Induced Xerostomia (RIX) using the COSMIN guidelines for methodological quality assessments of PROMs, to search for validated PROMs used to measure RIX in head and neck cancer patients. This systematic review identified four PROMs of which two were selected and validated on a population residing in London of RIX patients. These PROMs can be therefore incorporated in clinical interventions for RIX in future trials and in clinical practice. We hope this effort start a trend towards assessing PROMs validations before incorporating them in trials and not consider PROMs based on their 'face-value' validity.

Methodological assessments of outcome measures are fundamental in validating current RIX PROMs. A PROM validation study that is not of high methodological quality could inevitably compromise the confidence in these validations (Higgins et al., 2011).

There have been many recommendations in the literature about which tool or instrument should a clinician use in measuring HNC adverse effects or the QoL of HNC patients (Murphy et al., 2007, Ringash et al., 2015), these validations, however, usually always validate PROMs with no adherence to an appropriate validation methodology. That has encouraged studies to draw the first line towards developing guidelines and methodological frameworks for validating PROMs for their use in the literature. The Scientific Advisory Committee of the Medical Outcomes Trust (SAC-MOT) have made an attempt to create a comparison criterion for the assessment of measurements (Lohr, 2002), 8 criteria are listed in the SAC-MOT checklist, which includes: conceptual and measurement model, reliability, validity, responsiveness, interpretability, respondent and administrative burden, alternative forms and cultural and language adaptation. These criteria are meant to be the first step into forming a standard by which measurements can be methodologically compared (Lohr, 2002).

Terwee et al. 2006 noted that the SAC-MOT criteria are unclear on what makes "good measurement properties" (Terwee et al., 2007a). This study aimed at further refining SAC-MOT criteria by adding: content validity, internal consistency, criterion validity, construct validity, reproducibility, responsiveness, floor and ceiling effects, and interpretability. These developments were suggested to detect shortcomings and gaps in knowledge of measurement properties and to design validation studies (Terwee et al., 2007a).

The lack of a methodological assessment is linked primarily to the conflict of results shown while studying PROMs for statistical rigour, this notion lead Mokkink et al. to systematically review guidelines and appraise the methodological quality of studies on measurement properties (Mokkink et al., 2009).

Mokkink et al. looked at 148 systematic reviews and longitudinal studies with measurements of health status and ones that reported on the measurement properties of these measurement

instruments. Reporting that in the selected literature, the most common standards applied for reliability were interclass correlation coefficient (ICC), and using the Cronbach's alpha for internal consistency. Construct validity was performed by confirming the hypothesis. These standards were considered "adequate" if ICC > 0.70 and Cronbach's alpha > 0.07.

Mokkink et al. found no consensus on the most fundamental measurement properties or criteria of adequacy, reporting three major aspects:

1) A lack of methodological quality of systematic reviews of measurement properties (i.e. low quality of search strategy).
2) A lack of good reporting of the methods used to perform systematic reviews.
3) A lack of use of standards and criteria of adequacy to assess the methodological quality of the primary studies.

Upon these finding, the study suggested the need for developing guidelines for the process of reviewing measurement properties, including guidelines to assess the methodological quality of studies as well as guidelines for the criteria of adequacy for good measurement properties (Mokkink et al., 2009).

COSMIN stands for COnsensus-based Standards for the selection of health Measurement INstruments. It was developed in an international Delphi study, aiming to improve the selection process of health measurements instruments (Mokkink et al., 2006).

The COSMIN checklist is meant to tackle the issue of conflicting data and outcomes, unparalleled conclusions with similar purposes and to minimise non-evidence based practices. It also aims to reach consensus on which measurement properties should be evaluated of Health-Related Patient-Reported Outcome measures (HR-PROMs) and their definition, also develop standards for how these measurement properties should be evaluated in terms of study design and statistical analysis (Mokkink et al., 2010a).

The COSMIN checklist was developed with aim of:

1) Reach consensus on which measurement properties should be defined.

2) Develop standards for how these measurement properties should be evaluated in terms of study design and statistical analysis.

The COSMIN checklist can be thus used to evaluate the methodological quality of included studies on measurements and instruments properties as a systematic review or used to test the evidence on an instrument and help with measurement selection or even identify the need for further research on the measurement properties of a measurement instrument.

Many systematic reviews and measurement instruments validation studies have made use of the COSMIN checklist for assessment of PROMs on HR-QoL instruments in different fields of medicine (Weldam et al., 2013, Paiva et al., 2014, Yuen and Austin, 2014, Treanor and Donnelly, 2015, Winser et al., 2015, Abma et al., 2016, Heinl et al., 2016, Lee et al., 2016, Mokkink et al., 2006, Mokkink et al., 2018). However, to the best of our knowledge, no studies were assessing RIX PROMs using the COSMIN checklist. Moreover, no studies validating PROMs on RIX patients residing in London, UK exist.

Chapter Two

COSMIN systematic review

2. Evaluating the measurement properties of patient-reported outcome measures in radiotherapy-induced xerostomia: A COSMIN systematic review

2.1 Introduction

Radiotherapy-induced xerostomia (RIX) in head and neck cancer (HNC) survivors can limit oral functions and negatively impact on the quality of life (QoL) of affected patients. Xerostomia is a common permanent adverse effect of radiotherapy and one of the major causes of poor QoL in HNC survivors (Fang et al., 2004, Jensen et al., 2006). Measurement of RIX includes the subjective assessment of the severity of dry mouth symptoms, as well as the QoL of affected individuals, via PROMs (Ringash et al., 2015). In order for clinicians to be reassured that a PROM can adequately measure the symptom of interest, validation studies should be performed and its measurement properties should be evaluated in a high quality systematic review (Mokkink et al., 2018). According to COSMIN, assessment of the measurement properties of PROMs should include their reliability, validity and responsiveness (Mokkink et al., 2006, Mokkink et al., 2010c, Prinsen et al., 2018).

A systematic review of QoL in HNC patients, including measuring xerostomia, focused on methodological quality, was previously performed using the Scientific Advisory Committee of the Medical Outcome Trust (SAC-MOT) (Schellingerhout et al., 2012). This instrument sets out criteria for the evaluation and selection of QoL instruments (Terwee et al., 2011b). The SAC-MOT, however, has its limitations, including the complex nature of its administration and the lack of detail regarding the quality of measurement properties. In this review, we use the COSMIN guideline in critically appraising, pooling, and comparing the measurement properties of all PROMs measuring RIX (Prinsen et al., 2018). The study aim is to make an evidence-based recommendation on the most suitable PROMs to measure RIX outcomes and to highlight the PROMs that could be more suitable with more studies.

2.2 Methods

Search strategy

A systematic literature search was performed on Embase, Medline and PsycINFO up until May 2019. The search strategy consisted of three search filters:

1. Construct: radiotherapy-induced xerostomia.
2. Target population: HNC patients treated with radiotherapy
3. A validated search filter for instrument measurement properties (validity, reliability, and responsiveness) (Terwee et al., 2009).

Inclusion and exclusion

Articles were included based on the following criteria:

1. Construct: The PROM aim is to measure any aspects of xerostomia in HNC patients based upon their perspective. Any instruments measuring other symptoms or using a non-xerostomia specific PROM were excluded.
2. Target population: HNC patients that have developed RIX exclusively by receiving radiotherapy as a module of treatment. Any other xerostomia patients were excluded.
3. Study aim: Articles related to the evaluation of 1 or more measurement properties (validity, reliability, and responsiveness) and its development were to be included. Studies with insufficient methods of validity or using methods unidentifiable based on the COSMIN guideline were excluded (Mokkink et al., 2010b).

Assessment of methodological quality of included studies

The COSMIN taxonomy was employed to establish which measurement properties were assessed in each included study based on its definition (Table 2.1). The characteristics of each included PROM and characteristics of the included study populations were extracted. The COSMIN risk of bias was then used to assess the methodological quality of the included studies (Mokkink et al., 2018), each measurement property being rated as very good, adequate, doubtful or inadequate.

Assessment of measurement property results

The scores from the methodological quality assessment were compared against the criteria of good measurement quality (Mokkink et al., 2018).

Content validity is thought to be the most critical measurement property since the items in a PROM should first be clear, relevant, comprehensive and easily understandable before ensuring an appropriate internal structure (Mokkink et al., 2018, Terwee et al., 2018). With the absence of this information, the present study, did not report on content validity. To help with interpreting hypotheses for hypothesis testing, responsiveness and assessing correlations, these pre-defined hypotheses were set:

1. Correlations measuring a PROM against a similar construct should at least be higher than 0.50.
2. There should be a significantly reported change in correlations between subgroup and changes over time.

Evidence synthesis

The summarised results were then evaluated against the criteria for good measurement properties to obtain an overall rating; sufficient (+) insufficient (–) and indeterminate or Inconsistent (?) for each the measurement property. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was then applied (Prinsen et al., 2018). The GRADE level of evidence (High, Moderate, Low and Very low) is based on four points:

- Risk of bias: as determined using the COSMIN Risk of Bias checklist (the more the risk, the less trustworthiness of the evidence).
- Inconsistency of pooled results.
- Imprecision: assessing if the sample size is large or small (n > 100).
- Indirectness: this refers to evidence coming from different populations.

Table 2.1 COSMIN definitions of domains, measurement properties, and aspects of measurement properties

Term			Definition
Domain	**Measurement property**	**Aspects of measurement property**	
Reliability			The degree to which the measurement is free from measurement error
Reliability (extended definition)			The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: e.g. using different sets of items from the same PROM (internal consistency); over time (test-retest); by different persons on the same occasion (interrater); or by the same persons (i.e. raters or responders) on different occasions (intra-rater)
	Internal consistency		The degree of the interrelatedness among the items
	Reliability		The proportion of the total variance in the measurements which is due to 'true' differences between patients
	Measurement error		The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured
Validity			The degree to which a PROM measures the construct(s) it purports to measure
	Content validity		The degree to which the content of a PROM is an adequate reflection of the construct to be measured
		Face validity	The degree to which (the items of) a PROM indeed looks as though they are an adequate reflection of the construct to be measured
	Construct validity		The degree to which the scores of a PROM are consistent with hypotheses *(for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups)* based on the assumption that the PROM validly measures the construct to be measured
		Structural validity	The degree to which the scores of a PROM are an adequate

			reflection of the dimensionality of the construct to be measured
		Hypotheses testing	Idem construct validity
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted PROM are an adequate reflection of the performance of the items of the original version of the PROM
	Criterion validity		The degree to which the scores of a PROM are an adequate reflection of a 'gold standard'
Responsiveness			The ability of a PROM to detect change over time in the construct to be measured
	Responsiveness		Idem responsiveness
Interpretability			Interpretability is the degree to which one can assign qualitative meaning - that is, clinical or commonly understood connotations – to a PROM's quantitative scores or change in scores.

2.3 Results

One hundred seventy-eight articles were identified in the search strategy. 148 articles were screened (30 duplicates) and 142 articles were excluded on the basis of them not assessing measurement properties (n=78), using a non-specific xerostomia PROM instrument (n=33), being review studies (n=18), or not assessing xerostomia (n=13). From reference checking, three articles that met the inclusion criteria were added, as indicated in Figure 1.

A total of 9 articles with four different PROMs were scored in this review. Two PROMs measured the severity of xerostomia: the Xerostomia Questionnaire (XQ) and the Xerostomia Inventory (XI). The Groningen Radiotherapy-induced Xerostomia Questionnaire (GRIX) and the Xerostomia Quality of Life Scale (XeQoLS). The characteristics of the included PROMs are indicated in Table 2.2, while characteristics of the included study populations are detailed in Table 2.3.

The quality of evidence for each measurement properties result for each PROM is presented in Table 2.4. Instruments were placed in order of construct; severity and QoL outcome. A supplementary table including details on scoring is available in the appendices (Appendix M).

This includes the results of all the included articles on measurement properties for each PROM.

All included PROMs were found to have evidence supporting measurement properties including internal consistency, reliability, construct validity and responsiveness - except for the XeQoLS - which did not have reports on reliability in this review. XQ was the only PROM found to have evidence supporting its structural validity. A summary of each PROM with evidence supporting their measurement properties for use in HNC patients with RIX are indicated in table 2.4.

Figure 2.1 Search strategy
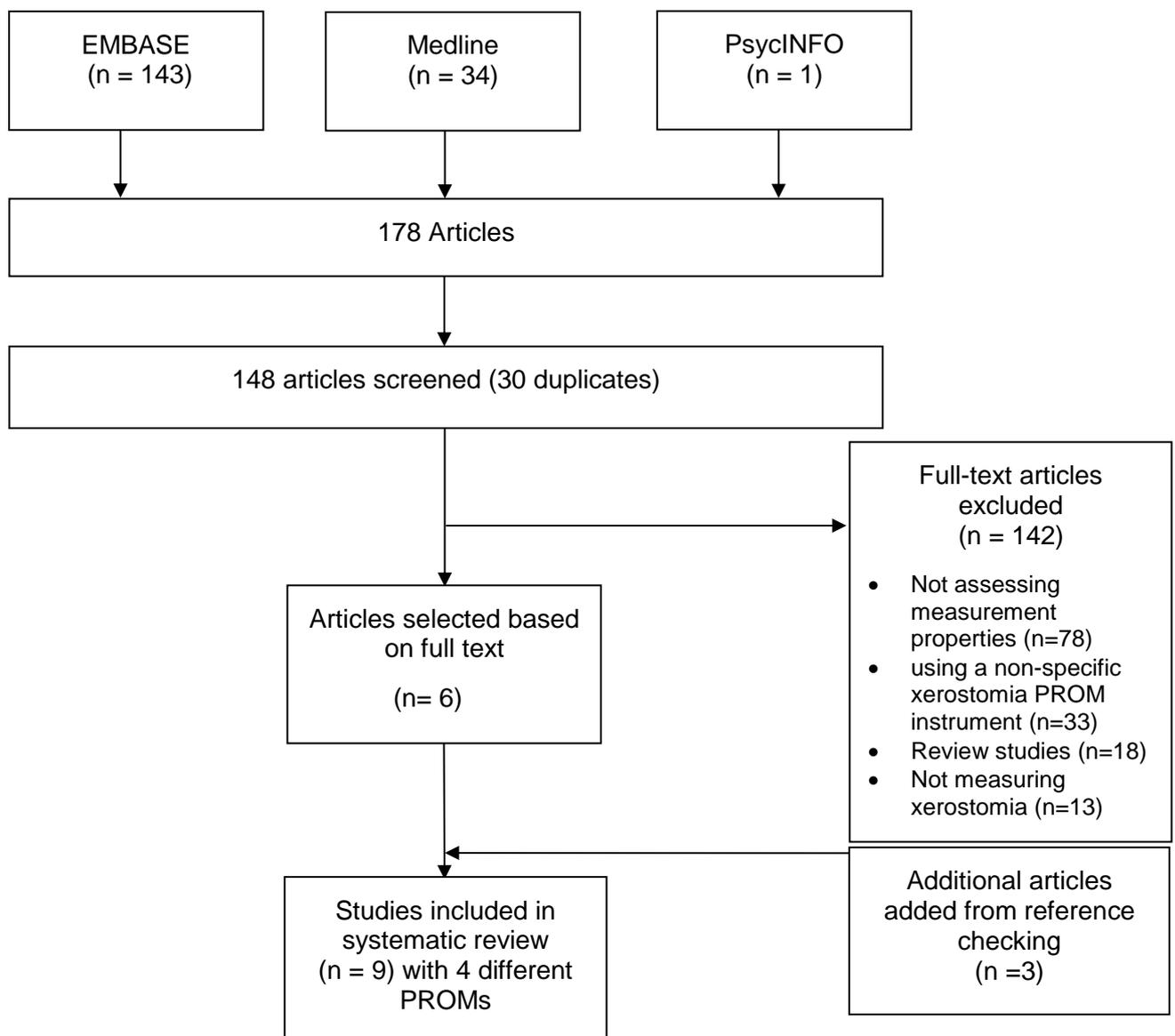
GRIX

The GRIX questionnaire assesses different aspects of patient-reported xerostomia to evaluate the impact of radiotherapy on patient QoL (Beetz et al., 2010). GRIX contains 14 items with four subscales, 2 for xerostomia and 2 for sticky saliva, which is completed twice during daytime and at night. A 4-point Likert-like scale (not at all, a little, quite a bit, very much) is used to score each item. Scores are then converted to a 0-100 scale, a higher scores indicating a greater degree of patient-reported xerostomia.

In the previous study the GRIX was found to have an indeterminate overall scoring of low-quality evidence for internal consistency and construct validity, an indeterminate overall scoring of very low-quality evidence for reliability and a sufficient overall scoring of very low-quality evidence for responsiveness.

XQ

The XQ was designed to measure subjective xerostomia by patients rating their symptom severity. It consists of 8 items, four items about dryness while eating and chewing, and the other four concerning dryness while not eating or chewing. Each item is rated on an 11-point numerical rating scale from 0 to 10, with higher scores indicating more dryness or more dryness discomfort. A final summary score is derived from summing the item scores and transforming it linearly to a 0-100 score, and the greater the overall score, the higher the xerostomia severity (Eisbruch et al., 2001).

The XQ was found to have a sufficient overall scoring of high-quality evidence for structural validity and internal consistency. Reliability of the instrument was found to have low quality evidence with an indeterminate overall scoring. A sufficient overall scoring was found for construct validity; with moderate-quality evidence, and responsiveness; with low-quality evidence.

XI

The Xerostomia Inventory is designed to measure the severity of symptoms associated with xerostomia. XI contains 11 items with a 5-point Likert-like response scale of never (scoring 1), hardly ever (2), occasionally (3), fairly often (4) and very often (5) (Thomson, 2007, Thomson and Williams, 2000).

The present study found sufficient overall scoring for XI for internal consistency; with moderate-quality evidence, and construct validity; very low-quality evidence, and responsiveness; low-quality evidence. Reliability was found to have an indeterminate overall scoring with very low-quality evidence.

XeQoLS

The XeQoLS is designed to measure QoL in patients with xerostomia. It consists of 15 items with a 5 Likert-like response scales (not at all, a little, somewhat, quite a bit, very much). This tool represents 4 QoL dimensions: physical functioning, pain/discomfort, personal/psychological functioning and social functioning (Henson, 2001).

The results on overall scoring reported in the present review show an indeterminate score with very low quality of evidence for internal consistency — also, a sufficient overall scoring with very low-quality evidence for construct validity and responsiveness.

 Recommendations for the most suitable PROM to measure RIX Outcome

The XQ was considered to be the most promising PROM for further use in clinical interventions for RIX, based upon the high level of evidence for structural validity and internal consistency, as well as a sufficient overall score with moderate quality of evidence for responsiveness. However, XQ was found to have an indeterminate overall score; of low-quality evidence, for reliability.

Table 2.2 characteristics of the included PROMs

PROM	Construct(s)	Target population	conceptual model used	Recall period	(Sub)scale (s) (number of items)	Response options	Range of scores/scoring	Available translations
GRIX (Beetz et al., 2010)	QoL related to xerostomia	HNC patients with RIX	Existing PROMs reviewed, expert opinion and a single patient opinion	Not specified	Four subscales: Xerostomia during the night, Xerostomia during the daytime, Sticky saliva during the night and Sticky saliva during daytime (14)	4 – point Likert, 0-3	All scores converted linearly to a 0-100 scale, with higher scores representing more xerostomia	English
XQ (Eisbruch et al., 2001)	Severity of xerostomia	Patients with xerostomia	Existing xerostomia-specific and general HNC QoL instruments PROMs reviewed surveys of patients and discussions with members of the research team.	Seven days	Two subscales: Dryness while eating or chewing and Dryness while not eating and chewing (8)	11-point numerical rating scale, 0-10	All scores converted linearly to a 0-100 scale, with higher scores representing more xerostomia	Italian, Taiwanese, Persian, Greek, French
XI (Thomson and Williams, 2000)	Severity of xerostomia	Patients with xerostomia	Used in HNC patients based on the validation study of the instrument on other dry mouth patients.	Two weeks	Symptom frequency (11)	5-point Likert, 1-5	Higher scores indicate severe xerostomia	Non-available
XeQoLS (Henson et al., 2001)	QoL related to xerostomia	Patients with xerostomia	Based on previous studies on QoL	Not specified	Physical functioning, Pain/discomfort issues, Personal/psychological functioning, Social functioning (15)	Not at all, a little, somewhat, quite a bit, very much	Averaging the values of all the respective items for that individual domain, a total average calculated	Italian

Table 2.3 Characteristics of the included study population

			Population		Instrument administration			
PROM	**Ref**	**N**	**Age** **Mean (SD, range) yr**	**Gender** **%** **female**	**Setting**	**Country**	**Language**	**Response rate**
GRIX	(Beetz et al., 2010)	315	Mean 62 Yrs (19-90 Yrs)	31%	Department of radiation oncology of the university medical centre of Groningen	The Netherlands	Dutch	Not reported
XQ	(Eisbruch et al., 2001)	132	Mean 51 Yrs	31%	The University of Michigan	USA	English	Not reported
XQ-T	(Lin et al., 2008)	50	Mean 54 Yrs (SD 14.42)	16%	The radiology oncology outpatient clinic of a medical centre	Taipei, Taiwan	Taiwanese	Not reported
XQ-G	(Memtsa et al., 2017)	100	63.4 Yrs (SD 7.5)	27%	Radiation Therapy Departments of University Hospitals of Larissa, Theagenio hospital of Thessaloniki and AXEPA hospital of Thessaloniki	Greece	Greek	Not reported
XQ-IT	(Pellegrino et al., 2015)	102	62.9 Yrs (24–85 Yrs)	18.6%	Radiotherapy Unit of the Veneto Oncology Institute-IOV	Padua, Italy	Italian	Not reported
XI	(Thomson and Williams, 2000)	112	Onset group 63 Yrs (SD 13 R 29-87Yrs) Normal group 75 (SD 7; R 52-90 Yrs)	Onset group 28.1% Normal group 32.7%	Radiotherapy units at each of Auckland, Waikato, Palmerston North, Wellington, Christchurch, and Dunedin hospitals. Controls from the membership list of the Otago Medical Research Foundation Auxiliary	New Zealand	English	57 (72.2%)
XI	(Thomson, 2007)	94	68.6 Yrs (SD, 12.9; R 29–90 Yrs)	Onset group 28.3% Normal group 38.1%	Radiotherapy units at each of Auckland, Waikato, Palmerston North, Wellington, Christchurch, and Dunedin hospitals. Controls from the membership list of the Otago Medical Research Foundation Auxiliary	New Zealand	English	Not reported
XeQoLS	(Henson et al., 2001)	20	55.8 (SD 12.8; R 24-80Yrs)	42%	the University of Michigan Radiation–Oncology	USA	English	Not reported
XeQoLS-IT	(Lastrucci et al., 2018)	35	R 18-83 Yrs	17.2%	Unit of Radiation Oncology, S. Donato Hospital	Arezzo, Italy	Italian	Not reported

Table 2.4 Summary of measurement property findings[a]

PROM	Structural Validity	Internal Consistency	Measurement Invariance	Reliability	Measurement Error	Validity		Responsiveness
						Criterion	Construct	
Severity Outcome								
XQ	+ (High)	+ (High)	NA	? (Low)	NA	NA	+ (Moderate)	+ (Low)
XI	NA	+ (Moderate)	NA	? (Very low)	NA	NA	+ (Low)	+ (Low)
QoL Outcome								
GRIX	NA	? (Low)	NA	? (Very low)	NA	NA	? (Low)	+ (Very low)
XeQoLS	NA	? (Very low)	NA	NA	NA	NA	+ (Very low)	+ (Very low)

Abbreviations: (+) sufficient overall measurement property rating; (?) indeterminate overall measurement property rating; GRIX, Groningen Radiotherapy-Induced Xerostomia; NA no available data; XeQoLS, Xerostomia Quality of Life Scale; XI, Xerostomia Inventory; XQ, Xerostomia Questionnaire.

[a] Level of evidence, High indicates that we are very confident that the true measurement property lies close to that of the estimate/pooled result of measurement property; moderate, we are moderately confident in the measurement property estimate: the true measurement property is likely to be close to the estimate of the measurement property, but there is a possibility that it is substantially different; low, our confidence in the measurement property estimate is limited: the true measurement property is likely to be substantially different from the estimate of the measurement property; very low. We have little confidence in the measurement property estimate: the true measurement property is likely to be substantially different from the estimate of the measurement property.

2.4 Discussion

Xerostomia is a common permanent adverse effect of radiotherapy to the head and neck. Radiotherapy-induced xerostomia (RIX) in head and neck cancer (HNC) survivors can affect speech and eating, cause persistent discomfort, and increase the risk of infections and dental disease, with consequent negative impact upon the quality of life (QoL) of affected individuals. (Fang et al., 2004, Jensen et al., 2006). Measurement of RIX includes the subjective assessment of the severity of dry mouth symptoms, as well as the QoL of affected individuals, via patient-reported outcome measures (PROMs) (Ringash et al., 2015). In order for clinicians to be reassured that a PROM can adequately measure the symptom of interest, validation studies should be performed and its measurement properties should be assessed (Mokkink et al., 2018). According to the Consensus-based standards for the selection of health measurement Instruments (COSMIN), assessment of the measurement properties of PROMs should include their reliability, validity and responsiveness (Mokkink et al., 2006, Mokkink et al., 2010a, Prinsen et al., 2018). Little is known regarding the measurement properties of PROMs relevant to RIX. In 2012 Ojo et al used the Scientific Advisory Committee of the Medical Outcome Trust (SAC-MOT) guidelines in order to assess the properties of QoL instruments in head and neck cancer, some of which included the RIX dimension (Ojo et al., 2012). Their results showed a lack of rigorous testing for the instruments measuring RIX (Terwee et al., 2011b).

In this present review, the COSMIN guidelines were used to critically appraise, pool and compare the measurement properties of all available PROMs measuring RIX (Prinsen et al., 2018). The aim is to provide clinicians with an evidence-based recommendation regarding the most suitable PROMs measuring RIX outcomes in clinical practice and future research.

A total of 4 PROMs were found to be used to measure RIX on HNC patients. These 4 PROMs measure various aspects of xerostomia, for example, XQ focuses on the intensity of xerostomia while eating and chewing (Eisbruch et al., 2001) while XI records severity symptoms related to

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xerostomia such as itching, dryness, burning and the means used to aid swallowing (Thomson and Williams, 2000). The XeQoLS determines the impact of xerostomia on the QoL of patients with domains including physical functioning, pain and psychosocial functioning (Duke et al., 2004). GRIX is the only tool explicitly developed in RIX population and focuses on temporal aspects of the presence of xerostomia and sticky saliva (Beetz et al., 2010). Also, XQ is the most frequently used questionnaire in studies measuring xerostomia outcome in research (Eisbruch et al., 2001, Eisbruch et al., 2003b, Hawkins et al., 2018, Meirovitz et al., 2006, Trotti and Eisbruch, 2011, Kamal et al., 2018, Lin et al., 2003, Lin et al., 2008, Memtsa et al., 2017, Pellegrino et al., 2015).

To measure content validity, data on it was extracted from development studies or studies focusing on content validity (Terwee et al., 2018). The included studies in this present review, however, did not explore this measurement property. Additionally, with the lack of a standardised consensus on what represents content validity in xerostomia research, content validity was not considered in this review.

The XQ scale type was a matter of debate among the reviewers, the XQ authors have described it as "an 11-point ordinal Likert scale" from 0-10 with a two-point threshold at the start and finish (e.g. Easy to Extremely difficult or No dryness to Extreme dryness) (Eisbruch et al., 2001). A Likert-like scale is described as a scale with meanings or descriptions attached to each point on the scale, and not a numerical scale with a description on the start and endpoint (Allen and Seaman, 2007). Therefore, the reviewers decided to consider the XQ as having a numerical scale and assessed it based on this description. This has reflected poorly on the PROM test-retest reliability rating since the tests done to assess it used inappropriate methods.

The evaluation of criterion validity for the GRIX validation study was considered by the reviewers as an evaluation of construct validity instead. The COSMIN taxonomy describes criterion validity as "the degree to which the scores of a PROM are an adequate reflection of a 'gold standard'" (Mokkink et al., 2010c). With the absence of comparison between the GRIX and its gold standard,

the COSMIN guideline recommends evaluating it instead as hypothesis testing for construct validity.

The COSMIN has recently published new guidelines for systematically reviewing PROMs and reporting on measurement properties and its evidential rigour (Prinsen et al., 2018, Mokkink et al., 2018). The application of the COSMIN guidelines can facilitate the selection of such an instrument to be used in clinical research and can highlight areas of further psychometric development that is required in existing PROMs based on available evidence. Importantly, it should be noted that not reporting on some of the measurement properties, or the low scoring of specific measurement properties of a PROM in this review is not always a reflection of a poorly developed PROM but may be a consequence of insubstantial testing of the PROM. That can be improved by further testing the measurement properties of the identified PROMs. All PROMs in this review were found to have some measurement properties with a relatively low level of quality evidence. Therefore future high-quality research examining the reliability of XQ is warranted. The GRIX, XI and XeQoLS instruments are recommended for further research. That is based on the low scores of both methodological quality and quality rating of available data. However, the low scores could reflect the scarcity of available validations studies.

2.5 Limitations

The COSMIN guidelines draw evidence-based recommendations for the most suitable PROM. It is suggested that the framework of assessment it offers allows for a critical overview of a PROM from all domains of validation. Therefore it is anticipated that validation studies with a challenging methodological construct will have low ratings. This essentially means that even if a PROM is well structured and usable but the validation approach the authors used to validated it was ill-constructed or did not include certain domains of validation, as proposed by the COSMIN guidelines, this will render the PROM of low quality rating. This should be taken into account when interpreting the results of a COSMIN methodology assessment.

Another limitation is the absence of content validity in the present study. The COSMIN guidelines encourage reviewers to seek content validity, even when data on it is lacking. That can be achieved by asking patients and clinicians on the relevancy and comprehensiveness of a PROM, and also asking patients on PROM comprehensibility. That is then assessed separately using the COSMIN standard for evaluating content validity (Terwee et al., 2018). This evaluation could be performed for all PROMs included in this review and could improve its methodological quality. Hence this could be evaluated in the future.

2.6 Conclusion

By applying the COSMIN guidelines for evaluating measurement properties of RIX in HNC patients on 4 PROMs, no rigorous high-quality studies on measurement properties of the included PROMs were found. However, overall evidence on XQ indicates that it has the highest potential as a measure of RIX severity compared to other existing PROMs, using a standardised, consensus-based methodology. The remaining PROMs; the GRIX, XI and XeQoLS, require further testing, particularly on content validity, to improve the quality of the standardised collection of RIX outcomes.

Chapter Three

Qualitative approach to RIX PROMs

3. Focus Group Interviews on the identified RIX PROMs

In this research thesis, the aim is to identify an appropriately validated PROM able to measure RIX. Four validated questionnaires were identified in the previous systematic review (XQ, XI, XeQoLS and GRIX), their validation methodology was assessed using the "COSMIN standard"; to test whether current PROMs for RIX are fit for purpose. The methodologies of all the validated questionnaires were found to be problematic. However XQ was found to have the most appropriate features of a PROM for radiotherapy induced xerostomia. Thus to validate the most suitable RIX PROM on population residing in London, the decision was made to conduct qualitative research; focus group interviews, with RIX patients in order to select the most suitable PROM(s) based on the participants' opinion, and validate it on a population of RIX patients residing in London, UK (Stevens, 2011).

3.2 Focus Group interviews (FGIs)

Focus Group Interviews (FGIs) are meant to capitalise on the communication between patients (as participants) to generate data or information (Kitzinger, 1995). FGIs are a convenient way of collecting data from a number of participants simultaneously (Willms and Johnson, 1993, Barbour, 2005). In Addition, the essence of the group interaction lends the collected data comprehensibility (Creswell and Clark, 2017). FGIs have been used previously to explore opinions on films and entertainment, marketing research and polls on public opinion, but has grown popular in healthcare and health-related issues (Basch, 1987). A qualitative study (semi-structured interviews), conducted on 58 cancer survivors, to "ascribe" meanings to cancer experience by long-term survivors, concluded that most long-term survivors retrospectively reported that cancer either positively influenced their lives or had little long-term impact. In addition, pain, physical deformities and social isolation were reported only in those who express resentment, whom also reported a significantly reduced QoL (Foley et al., 2006). Moreover, similar qualitative, semi-structured interview study to describe experiences with food and eating in 13 patients with HNC following radiotherapy, the study was able to provide new information on the long-term aspects of food and eating, and highlight the lengthy

journey with problems affecting physical, psychological and social aspects of food (Ottosson et al., 2013).

By using FGIs the issues and themes that arise from collective focus group interviews may help in understanding the impact of RIX upon a affected individuals more, and identify which RIX PROM is most suitable to measure RIX symptoms - from the participants' point of view (Britten, 1995, Sandelowski, 1995). In this exercise, the aim was to select the most suited PROM between the four based on the participants' recommendations and suggestions manifested by how many themes/issues participants can identify with each PROM. Scores that the participants place upon the importance scale of each item in each PROM could help direct us towards determining the most favourable PROM among the four PROMs. In turn this would validity and reliability of a selected PROM in RIX HNC patients on a population residing in London, UK.

3.3 Methods

Design

Three focus group interviews were conducted, with one facilitator and one observer. The participants filled in the questionnaires item by item, and were encouraged to speak their thoughts about each item in the questionnaires, also known as the 'think aloud method' (Kucan and Beck, 1997). Plus, the participants had to fill an importance scale for each questionnaire (Appendix I to L) that had a 5-point scoring system for each item of each questionnaire. An example of the scale is indicated in Figure 2.1. The scale is used to measure each PROM's item relevance and importance to the symptoms of RIX (Nevo, 1985). The interviews were conducted at the Eastman Clinical for Investigation Centre, Eastman Dental Institute, UCL.

Figure 3.1 Example of the importance scale

1. Have you had a dry mouth during the day?

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

Participant recruitment

11 participants; who had received radiotherapy to the head and neck as a method of primary or adjuvant treatment for HNC and had developed dry mouth as a direct consequence of therapy, were recruited from the Oral Medicine Unit, UCLH, Eastman Dental Hospital. Inclusion and exclusion criteria are noted below:

Inclusion criteria

- Patients developed RIX exclusively as a direct result of radiotherapy to the head and neck.

- Able to consent, read and write English and score the questionnaires independently.

- 18 years and above.

- Finished their treatment at least past the acute phase of post-therapy side-effects.

Exclusion criteria

- Patients who developed xerostomia through other means; drug-induced, autoimmune disorders (i.e. Sjogren's disease, amyloidosis, lupus, sarcoidosis), chronic disease (i.e. diabetes mellitus), viral disease (i.e. HIV), graft versus host disease or surgical trauma to the salivary glands among others.

- Inability to consent or read and write in English independently.

- Under 18 years old.

- Have not commenced their treatment regimen or still in the acute phase of side-effects post radiotherapy.

Data Collection and analysis

The participants were provided with a participant information sheet (Appendix E) prior to providing a written consent of participation in the study (Appendix G). Background information were collected from the participants for sample description (Table 3.1). Ethical approval was granted for this qualitative study (Phase I) by the Health Research Authority, NHS, REC reference (17/SC/0485) and IRAS project ID (21586), and is sponsored by the Joint Research Office, UCL.

Three FGIs were held until 'data saturation' is reached (Creswell, 2000), this is accomplished when no new themes or topics arise in the consecutive interviews. All three FGIs were held with a total of 11 participants attending (5 for the first, 3 for the second and the third FGI). The FGIs were facilitated using an interview guide (Barbour, 2005) to initiate discussion on the topic, explaining the aim of the interviews and asking participants to fill in the questionnaires and voice their opinion about each questionnaire in a semi structured approach. At the end of each FGI, participants were asked to choose the questionnaire they felt best describes their symptom needs. The interviews were audio recorded and transcribed verbatim by outsourced professional transcribers. The four identified questionnaire were rotated in order of first to be discussed to compensate for participant fatigue and to extract all relevant information on all questionnaires equally (Appendix A to D).

Transcripts were analysed using the thematic approach (Creswell, 2000, Miles et al., 1994). Each extracted theme was then used in the subsequent FGI, any new themes arising were added to the overall themes explored and used for the subsequent FGI, and themes that were not confirmed by 2 subsequent FGIs were dismissed. Themes and topics discussed are elaborated on further in the results, with a thematic analysis for each FGI explained separately.

3.4 Results

Eligibility of participants and their enrolment is shown in Figure 3. 11 recruited participating patients with HNC have agreed to participate from a total of 25 eligible participants (%44).

Figure 3.2 Eligibility and enrolment of participants.
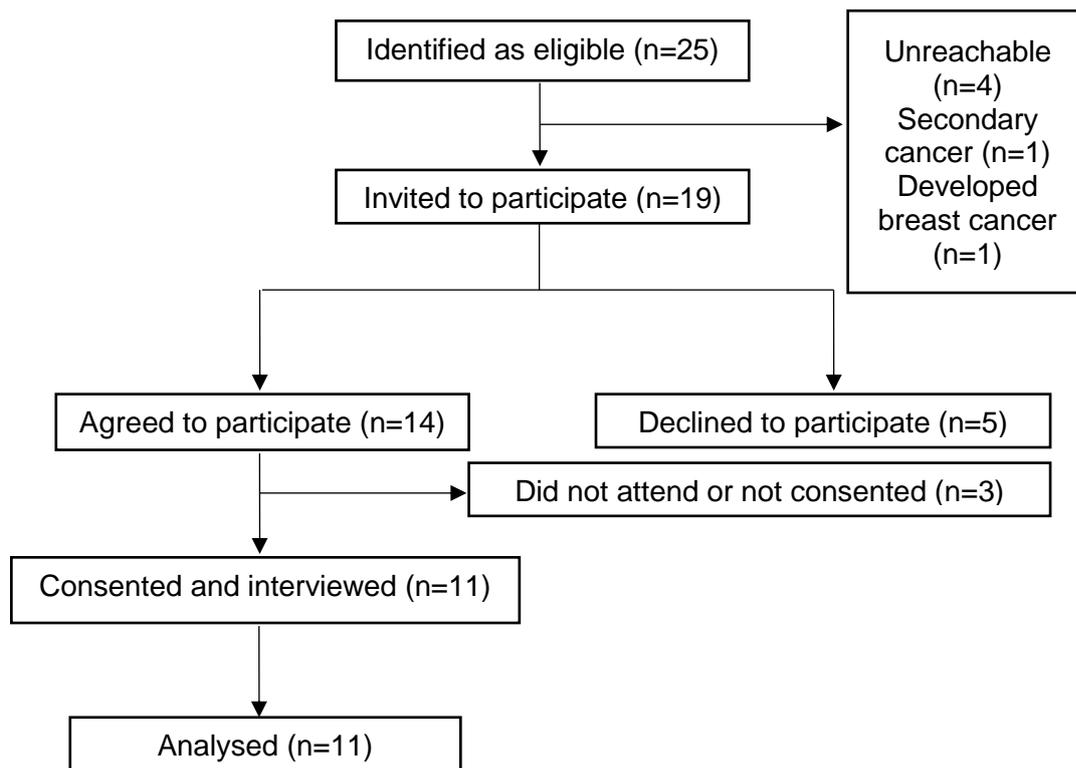
Demographics of participating patients

All participants had completed their treatment of their HNC. The demographic details of the patients are detailed in Table 3.1.

Thematic matrix

The theme matrix for each PROM is listed in Table 3.2. Each theme was discussed and examples of participants' quotes elaborating on each PROM themes are detailed in Table 3.3. The results for each theme for each PROM and the results for the importance scale are detailed below.

Table 3.1 Participant demographics and HNC treatment

FGI number	ID	Age	Sex	Cancer Diagnosis	Stage	HNC Treatment	Year treatment received
1	FG01	70	M	SCC Base of tongue	T2	Post-op RT&CT	2010
1	FG02	60	M	SCC nasopharynx	T3N1	Chemo-radiation	2005
1	FG03	67	M	Tonsillar SCC	T1N1	Chemo-radiation	2008
1	FG04	65	M	Tonsillar SCC	T2N2c	Chemo-radiation	2010
2	FG05	72	F	Tonsillar SCC	T4N2a	Chemo-radiation	2012
2	FG06	70	M	Supraglottis SCC	T3/T4N2b	Chemo-radiation	2010
2	FG07	57	M	Tonsillar SCC	T3	Chemo-radiation	2016
3	FG08	64	M	Tonsillar SCC	T1N2b	Chemo-radiation	2017
3	FG09	67	M	Oropharynx SCC	TxN1	Chemo-radiation	2009
3	FG10	75	M	SCC of the soft palate	T2/T4N2	Chemo-radiation	2013
3	FG11	69	M	SCC left mandible	T1N1	Post-op RT&CT	2014

Table 3.2 The themes matrix for each PROM

PROM	Xerostomia Questionnaire (XQ)	Xerostomia Inventory (XI)	Groningen Radiotherapy-induced Xerostomia Questionnaire (GRIX)	the Xerostomia Quality of Life Scale (XeQoLS)
Themes	• Wording. • Chewing versus Lubrication • Water versus Liquids. • Night time dry mouth • The efficiency of the scale used in XQ	• Dryness of the skin, eyes and nose versus throat • Wording and XI scale efficiency	• Night-time relevance • Sticky saliva relevance • Lack of social activities in GRIX	• Inclusion of both mouth and throat dryness Unembellished phrasing of item 15

Table 3.3 Main themes and examples of participants' quotes for each PROM theme.

PROM	Theme	Quotes
Xerostomia Questionnaire (XQ)	Wording of the XQ questionnaire	FG01: *"…I'm supposed to wear dentures. Due to drugs, my teeth have broken so every time I put dentures in, I've had to have them refitted"*. *"…the discomfort wasn't because of the dry mouth so eating or talking or whatever so wearing dentures is a problem. Putting them in and keeping them in because my teeth are so brittle..."*
	Chewing vs. Lubrication	FG05: *"…Nine times out of 10 it's not that I can sit down and have a sandwich. But, trying to eat anything at all, it seems that you can eat a biscuit with a cup of tea or coffee but if you try and eat that same biscuit, it's like 20 minutes later you're eating the same biscuit, there's nothing there to swallow. So, my opinion, mainly with me it's the mouth…"*
	The efficiency of the scale used in XQ.	FG06: "No (dislike). Because it's an interpretation I mean my scale of 1 to 10 is probably different to yours… it's just that the great difficulty you experience is speaking due to dryness of your mouth and tongue and I, if I put myself in a situation I want a bottle of water with me so when that's coming in I will sip my water, so I can't rate, if I didn't have that bottle of water it would be extremely difficult, I wouldn't be able to talk so what do I answer. You see what I mean because I would not perhaps put myself in the position".

	Water vs. Liquid.	FG07: "Not really, no, I mean it says the frequency and, you know, I do think there's a bit of a problem but it's quite, it's kind of a one thing to catch all and that's extremely important to understand that and I may occasionally get a very good night's sleep. But it didn't take in about, you know, whereas the others mention, you know, particular things".
	Night-time dryness	FG03: *"…Night-time, as you indicate here about night-time, very pertinent because during the day I don't have much symptoms at all of dry mouth. But, at night I do, so I have to keep water there to hydrate during the night, three or four times a night…"* FG06: "Not really, no, I mean it says the frequency (of the scale) and, you know, I do think there's a bit of a problem but it's quite, it's kind of a one thing to catch all and that's extremely important to understand that and I may occasionally get a very good night's sleep. But it didn't take in about, you know, whereas the others mention, you know, particular things".
Xerostomia Inventory (XI)	Dryness of the skin, eyes and nose vs. throat	FG03: *"My eyes get dry, I wear contact lenses. It's hard to know the cause whereas my throat, in this weather I have to wear a high collar or a scarf"* FG04:"*…I would say that the question of nose and eyes, surely that's not the area that's causing pain so it's irrelevant…"*. FG07: *"…I do*

		suffer from dry skin anyway, but I think it has been worse, it's something I notice more than my wife notices…. So, I think dry skin is important but not, I don't have any eye issues, my lips sometimes are dry that can be…. but my nose not particularly…", FG06: "Yes, (important) because everybody's different you see, this gentleman has, but I didn't have an issue with dry(ness)…".
	Wording of XI item on eating food (item5)	FG05: *"Having to think is, eating dry food, I mean because the only thing I can, example I can give, bread, you have a slice of bread, you will lose your saliva and if you have a slice of toast you won't so toast is dry so I'm getting a bit, I get a bit confused, you see what I mean".* FG06: *"Someone says, oh, you know, the thing is you won't be able to eat fish and chips and I guarantee you that I finish my treatment at the end of April….and I had fish and chips".*
	Wording and XI scale efficiency	FG02: *"I think it's relevant, for me, to have them running like this because the XI questionnaire when it says quite simply 'I get up at night to drink,' and then you have to rate how important that is to you which I think is important because if you do it now, I do it absolutely routinely, it doesn't really disturb me, I get the water, have a sip and so it's fine. So, it's not of great importance to me although it happens every night, I don't find it that important, I just get on with it so it's fine."*

Groningen Radiotherapy-induced Xerostomia Questionnaire (GRIX)	Night-time dryness relevance	FG07: *"I only mostly get the problem at night and when you wake up in the morning".*
	Lack of social activities in GRIX	FG06: *"Well, I think eating and drinking it doesn't cover enough really, I think, you know, some of the other things have been, covering eating, eating and drinking…. mainly in sections when you looked at the dry mouth, you know, eating, sticky saliva, you know, sleep, you know, if you kind of put that up in to sections you will have the best questions around all those areas and this covers sticky saliva and a bit of sleeping quite well".*
	The GRIX construct efficiency	The participants agreeing that the "*questioning*" of the items is "*relevant*" and *"simplistic"* in the first FGI. However, FG05 said: *"To be honest, I'm not sure that the top bit kind of worries me too much, you know, very much or often, probably, you know, they're very similar. I mean I think maybe often might be better rather than very much, but, you know, that doesn't kind of worry me …".*
the Xerostomia Quality of Life Scale (XeQoLS)	Unembellished phrasing of item 15	FG03: "*hard to answer*". FG02: *"…It's such a statement talking about having this condition forever and how do you feel about that, I don't know what the gentlemen feel about when you're going through your treatment and dryness the way it is now, and you talk about seven days as well, it's hard to answer.".* FG05: "*I put (scored it) mostly dissatisfied…see if you were to spend the rest*

		of your life doing that, I haven't got a choice in that. That, I've had to accept that I have to spend the rest of my life like this, so if you were to spend I can't, do you see what I'm trying to say, if you were to spend there is no choice, I have to accept I have to spend and manage my life this way".
	Mouth Dryness vs. lack of saliva	FG07: *".... because, well that is the problem with most of our problem, well I see it, it's due to the lack of saliva is why we're having the problems, because the saliva and the radiotherapy obviously.... can feel a layer has been destroyed by the radiotherapy which according to the dental people here is going to take years to heal. If it ever. So, it's just about managing".*

Xerostomia Questionnaire (XQ)

Wording of XQ

The participants noticed that wording of the XQ questionnaire was "unclear". The rating system of XQ is based on asking the participants to rate 'severity' rather than rating 'relevance' of associated symptoms, especially whilst describing denture related xerostomia. This is a practical issue for them due to the lack of differentiation between partial denture wearers and complete denture wearers. Also, the questionnaire asks only about the 'discomfort' while inquiring about denture use, and dentures in the opinion of the participants caused more problems than discomfort alone. One participant noted that *"…I'm supposed to wear dentures. Due to drugs, my teeth have broken so every time I put dentures in, I've had to have them refitted"*. When asked to elaborate further by the facilitator, the participant added *"…the discomfort wasn't because of the dry mouth so eating or talking or whatever so wearing dentures is a problem. Putting them in and keeping them in because my teeth are so brittle..."* This explicitly indicates that the problem with dentures in patients with dry mouth is far beyond discomfort alone.

The focus on chewing versus the focus on lubrication

Participants discussed the relevance of Chewing vs. Lubrication: which one should be focused more on? Participants reported that although swallowing was a valid issue in dry mouth, the XQ have focused its queries on swallowing rather than attending to other relevant oral functions, such as chewing and speaking. One the matter, one participant said "*…Nine times out of 10 it's not that I can sit down and have a sandwich. But, trying to eat anything at all, it seems that you can eat a biscuit with a cup of tea or coffee but if you try and eat that same biscuit, it's like 20 minutes later you're eating the same biscuit, there's nothing there to swallow. So, my opinion, mainly with me it's the mouth…"*. This might be due to both chewing and lubrication carry a co-dependency and are synonymous. Therefore the focus should be divided between them.

Using the word Water versus using the word Liquids

Participants noted the difference in 'Water versus Liquids' and which wording is conclusive. Using the word 'liquids' is more conclusive as one participant states *"… saliva, it's not 100% water, there's other enzymes which give you lubrication and plain water simply washes away that lubrication and if I'm eating, I will sip milk. But, if I'm sipping water then things get suck in my throat. If something is stuck in my throat, drinking water doesn't help at all…"*.

Night-time dryness

It terms of night-time dryness, XQ was found to consider night-time dryness in more of a generic approach, with a low level of specificity compared to the other questionnaires, one participant, when asked about this, said *"Not really, no, I mean it says the frequency and, you know, I do think there's a bit of a problem but it's quite, it's kind of a one thing to catch all and that's extremely important to understand that and I may occasionally get a very good night's sleep. But it didn't take in about, you know, whereas the others mention, you know, particular things"*. Night time dry mouth was described by some of the participants to be a major issue, they believed that dry mouth symptoms are more prevalent during night time and more attention should be given to sleep time dry mouth symptoms, one participants stated that *"…Night-time, as you indicate here about night-time, very pertinent because during the day I don't have much symptoms at all of dry mouth. But, at night I do, so I have to keep water there to hydrate during the night, three or four times a night…"* so more explaning should have be given to this problem in the questionnaire.

The efficiency of the scale used in XQ

One participant expressed frustration with the 1-10 scale of the XQ, stating *"No (dislike). Because it's an interpretation I mean my scale of 1 to 10 is probably different to yours… it's just that the great difficulty you experience is speaking due to dryness of your mouth and tongue and I, if I put myself in a situation I want a bottle of water with me so when that's coming in I will sip my water, so I can't rate, if I didn't have that bottle of water it would be extremely*

difficult, I wouldn't be able to talk so what do I answer. You see what I mean because I would not perhaps put myself in the position".

Xerostomia Inventory (XI)

Dryness of the skin, eyes and nose versus dryness of the throat

XI asks about the dryness in of the skin, eyes and nose, some participants considered that throat dryness should be given equal attention, one said *"…I do suffer from dry skin anyway, but I think it has been worse, it's something I notice more than my wife notices…. So, I think dry skin is important but not, I don't have any eye issues, my lips sometimes are dry that can be…. but my nose not particularly…"*. Another participant thought that it might be of relevance, saying *"Yes, because everybody's different you see, this gentleman has, but I didn't have an issue with dry(ness)..."*. Also, some participants noted that XI asks about the dryness of the eyes and nose, which they believed are not highly related. The troubled areas in their opinion are the dryness mouth and throat. One participant said "*My eyes get dry, I wear contact lenses. It's hard to know the cause whereas my throat, in this weather I have to wear a high collar or a scarf.*" Another participant said "*…I would say that the question of nose and eyes, surely that's not the area that's causing pain so it's irrelevant…*" A third participant responded to the facilitator question about its relevance by stating that "*they didn't seem relevant to me at all.*"

Wording and XI scale efficiency

In the first FGI the "wording" of the questionnaire was considered to be better in XI than XQ. The format of the XI is essentially statements such as 'I sip liquids to help sallow food' followed by five-point responses. One participant responded to this by saying "*I think it's relevant, for me, to have them running like this because the XI questionnaire when it says quite simply 'I get up at night to drink,' and then you have to rate how important that is to you which I think is important because if you do it now, I do it absolutely routinely, it doesn't really disturb me, I get the water, have a sip and so it's fine. So, it's not of great importance to me although it happens every night, I don't find it that important, I just get on with it so it's fine.*" However, the wording of XI questionnaire in the second FGI was found to be challenging, where the

questionnaire asks participants to answer to 'I have difficulty eating dry foods' it doesn't necessarily specify the type of dry foods. One participant said when asked by the facilitator *"Having to think is, eating dry food, I mean because the only thing I can, example I can give, bread, you have a slice of bread, you will lose your saliva and if you have a slice of toast you won't so toast is dry so I'm getting a bit, I get a bit confused, you see what I mean"*. Furthermore, the participant explained, *"I'm finding that I'm answering this, just for me personally, that the first question is I sip liquids to help swallow food, well I do, but difficulty eating dry foods I'm not, I can eat fish and chips because it's not taken saliva from my, but I would drink water as I find it a bit, I'm finding it a bit confusing, so I don't (understand)"*. Another participant said as to the lack of explaining of the types of dry foods *"Someone says, oh, you know, the thing is you won't be able to eat fish and chips and I guarantee you that I finish my treatment at the end of April….and I had fish and chips"*. If the questionnaire was elaborated further on specific types of dry foods known to cause dry mouth or foods that are stable dishes enjoyed by the population, this could help distinguish the change in quality of life of patients.

Groningen Radiotherapy-induced Xerostomia Questionnaire (GRIX)

<u>Night-time dryness relevance</u>

Night-time dryness, was thought by participants in the first FGI to be relevant, one participant summed it up as *"I only mostly get the problem at night and when you wake up in the morning"*. Albeit this was not prevalent with future FGI participants. When participants in later FGIs were asked about night-time dryness, none thought that it meant a great deal to them.

<u>Sticky saliva relevance</u>

The GRIX focuses on sticky saliva as a hindrance in RIX, this was explored by the facilitator who asked directly about what the participants felt regarding the questions about sticky saliva as a major variable. One participant felt "*confused*" by the attention to sticky saliva and did not understand its relevance to dryness of the mouth.

<u>Attention to social activities</u>

The participants highlighted the lack of attention to social activities, such as eating and drinking. One said *"Well, I think eating and drinking it doesn't cover enough really, I think, you know, some of the other things have been, covering eating, eating and drinking…. mainly in sections when you looked at the dry mouth, you know, eating, sticky saliva, you know, sleep, you know, if you kind of put that up in to sections you will have the best questions around all those areas and this covers sticky saliva and a bit of sleeping quite well".*

The Xerostomia Quality of Life Scale (XeQoLS)

<u>Inclusion of both mouth and throat dryness</u>

Both mouth and throat are included in the items of XeQoLS questionnaire, which was praised by participants in the first FGI. However, in the second FGI, one participant felt that it should include "lack of Saliva" as well. The participant said that *"…. because, well that is the problem with most of our problem, well I see it, it's due to the lack of saliva is why we're having the problems, because the saliva and the radiotherapy obviously…. can feel a layer has been destroyed by the radiotherapy which according to the dental people here is going to take years to heal. If it ever. So, it's just about managing".*

<u>Unembellished phrasing of item 15</u>

Item 15, which addresses the lifelong impact of dry mouth on the quality of life of patients was found by participants to be worded with a high degree of simplicity, given the complex nature of the symptom and aetiology behind it. Participants in all three FGIs agreed that the item is "*a little bit too simplistic*", which makes it "*hard to answer*". One participant stated that "…*It's such a statement talking about having this condition forever and how do you feel about that, I don't know what the gentlemen feel about when you're going through your treatment and dryness the way it is now, and you talk about seven days as well, it's hard to answer.*". Another participant said *"I put (scored it) mostly dissatisfied…see if you were to spend the rest of your life doing that, I haven't got a choice in that. That, I've had to accept that I have to spend the rest of my life like this, so if you were to spend I can't, do you see what I'm trying to say, if you*

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were to spend there is no choice, I have to accept I have to spend and manage my life this way". Another participant disagrees and says, *"I've put, for the same reason I put mostly satisfied because I'm managing it, well ok, it could be worse, you know, I haven't got a PEG, so I have just say that's it good, there's lots of things I haven't got issues with, so I have to say mostly satisfied".* This could refer to the phrasing of the questionnaire causing participants to have a different understanding of how they experience living with a lifelong symptom. Some might find it a burden and others might learn to live with it. Still, naturally, this question carries varied meanings and could not necessarily mean one thing or the other.

Importance Scale Score

Each participant was asked to complete an importance score of each item for each of the four PROMs. The mean and median scores for each participant for each item were then calculated and if the median score was found to be less than the mean score in an item, the item is deemed important, and if the median score was found to be greater than the mean score, the item is deemed unimportant (Nevo, 1985). Below are tables 3.4 to 3.7 for each PROM. Missing items accounted for total items scored 27%. The XQ had 44% overall important items, GRIX had 42.8%, XeQoLS had 46% and XI had 27%.

Table 3.4 The XQ importance rating score of participants of the 3 focus group interviews

	FG01	FG02	FG03	FG04	FG05	FG06	FG07	FG08	FG09	FG10	FG11	Mean score	Median score	Importance rating
1	2	2	0	0	0	0	0	0	2	3	0	0.8	0	important
2	3	1	1	2	4	3	2	2	2	2	0	2	2	unimportant
3	4	4	4	2	4	3	2	2	3	3	1	2.9	3	unimportant
4	4	4	3	2	4	4	3	2	3	3	1	3	3	unimportant
5	4	4	3	N/A	2	4	2	2	3	2	1	2.7	2.5	important
6	3	3	3	N/A	2	3	2	2	2	3	1	2.4	2.5	unimportant
7	4	4	2	N/A	3	4	2	4	3	4	1	3.1	3.5	unimportant
8	3	3	2	N/A	4	3	2	2	1	2	2	2.4	2	important
9	3	N/A	N/A	4	2	4	0	2	2	2	3	2.4	2	important

Table 3.5 The XI importance rating score of participants of the 3 focus group interviews

	FG01	FG02	FG03	FG04	FG05	FG06	FG07	FG08	FG09	FG10	FG11	Mean score	Median score	Importance rating
1	4	4	4	4	4	4	3	4	2	2	N/A	3.5	4	unimportant
2	4	4	4	4	3	4	3	4	1	2	N/A	3.3	4	unimportant
3	4	3	3	3	1	4	2	2	2	1	N/A	2.5	2.5	unimportant
4	4	3	4	2	2	3	2	3	1	3	N/A	2.7	3	unimportant
5	4	4	4	4	2	3	2	4	1	3	N/A	3.1	3.5	unimportant
6	2	0	4	0	0	2	1	3	0	0	N/A	1.2	0.5	important
7	4	4	4	3	3	4	2	4	1	4	N/A	3.3	4	unimportant
8	N/A	0	2	2	1	1	1	3	0	0	N/A	1.1	1	important
9	N/A	0	2	0	1	2	1	2	0	0	N/A	0.8	1	unimportant
10	2	1	2	2	1	1	1	2	0	0	N/A	1.2	1	important
11	N/A	0	3	0	1	1	1	2	0	0	N/A	0.8	1	unimportant

Table 3.6 The GRIX importance rating score of participants of the 3 focus group interviews

	FG01	FG02	FG03	FG04	FG05	FG06	FG07	FG08	FG09	FG10	FG11	Mean score	Median score	Importance rating
1	2	3	3	3	2	1	1	1	4	1	4	2.1	2	important
2	2	3	3	3	2	1	2	1	4	1	4	2.2	2	important
3	4	3	4	3	4	1	2	3	4	0	4	2.8	3	unimportant
4	1	3	3	3	4	0	2	2	4	0	4	2.2	2.5	unimportant
5	1	3	2	3	3	3	1	2	3	1	4	2.2	2.5	unimportant
6	1	1	2	3	3	2	3	1	3	0	4	1.9	2	unimportant
1	4	4	2	3	4	0	3	1	3	1	4	2.5	3	unimportant
8	2	4	1	3	4	2	3	2	2	0	4	2.3	2	important
9	1	N/A	2	2	3	0	3	1	3	N/A	4	1.875	2	unimportant
10	1	N/A	2	2	4	1	1	2	3	0	4	1.78	2	unimportant
11	1	N/A	0	2	4	2	1	2	3	0	4	1.67	2	unimportant
12	1	1	1	2	4	3	1	2	3	0	4	1.8	1.5	important
13	1	N/A	2	2	3	0	1	1	3	0	4	1.4	1	important
14	1	N/A	N/A	3	3	0	1	0	2	0	4	1.25	1	important

Table 3.7 The XeQoLS importance rating score of participants of the 3 focus group interviews

	FG01	FG02	FG03	FG04	FG05	FG06	FG07	FG08	FG09	FG10	FG11	Mean score	Median score	Importance rating
1	4	3	4	3	2	1	3	2	4	0	4	2.7	3	unimportant
2	1	2	1	3	3	1	3	2	3	1	4	2.18	2	important
3	1	2	1	3	1	2	1	2	2	1	3	1.7	2	unimportant
4	1	4	2	1	3	1	1	2	3	0	4	2	2	unimportant
5	4	4	3	3	3	2	1	2	4	0	3	2.6	3	unimportant
6	2	1	0	2	3	2	1	2	3	0	2	1.6	2	unimportant
7	0	0	0	2	3	1	0	3	2	0	2	1.18	1	important
8	0	4	1	2	4	1	1	2	4	1	2	2	2	unimportant
9	1	3	1	2	2	0	0	3	3	0	3	1.6	2	unimportant
10	0	1	1	2	3	0	1	3	3	0	3	1.5	1	important
11	0	1	0	1	4	0	1	3	4	0	2	1.4	1	important
12	0	4	2	3	3	2	2	2	4	0	3	2.27	2	important
13	0	4	1	2	4	0	0	2	3	0	3	1.7	2	unimportant
14	0	1	0	2	3	0	0	2	3	0	3	1.2	1	important
15	2	4	3	2	2	1	1	1	3	1	3	2.09	2	important

3.5 Discussion

Qualitative research approach is employed when no certainty can be reached with quantitative means, when exploring or testing the rigour of subjective measures used in clinical research or practice (Willms and Johnson, 1993). Also Qualitative research proves useful when there is little or not enough available information on a certain topic or matter of interest (Britten, 1995). Qualitative methods were employed in the present study to help select the most suitable PROM to be used to measure RIX in patients with HNC, through FGIs and thematic analysis. Below are the interpretation of the FGIs results:

Interpreting the results

Xerostomia Questionnaires

The XQ was criticised in the FGIs for having its items not being clear in terms of wording and what each item exactly refers to, as well as being focused on the chewing limitations of RIX rather than lubrication or both, which are both needed to eat food easily. Moreover, XQ asks about the use of water to ease xerostomia symptoms whereas participants sensed that asking about liquids would be more effective since water is not the only liquid used to ease xerostomia symptoms. Also, water is structurally different in physio-chemical composition than other more useful liquids (salivary substitutes, dentifrices, aloe Vera gel) and could not, in their opinion, be the only asked about source of indigestion aid. Additionally, the continuous scale used to score each aim in the XQ was thought to be not as efficient as the other PROMs. These points of discussion could indicate that the XQ is in theory not the most appropriate compared with the other PROMs discussed in the FGIs.

The XI items include items concerning dryness of the eyes, skin, lips and nose. These items were complimented by participants, although some participants pointed towards the need to add items on throat dryness, which could be equally important. The XI was also found by participants to have better wording than the XQ, apart from item six "I have difficulty eating dry foods"; there are a variety dry foods, some of which RIX patients can tolerate and consume and some they cannot. However, swallowing dry foods is probably a major digestion limitation

in RIX patients, relying usually on oral lubrication and salivation in order to be swallowed without traumatising the surrounding oral and pharyngeal soft tissue, which could cause further complications if there is a lack of lubrication (Patterson et al., 2015). Moreover, item six was found, based on the importance scale score to be an important and relevant item. The XI was perceived by participants to be well constructed and catered to measure the outcome of xerostomia from a patient point of view.

The GRIX is unique to other PROMs explored by the participants in that it measures morning and night-time xerostomia as well as focusing upon sticky saliva. There were conflicting views by the participants as to the night-time relevance of xerostomia measurement. Some felt that items on this were relevant except for one participant stating "***I only mostly get the problem at night and when you wake up in the morning",*** whereas others felt that xerostomia affects the QoL throughout the day and not at well-defined times of the day. As for sticky saliva, there was a lack of any confirmation by participants of the importance of sticky saliva. One participant was "***confused***" as to why sticky saliva was focused on. Another major shortcoming of the GRIX was the lack of attention to the effect of xerostomia upon social activities, contrary to the other QoL PROM employed in this study. The participants thus considered the GRIX to be less able to capture all the xerostomia effects outlined by participants is FGIs collectively.

The XeQoLS was complimented by participants on its focus upon both mouth and throat dryness. But item 15 "***if you were to spend the rest of your life with your mouth/throat dryness just the way it is now, how would you feel about this?"*** (with answers being Delighted, Mostly satisfied, Mixed: equally satisfied/dissatisfied, Mostly dissatisfied, Terrible) was problematic to participants as to its even-handed wording but probably the answer scale was suggested to be more taxing and difficult to answer. However, the XeQoLS was believed to be, based on participants' opinion, able to measure different aspects of xerostomia in RIX patients, especially social and functional aspects.

Importance Scale Score

The results of the scores of each item in each questionnaire highlight participants' considerations of the importance of the items. The comparison of results between each questionnaire was to allow extracting the most suitable exciting PROM (Nevo, 1985). XQ was found to have only four items to be important, based on the scoring of the participants, out of nine items (44% item importance). The XI had only three important items out of 11 (27% item importance). The GRIX had 6 important items out of 14 (42.8% item importance). The XeQoLS had 7 important items out of 15 (46% item importance).

Based on this, the PROMs with the highest number of important items was the XeQoLS followed by the XQ, the GRIX and the XI respectively. However, missing items account for 27% of the scores. This might indicate that participants either did not understand what they were supposed to record or if they scored it in the same format as scoring the questionnaires, which they were asked to score simultaneously. Therefore the scores should be interpreted with some caution.

Selecting the most suitable PROM

These FGIs were conducted to ask RIX patients in London on the most suitable RIX PROM available that could best relate to their symptom of dry mouth, in order to choose a PROM(s) that could be then validated and tested in England of RIX in HNC patients. All questionnaires were suggested by participants in the FGIs to have advantages and disadvantages in their structure, item construct or scale. This is expected since these questionnaires were not developed with a population residing specifically in London, UK (Basch, 1987). However, some questionnaires were critiqued less and when asked by participants to vote for the most suitable questionnaire, two questionnaires ranked highest, the XI and the XeQoLS. This was based on their relativity to the symptom of RIX, in terms of questions asked, and the ease of the scoring system and scale (Barbour, 2005). This should not necessarily indicate that the other questionnaires (XQ and GRIX) are not suitable for RIX patients residing in London but are not the most suitable PROMs available (Kitzinger, 1995). Also, even though the XQ was

found to have a better outcome when assessed for its methodological quality validation, it has not been selected by the participants in the FGIs. Moreover, and since FGIs are considered to be empirically and evidentially more relevant we have decided to include the XI and XeQoLs regardless of what the systematic review might have indicated (Ottosson et al., 2013, Barbour, 2005, Creswell, 2000, Britten, 1995, Sandelowski, 1995, Kitzinger, 1995, Miles et al., 1994, Willms and Johnson, 1993, Basch, 1987).

3.6 Conclusion

Based on the qualitative research conducted, remarks by participants and their suggestions as to which of the PROMs included were best suited to measure the outcome of xerostomia in RIX patients from a patients point of view and based on results from the importance scale score, the XI and the XeQoLS were selected for further testing of its validity and reliability on RIX patients residing in London, UK.

Chapter Four

Validity of XI and XeQoLS on RIX patients with HNC in England

4. Testing the validity and reliability of the Xerostomia inventory (XI) and Xerostomia Quality of Life Scale (XeQoLS) questionnaires for radiotherapy-induced xerostomia (RIX) residing in London, UK

4.1 Introduction

Radiotherapy-induced xerostomia (RIX) is the subjective feeling of dry mouth by head and neck cancer (HNC) patients following radiotherapy treatment to the head and neck area (Jensen et al., 2010). RIX can significantly decrease oral functions and the Quality of Life (QoL) of patients, RIX is thought to be one of the major causes of poor oral function and Health-related Quality of Life (Dirix et al., 2006, Jellema et al., 2007).

The XI and XeQoLS have been used to measure the outcome of RIX in HNC patients following radiotherapy (Thomson and Williams, 2000, Rogers et al., 2010, Lastrucci et al., 2018, Thomson, 2007). The XI assesses the severity xerostomia and has been validated in HNC patients following radiotherapy (Thomson and Williams, 2000). The XeQoLS measures the QoL of xerostomia patients, it has been equally validated on RIX patients (Rogers et al., 2010). However, they have not been validated on a cohort of HNC patients with RIX in the England. Validating these tools would enable researchers to use them in clinical investigations or practice with confidence.

A methodological assessment of all validated RIX PROMs present in the literature in a systematic review identified four PROMs XQ, GRIX, XI and XeQoLS). The assessment was performed by applying the COSMIN guidelines (Mokkink et al., 2018, Prinsen et al., 2018). The results from this assessment reported a low rigor of validity for all four PROMs. Afterwards, focus group interviews were conducted to shortlist the most suitable and appropriate PROMs (XI and XeQoLS). The aim of the present study is to validate these PROMs on RIX patients residing in England.

4.2 Methods

Participants

The study group comprised of 75 patients who had developed RIX as a consequence of receiving radiotherapy as part of their treatment of HNC were asked to join the study at the Oral Medicine Unit, Eastman Dental Hospital, UCLH, London, England. Participants were approached by their treating physician and provided with a participant information sheet (Appendix F) describing the study aim and explaining how they are expected to participate. Then, participants were consented (Appendix H) after agreement and filled in the XI and XeQoLS twice, two weeks in between. Ethical approval was granted for this qualitative study (Phase II) by the Health Research Authority, NHS, REC reference (17/SC/0485) IRAS project ID (21586), and is sponsored by the Joint Research Office, UCL. As in the previous chapter, below are the inclusion and exclusion criteria:

Inclusion criteria

- Patients developed RIX exclusively as a direct result of radiotherapy to the head and neck.

- Able to consent, read and write English and score the questionnaires independently.

- 18 years and above.

- Finished their treatment at least past the acute phase of post-therapy side-effects.

Exclusion criteria

- Patients who developed xerostomia through other means; drug-induced, autoimmune disorders (i.e. amyloidosis, lupus, sarcoidosis, Sjögren's disease), chronic disease (i.e. diabetes), viral disease (i.e. HIV), graft versus host disease, surgical trauma to the salivary glands among others.

- Inability to consent or read and write in English independently.

- Under 18 years old.

- Have not commenced their treatment regimen or still in the acute phase of side-effects post radiotherapy.

Outcome measures

Xerostomia Inventory

The Xerostomia Inventory assesse the severity of xerostomia, it comprises of 11 items with a 5-point scale for each item (1 for never, 2 hardly ever, 3 occasionally, 4 fairly often and 5 very often). As indicated previously in chapter three, the XI is well structured, attentive to many aspects of xerostomia and easy to fill or score by patients, in their opinion.

Xerostomia Quality of Life Scale

The XeQoLS measures the QoL of patients with xerostomia. It consists of 15 items and 4 dimensions (physical functioning, pain/discomfort, personal/psychological functioning and social functioning) with 5 scales (not at all, a little, somewhat, quite a bit, very much). As concluded in chapter three, patients consider that XeQoLS emphasises the social aspects of xerostomia, its items focus on both the dryness of the mouth and throat and has an easy to administer scale.

Statistics

To validate the XI and XeQoLS, the aim is to evaluate their the validity and reliability, as proposed by the COSMIN guidelines (Mokkink et al., 2010c). Validity of a PROM is described as "The degree to which a PROM measures the construct(s) it purports to measure" (Mokkink et al., 2010c). To achieve this construct validity is to be evaluated; which includes testing its structural validity and hypothesis testing. Reliability of a PROM is defined by the COSMIN guidelines as "The degree to which the measurement is free from measurement error" (Mokkink et al., 2010c). The aim in this present study is to evaluate internal consistency (Cronbach's Alpha) and test-retest (Weighted Kappa) (Terwee et al., 2011a). Table 4.1 details the relevant tests to be used to evaluate each measurement property.

Internal consistency, test-retest and hypothesis testing was performed using IBM SPSS version 26 2019 64-bit edition. Factor analysis was performed using IBM SPSS AMOS version 26.

Table 4.1 Domains, measurement properties and tests to be used.

Domain	Measurement property	Aspect of measurement property	remarks	Test(s) to be used
Validity	Construct Validity	Structural validity	This test intertwines with the internal consistency. The aim is to calculate it using the classic test theory (CTT) for confirmatory factor analysis (CFA), using the comparative fit index (CFI) and tucker-Lewis Index (TLI) for goodness of fit since the sample size is 75. This might prove to be a limitation. Participants. Root-mean-square Error of Approximation (RMSEA) could be used if necessary (Thompson, 2004).	CFI & TLI (> 0.95) RMSEA (< 0.06) (Thompson, 2004).
		Hypothesis testing	The hypothesis is that both PROMs are expected to correlate since XeQoLS; measuring QoL. The XI; measuring severity, have a positive relationship. The more symptom severity the more the effect on patients' QoL (Scott, 2005, Akoglu, 2018).	Comparison with other measurement instrument (convergent validity) using non-parametric methods due to un-normality (Spearman < 0.5) (Scott, 2005, Akoglu, 2018, Zar, 1972).
Reliability	Internal consistency		The I.C score measures the degree of the interrelatedness among the items (Taber, 2018, Mokkink et al., 2010c).	Cronbach Alpha to test the interrelatedness > 0.7 (Streiner, 2003, Taber, 2018).
	Test-retest		Since the scales are Ordinal scales, weighted kappa will be calculated (Chmura Kraemer et al., 2002, Streiner et al., 2015).	Weighted Kappa: Excellent (>0.75) Fair to good (0.40 to 0.75) Poor (< 0.4) (Fleiss et al., 2013).

4.3 Results

Patients comprised of 75 participants, 22 females (22%) and 53 males (53%). With ages ranging from under 25 to over 80 years old. Patients' demographics are detailed in Table 4.2. The scores for factor analysis are shown in diagrams 1 and 2 and baseline comparisons in Table 4.3. Internal consistency, test-retest reliability and hypothesis testing are detailed in Tables 4.4 to 4.6.

Table 4.2 Previous treatments of HNC of the participants

		Frequency	Percent
Type of RT[5]	Conventional RT	5	6.7
	IMRT[6]	26	34.6
	IMRT PTV[7]	3	4.0
	Radical RT	31	41.3
	VMAT IMRT[8]	2	2.7
	Parotid sparring RT	1	1.3
	Post-Operative RT	4	5.3
	IMRT & Post-Operative RT	1	1.3
	IMRT & Radical RT	2	2.7
	Total	75	100.0
Dose of RT	65 Gy	53	70.7
	60 Gy	11	14.7
	64 Gy	3	4.0
	55 Gy	5	6.7
	66 Gy	1	1.3
	Total	73	97.3
Type of Cancer	SCC	63	84.0
	Pleomorphic Adenoma carcinoma	3	4.0
	Mucoepidermoid	1	1.3
	Neuroblastoma	1	1.3
	Adenocarcinoma	3	4.0
	Adenoid cystic carcinoma	1	1.3
	Acinic cell carcinoma	1	1.3
	Salivary duct carcinoma	1	1.3
	Basal cell carcinoma	1	1.3
	Total	75	100.0

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[5] Radiotherapy
[6] Intensity modulated radiation therapy
[7] Intensity modulated radiation therapy with Planning Target Volume
[8] Intensity modulated radiation therapy with Volumetric Modulated Arc Therapy

Validity

Factor analysis

**Diagram 4.1** Confirmatory Factor Analysis for XI
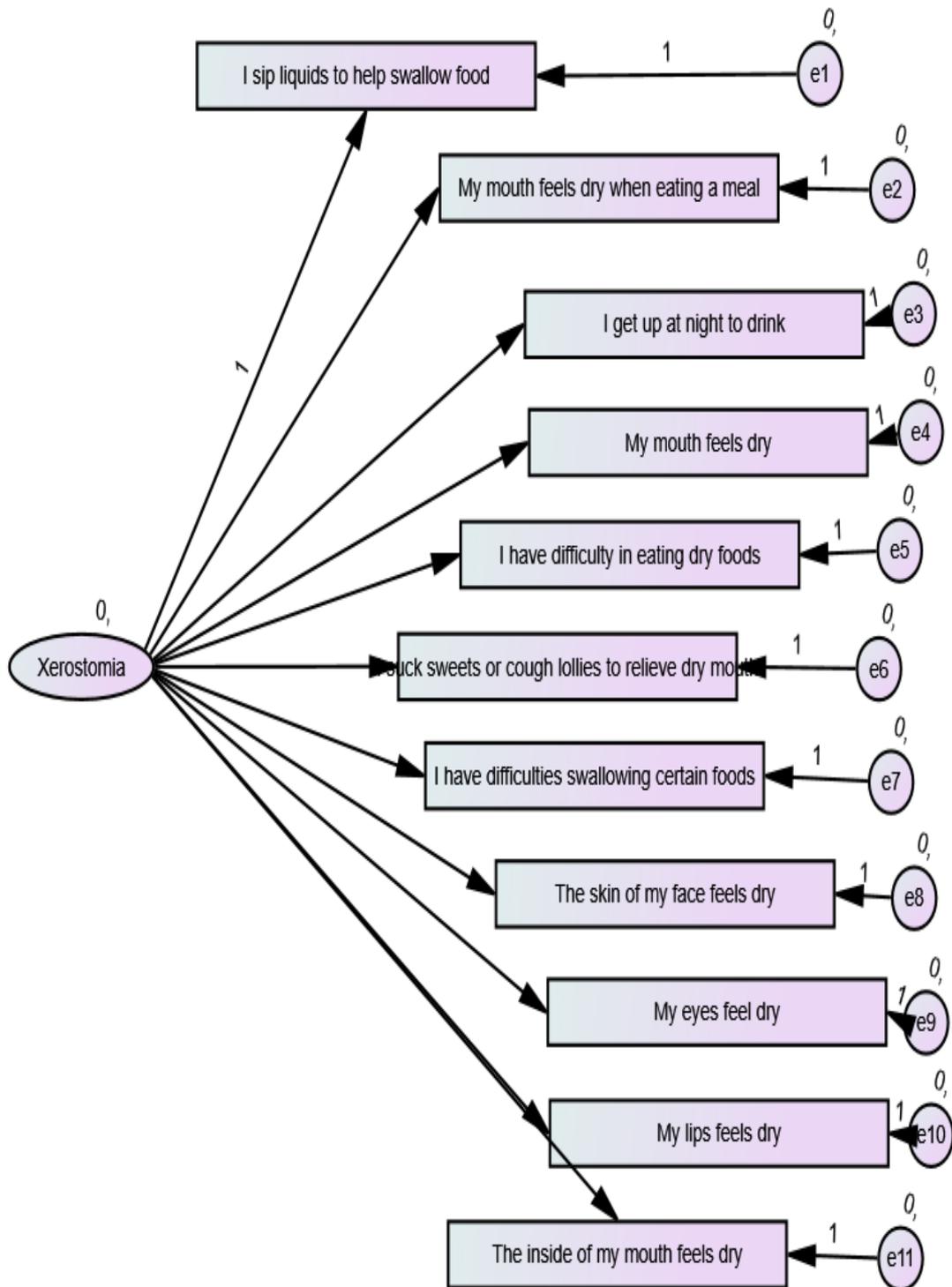
Diagram 4.2 Confirmatory Factor Analysis for XeQoLS
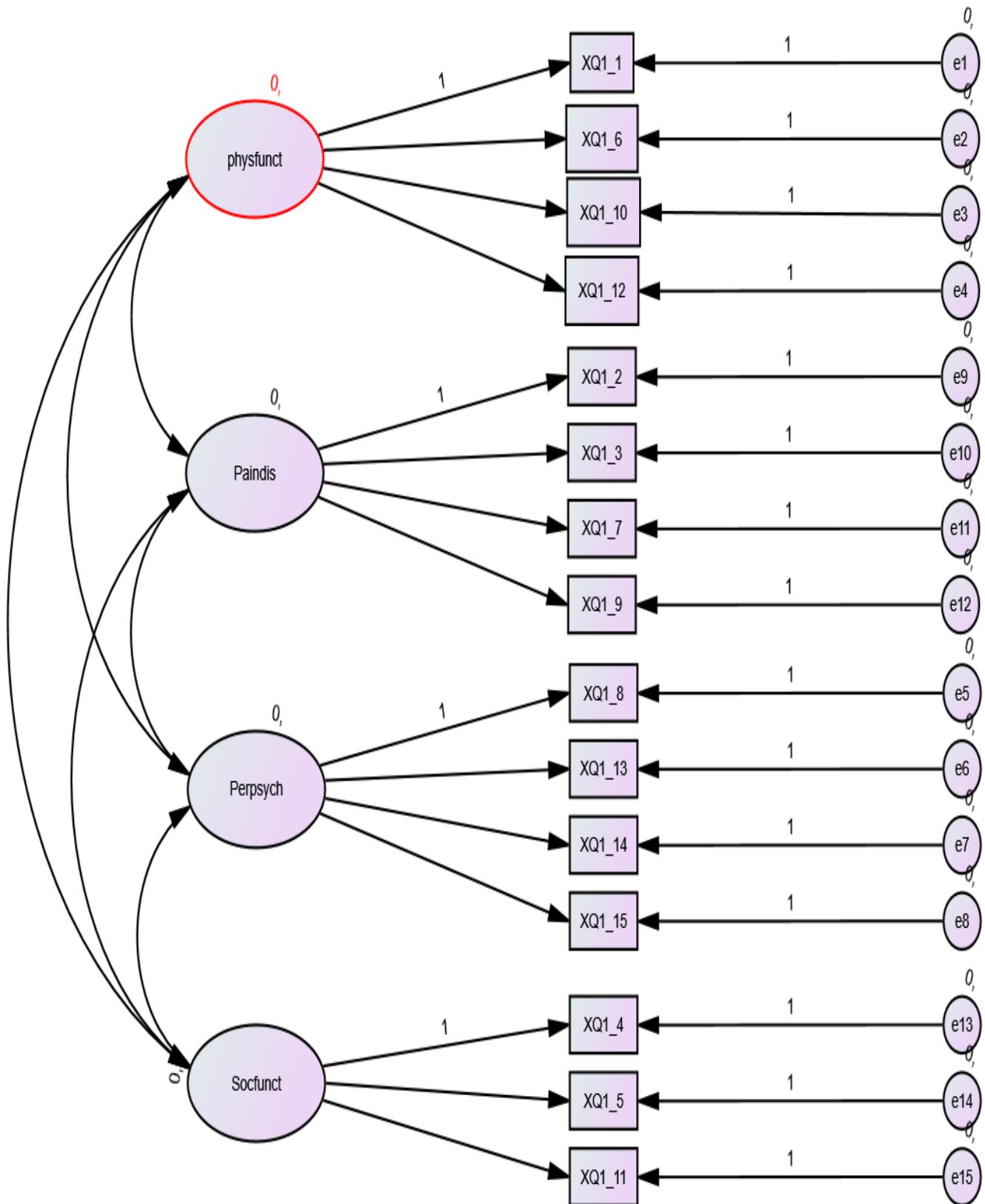
Baseline comparisons

Table 4.3 Confirmatory Factor Analysis scores for XI and XeQoLS

PROM	Model	TLI	CFI	RMSEA
XI	Default model	.632	.755	.144
	Independence model	.000	.000	.238
XeQoLS	Default model	.838	.887	.124
	Independence model	.000	.000	.308

XI confirmatory factor analysis scores for CFI and TLI (0.632 and 0.755) indicate a fair model fit, albeit less than 0.95; the least accepted value/indicator of a good fit.

XeQoLS confirmatory factor analysis scores for CFI and TLI (0.887 and 0.838) indicate a better outcome than XI, also a higher model fit. However, these scores still are less than 0.95, however fails to show a good fit.

Hypothesis Testing

Spearman's Correlation

Table 4.4 XI and XeQoLS spearman correlation scores for each subscale

Spearman's rho					
	XeQoLS subscales				
	Physical functioning (4 items)	Pain/Discomfort (4 items)	Psychological functioning (4 items)	Social functioning (3 items)	XeQoLS Total score
XI unidimensional scale (frequency) 11items	.753[**]	.681[**]	.638[**]	.591[**]	0.72

All Spearman's rho correlation coefficients had positive scores and were significant at the 0.01 level. The XI is unidimensional with frequency as a subscale for all items, its score ($\rho = 0.835$) indicates a strong correlation with total score of XeQoLS ($\rho = 0.72$) and all subscales, except for the 'social functioning' subscales score, with a 'moderate' correlation with XI with a

'moderate' score of 0.591, falling short from the range of 0.6-0.8 for a strong correlation. This however indicates that at least 75% of the formulated a priori were found to be in accordance with the hypothesis (Zar, 1972, Akoglu, 2018).

Reliability

<u>Internal consistency</u>

Table 4.5 Cronbach's Alpha scores for XI and XeQoLS and subscales

PROM	Subscale	Cronbach's Alpha	N of Items
XI	Frequency	0.835	11
XeQoLS	Physical Functioning	0.799	4
	Pain/Discomfort	0.86	4
	Personal/Psychological functioning	0.85	4
	Social Functioning	0.78	3
	Total XeQoLS Score	0.950	15

Internal consistency Cronbach's Alpha scores for XI and XeQoLS subscales are over 0.7, this refers to a sufficient internal consistency for both PROMs on each subscale. The total XI Cronbach's Alpha score (α = 0.835) marks a good internal consistency for its 11 scales/items. Total Cronbach's Alpha score for XeQoLS (α = 0.95) is also indicative of a good internal consistency (Taber, 2018)

Test-retest reliability

Table 4.6 Weighted Kappa and percentage agreement values for XI and XeQoLS items, subscales and total scores

PROM	subscale	Item number	item	Weighted kappa	CI interval 95%	percentage
XI	Frequency (unidimensional)	1	I sip liquids to help swallow foods	0.469	0.294-0.644	81%
		2	My mouth fells dry when eating a meal	0. 445	0.301-0.589	83%
		3	I get up at night to drink	0.433	0.28-0.585	82%
		4	My mouth feels dry	0.4	0.239-0.557	80%
		5	I have difficulty in eating dry foods	0.497	0.327-0.668	82%
		6	I suck sweets or lollies to relieve dry mouth	0.401	0.243-0.56	80%
		7	I have difficulties swallowing certain foods	0.502	0.338-0.667	83%
		8	The skin of my face feels dry	0.344	0.182-0.506	75%
		9	My eyes feel dry	0.464	0.32-0.607	84%
		10	My lips feel dry	0.473	0.318-0.628	83%
		11	The inside of my nose feels dry	0.333	0.165-0.502	74%
Total score				0.484	0.349-0.619	85%
XeQoLS	Physical Functioning	1	My mouth/throat dryness limits the kinds or amounts of foods I eat	0.497	0.347-0.648	84%
		6	My mouth/throat dryness makes me uncomfortable speaking in front of other people	0.401	0.237-0.566	80%

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		10	My mouth/throat dryness interferes with my daily activities	0.411	0.267-0.544	82%
		12	My mouth/throat dryness has a bad effect on tasting food	0.487	0.319-0.655	83%
	Total subscale score			0.451	0.314-0.588	84%
	Pain/discomfort	2	My mouth/throat dryness causes discomfort	0.406	0.24-0.572	80%
		3	My mouth/throat dryness causes lot of worry or concern	0.258	0.102-0.413	70%
		7	My mouth/throat dryness makes me nervous	0.339	0.160-0.519	72%
		9	My mouth/throat dryness keeps me from enjoying life	0.461	0.28-0.642	80%
	Total subscale score			0.427	0.284-0.57	83%
	Personal/psychological functioning	8	My mouth/throat dryness makes me concerned about the looks of my teeth and mouth	0.379	0.205-0.552	76%
		13	My mouth/throat dryness reduces my general happiness with life	0.466	0.306-0.626	82%
		14	My mouth/throat dryness affects all aspects of my life	0.453	0.291-0.615	81%
		15	If you were to spend the rest of your life with your mouth/throat dryness just the way it is now, how would you feel about this?	0.487	0.325-0.649	83%
	Total subscale score			0.456	0.313-0.6	84%
		4	My mouth/throat dryness keeps me from socialising (going out)	0.347	0.166-0.529	73%
		5	My mouth/throat dryness makes me uncomfortable eating in front of other people	0.557	0.403-0.711	85%
		11	My mouth/throat dryness interferes with my intimate relationships	0.377	0.174-0.579	72%
	Total subscale score			0.466	0.312-0.619	83%
Total score				0.473	0.329-0.617	84%

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Weighted kappa values for items, subscales and total values range between 0.258-0.557. Most values are within the range for a fair or good agreement (0.4 to 0.75) except for XI items 8 and 11 (0.344 , 0.33 respectively) and XeQoLS items 3,4,7,8 and 11 (0.258, 0.347, 0.379 and 0.377 respectively) indicating a poor agreement (Chmura Kraemer et al., 2002, Fleiss et al., 2013, Fleiss and Cohen, 1973, Cohen, 1968). However, the overall scores for both PROMs display an acceptable agreement.

4.4 Discussion

The XI and XeQoLS had been used to measure the symptom dry mouth, caused by radiotherapy to the head and neck region as means of therapy, from a patient's prospective (Thomson and Williams, 2000, Thomson, 2007, Rogers et al., 2010, Lastrucci et al., 2018). This study is the first to test these PROMs validity and reliability in England on RIX patients with HNC.

Factor analysis for XI and XeQoLS had a fair model fit (CFI = 0.755 and 0.887) respectively. However this score is less than 0.95, which is considered the least acceptable score for goodness of fit. Therefore, We have tried to overcome this shortcoming by testing the TLI, which is thought to be insensitive to the effects of a small sample size, however the TLI score also did not indicate a goodness of fit for the XI and XeQoLS TLI 0.632 and 0.838 < 0.95 (Thompson, 2004). This could be due to the smaller sample size effect (n <100) and this again could prove challenging when reporting on it since the role of thumb for factor analysis is a sample of 5-10 for each item (55-110) or at least above 100 (Thompson, 2004, Mokkink et al., 2018). This might indicate that the PROMs are not necessarily 'not valid' in terms of structure, but rather in need for a larger sample size to report on its structural validity with accretion.

We have hypothesised that since the XI measures the severity of RIX and XeQoLS measures the QoL of RIX patients, and the increase in symptom severity or impact could affect the QoL of RIX patients (Epstein et al., 1999, Epstein et al., 2001, Jellema et al., 2007). The correlation score of 0.72 refers to a strong correlation, which is in accordance with the hypothesis proposed (Zar, 1972, Scott, 2005).

Cronbach's Alpha coefficient scores were 0.950 and 0.835 for XI and XeQoLS respectively. This should indicates an acceptable interrelatedness for both PROMs > 0.7 (Taber, 2018).

As for test-retest reliability, both Cohen's Kappa scores for XI (0.484) and XeQoLS (0.473) were indicative of a good or fair score (Fleiss et al., 2013). This should point to the fitness of repeatability of these PROMs. The XI items 8 (the skin of my face feels dry) and item 11(the inside of my nose feels dry) scored a fair agreement, as well as XeQoLS item 3 (my mouth/throat dryness causes me a lot of worry or concern) item 4 (my mouth/throat dryness keeps me from socialising (going out)), item 7 (my mouth/throat dryness makes me feel nervous), item 8 (my mouth/throat makes me concerned about the looks of my teeth and mouth), and item 11 (my mouth/throat dryness interferes with my intimate relationships). Although both the XI and XeQoLS have ordinal scales and could only be assessed for reliability by calculating weighted kappa for test-retest, to the best of our knowledge, they were not assessed for test-retest reliability by calculating weighted kappa values previously in the literature. Therefore, based on point of reference unavailability, we could not draw comparisons on why these PROMs had low agreements and whether other studies had better values (Thomson et al., 2011). We have based our 2 week interval for test-retest on recommendations from COSMIN (Mokkink et al., 2010c, Terwee et al., 2011a) and in hindsight the time intervals should have been shorter, to compensate for the changes in scores that might occur, xerostomia is a subjective symptom and could oscillate in short time periods and could be easily influenced by other accompanying radiotherapy adverse effects. Also, although we have assumed that patients would remain in a stable condition throughout the assessment, it is factually uncertain if they would remain stable, due to the complex and subjective nature of xerostomia and its influence on different functions as well as its effects on many aspects of patients' QoL (Dirix et al., 2008).

The symptom of RIX is thought to be the most prevalent among other radiotherapy adverse effects (Braam et al., 2007, Cheng et al., 2011, Dirix et al., 2008, Eisbruch et al., 2003b). RIX affects the QoL and oral functions of HNC patients greatly and measuring the outcome of RIX

could help clinicians in assessing the true extent of dry mouth and its influence on patients' treatment plan (Cheng et al., 2011, Eisbruch et al., 2003a, Eisbruch et al., 2003b, Germano et al., 2015, Jellema et al., 2007). Moreover, using PROMs in studying interventions for HNC patients can help convey patients' prospective on new interventions and increase its chances of success (Osoba, 2011).

The validity of the XI and XeQoLS is in need of further research in terms of structural validity, probably if a larger sample size were to test for factor analysis it would be possible to report on an acceptable factor analysis score on both PROMs, since the factor score for this study is slightly below the accepted score (0.632 and 0.887 < 0.95).

Apart from structural validity, the XI and XeQoLS, based on the results of this study, are valid and reliable for their use in clinical trials and interventions for in England.

Chapter Five

General discussion

5. General Discussion and direction to further work

The National Institute for Health Research (NIHR) reports that between 2018 and 2019 there were 6,106 clinical trials in England, with 67,652 peoples in cancer research, testing new interventions. However, it is not known if those thousands of participants had their symptoms measured subjectively. Many trials have had drop-outs and patients discontinuing their participation, which is usually related to adverse effects intolerance, however how do objective measures explain these incidences? Therefore a subjective measurement tool could help further explore this particular aspect and help measure progress/regress in participants' symptom more accurately. Listening to patients' opinions and input on a treatment or intervention is believed to become more prominent in clinical care and research.

In recent times, there has been a steady increase in number of clinical investigations and trials employing patient reported measures. In a study, using evidence from (clinicaltrials.gov), to estimate how many trials utilised PROMs as a method of measure, the field of oncological-related trials were identified as the most trials to use one or more PROM (29% of all trials between 2007-2013) (Vodicka et al., 2015). This stems from healthcare professionals aiming at better understanding the effects many cancer treatments have on patients and to gain an enhanced prospective when planning HNC treatment (Hasnain-Wynia and Beal, 2014). Moreover, It is thought that PROMs help translate clinical progress on patients' reported outcomes as proof of improvement, it also adds more layers of information to clinical endpoints, which might not have been caught otherwise (Wiklund, 2004). Furthermore, PROMs can help predict survival rates, patients' acceptance and response to cancer treatment as well as its ability to measure the effects on patients' HR-QoL (Lipscomb et al., 2004, Gotay et al., 2008).

This has encouraged many oversight bodies to recommend the inclusion of PROMs in clinical trials, interventions and in practice, issuing also guidelines and frameworks for reporting PROMs in clinical trials, in order to improve intervention outcomes as primary or secondary endpoints in clinical trials or supplementing other clinical assessments (Shields et al., 2006,

Bevans et al., 2014, Calvert et al., 2018, Johnston BC, 2019). Recently, a Cochrane review that issued guidelines and recommendations for when systematically screening and assessing the psychosocial well-being and care needs of people with cancer, recommended that PROMs should be included in tandem with objective outcome measures, this is so patients' views can be prospectively included and accounted for. This is thought to inevitably make patients' prospective a vital indispensable part in treatment planning and in research (Schouten et al., 2019).

However, PROMs measurements are trustworthy when their validity and reliability assessments are done appropriately. At present, validation criteria and assessment standards of methodological validity are relatively newly developed in the literature (Terwee et al., 2007b, Ojo et al., 2012, Terwee et al., 2018, Prinsen et al., 2018).

The COSMIN guidelines for methodological quality (Mokkink et al., 2018) have been used extensively in the literature to assess the validity and reliability of available PROMs (Powell et al., 2019, Ma et al., 2019, Gondivkar et al., 2019, Speyer et al., 2018, McKenna et al., 2018, Crossley et al., 2018). The COSMIN guidelines aim to ensure the appropriateness of the validity of a PROM, to allow its use in clinical trials and ensuring that the data a PROM gathers is trustworthy.

RIX is thought to be a common adverse late effect of radiotherapy in HNC treatment. It consequently affects many oral functions. Dry mouth can affect digestion, speech, and oral health and above all can be naturally subjective and hard to measure decisively by clinicians or at times by objective means.

This thesis aimed to identify a methodologically validated PROM that can be used to measure RIX patients with HNC residing in England, using the COSMIN guidelines for systematic reviews of PROMs. The systematic review identified four PROMS (XQ, XI, GRIX and XeQoLS), these four PROMs were all found to have shortcomings in their method of validation.

Using qualitative methods (FGIs), and with the help of RIX patients, the most suitably appropriate PROMs were selected, the XI and XeQoLS. These two PROMs were then tested for their validity and reliability on a sample of RIX patients with HNC in England and conclusions were drawn on their suitability in terms of validity and reliability.

The XI and XeQoLS were found to be valid and reliable, except for their structural validity, which could be further tested on a larger sample size. A larger sample size is needed when testing for Structural validity to augment factor analysis results and help draw results clearly. In order to consider a PROM's factor analysis score as having a good model fit, its CFI and RMSEA scores should exceed 0.95, which PROMs in this work failed to achieve. This might be attributed to the sample size (n = 75) which is not optimal. Structural validity or factor analysis is thought to be best preformed with a sample size of at least 100 participants if not more (Thompson, 2004). The TLI scores were calculated to overcome the challenging and relatively small sample size, since it is thought that TLI scores are not affected by a small sample size, however the TLI scores were also underwhelming.

Factor analysis is meant to explore/confirm the items relevance to the structure proposed to measure a certain symptom, based on the subscales/factors related to said symptom, hence the more the items are answered by a large cohort the more/less the item relevance to the structure is made known.

These findings should enable clinicians and researchers to have an improved prospective on these PROMs and whether to incorporate them in future research or clinical practice.

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7. Appendices

IRAS [215186] JRO [17/0051] Version 1.0 DATED 17th August 2017	Patient Reported Outcome Measures in Radiotherapy Induced Xerostomia (REMIX)	Patient Initials: Staff Completing forms: Date: Visit:

APPENDIX A: GRIX

The Groningen Radiotherapy-induced Xerostomia questionnaire (GRIX):

Below are several questions that will help describe the dryness in your mouth and how that dryness affects your daily life. Please check the box that corresponds to your condition during the last week, in each of the following area

Question	Not at all	A little	Quite a bit	Very much
Have you had a dry mouth during the day?	▣	▣	▣	▣

Have you had a dry mouth outdoors?	◘	◘	◘	◘
Have you had difficulties with eating due to a dry mouth?	◘	◘	◘	◘
Have you had a dry mouth during activities?	◘	◘	◘	◘
Have you had difficulties with talking due to a dry mouth?	◘	◘	◘	◘
Did you drink more during the day due to a dry mouth?	◘	◘	◘	◘
Have you had a dry mouth during the night?	◘	◘	◘	◘
Have you had difficulties with sleeping due to a dry mouth?	◘	◘	◘	◘
Did you need to drink during the night due to a dry mouth?	◘	◘	◘	◘
Have you had sticky saliva during the day?	◘	◘	◘	◘
Have you had difficulties with eating due to sticky saliva?	◘	◘	◘	◘
Have you had difficulties with talking due to sticky saliva?	◘	◘	◘	◘
Have you had sticky saliva during the night?	◘	◘	◘	◘

Have you had difficulties with sleeping due to sticky saliva?	▫	▫	▫	▫

APPENDIX B: XeQoLs
The University of Michigan Xerostom
ia-Related Quality of Life Scale (XeQoLs):

These questions are concerned with your oral health and how it affects your life. Please answer the questions by checking the box that describes best how true each statement has been for you during **the past 7 days**:

1.   My mouth/throat dryness limits the kinds or amounts of food I eat.

❑ Not at all   ❑ A little   ❑ Somewhat   ❑ Quite a bit   ❑ Very much

2.   My mouth/throat dryness causes discomfort.

❑ Not at all   ❑ A little   ❑ Somewhat   ❑ Quite a bit   ❑ Very much

3.   My mouth/throat dryness causes a lot of worry or concern.

❑ Not at all   ❑ A little   ❑ Somewhat   ❑ Quite a bit   ❑ Very much

4.   My mouth/throat dryness keeps me from socializing (going out).

❑ Not at all   ❑ A little   ❑ Somewhat   ❑ Quite a bit   ❑ Very much

5.   My mouth/throat dryness makes me uncomfortable when eating in front of other people.

❑ Not at all   ❑ A little   ❑ Somewhat   ❑ Quite a bit   ❑ Very much

6.   My mouth/throat dryness makes me uncomfortable speaking in front of other people.

❑ Not at all   ❑ A little   ❑ Somewhat   ❑ Quite a bit   ❑ Very much

7.   My mouth/throat dryness makes me nervous.

❑ Not at all   ❑ A little   ❑ Somewhat   ❑ Quite a bit   ❑ Very much

8.   My mouth/throat dryness makes me concerned about the looks of my teeth and mouth.

❑ Not at all   ❑ A little   ❑ Somewhat   ❑ Quite a bit   ❑ Very much

IRAS [215186] JRO [17/0051] Version 1.0 DATED 17th August 2017	Patient Reported Outcome Measures in Radiotherapy Induced Xerostomia (REMIX)	Patient Initials: Staff Completing forms: Date: Visit:

APPENDIX C: XQ

Xerostomia Questionnaire (XQ)

Below are several questions that will help describe the dryness in your mouth and how that dryness affects your daily life. Please encircle the number that corresponds to your condition during the last week, in each of the following areas:

Example
If your mouth is dry part of the time (such as only at night) you might circle "5."
If your mouth is dry only at certain times such as during exercise, you might circle "3" (see below).

Not Dry   0   1   2   3   4   5   6   7   8   9   10   Extremely Dry

1. Rate the discomfort of your dentures due to dryness (if you do not wear dentures, please check)

Comfortable   0   1   2   3   4   5   6   7   8   9   10 Extreme Discomfort

2. Rate the difficulty you experience in speaking due to dryness of your mouth and tongue:

Easy   0   1   2   3   4   5   6   7   8   9   10   Extremely Difficult

3. Rate the difficulty you experience in chewing food due to dryness:

Easy   0   1   2   3   4   5   6   7   8   9   10   Extremely Difficult

4. Rate the difficulty you experience in swallowing food due to dryness

Easy   0   1   2   3   4   5   6   7   8   9   10   Extremely Difficult

5. Rate the dryness your mouth feels when eating a meal:

No Dryness   0   1   2   3   4   5   6   7   8   9   10   Extreme Dryness

6. Rate the dryness in your mouth while not eating or chewing:

No Dryness   0   1   2   3   4   5   6   7   8   9   10   Extreme Dryness

7. Rate the frequency of sipping liquids to aid swallowing food:

Non-required 0   1   2   3   4   5   6   7   8   9   10 Extremely frequent

8. Rate the frequency of fluid intake required for oral comfort when not eating:

Non-required 0   1   2   3   4   5   6   7   8   9   10 Extremely frequent

9. Rate the frequency of sleeping problems due to dryness:

Non-required 0   1   2   3   4   5   6   7   8   9   10 Extremely frequent

APPENDIX D: Xerostomia Inventory

Xerostomia Inventory (XI):

Below are several questions that will help describe the dryness in your mouth and how that dryness affects your daily life. Please check the box that corresponds to your condition during the last week, in each of the following area.

Question	Response options				
	Never	Hardly	Occasionally	Fairly Often	Very often

I sip liquids to help swallow food	1	2	3	4	5
My mouth feels dry when eating a meal	1	2	3	4	5
I get up at night to drink	1	2	3	4	5
My mouth feels dry	1	2	3	4	5
I have difficulty in eating dry foods	1	2	3	4	5
I suck sweets or cough lollies to relieve dry mouth	1	2	3	4	5
I have difficulties swallowing certain foods	1	2	3	4	5
The skin of my face feels dry	1	2	3	4	5
My eyes feel dry	1	2	3	4	5
My lips feel dry	1	2	3	4	5
The inside of my nose feels dry	1	2	3	4	5

APPENDIX E: Participant Information Sheet (PFI) Phase I

Participant Information Sheet

Lay Title of the Project: Patient Reported Outcome Measures in Radiotherapy Induced Xerostomia – Which Instrument Should We Use? Phase 1

[**Scientific title**: Measurement Properties of Patient-Rated Outcome Measures in Radiotherapy Induced Xerostomia (**REMIX**)].

Please read this sheet carefully. Please ask if you do not understand or would like more information

1. Invitation to participate

We would like to invite you to take part in our research study. This study forms a part of an educational project (PhD). Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have.

You have been selected as a potential participant because you might have the appropriate condition that we are studying. The following information is provided so that you can make an informed decision regarding your willingness to participate. We encourage discussing with family and friends and ask us if there is anything which is not clear or if you would like more information.

2. What is the purpose of the study?

The majority of patients with cancer of the head and neck (e.g. cancer of the mouth or throat) receive radiotherapy as part of their treatment. Radiotherapy to the head and neck often causes

5 What will happen to me if I take part?

Each study participant will be asked to attend one focus group interview, which is a meeting where a group of people (usually 6 to 12) will be asked about their perceptions and opinions towards the questionnaires that have been used so far to assess dry mouth symptoms of radiotherapy.

Each focus group interview will have a moderator and an observer in addition to the 6-12 participants. These settings will be audio recorded for analysis purposes. We plan to run at least 3 focus groups interview for a total of up to 36 patients, although we might need a few more. Each visit will have a single focus group interview.

6. Expenses and payments

We will reimburse your travel expenses and refreshments will be present at each setting.

7. What will I have to do?

In the focus group interview, you will be asked to fill in the questionnaires in question and discuss them simultaneously, as guided by the moderator. This is called the 'Think-Aloud' method. The moderator will be conducting the group discussion and the observer will be only taking notes for the sake of data analysis. The discussion will be recorded.

8. What are the possible disadvantages and risks of taking part?

There is a possibility that sensitive issues night be discussed, for example one of the questionnaires includes items on the impact of RIX on intimate relationships.

9. What are the possible benefits of taking part?

There will be no direct benefits associated with your participation in the study. However, the study will help clinicians understanding which questionnaires is best suited to assess dry mouth symptoms after radiotherapy and the effects of the therapy they provide.

10. What happens when the research study stops?

On study completion, you will be offered the return to you usual NHS clinics.

11. Will my taking part in the study be kept confidential?

The Investigators (study doctors) will make every possible effort to keep your personal information confidential. All the information collected during the study will be anonymised and kept by the research team in a secured facility. The Chief Investigator is responsible for safety and security of

Riordain and Dr Stefano Fedele by phone, letter or email. **This study will form part of an educational project (PhD).**

You can contact the investigator team on: **Prof Stephen Porter** at 020 3456 1142 or **Dr Richeal Ni Riordain** or **Prof Stefano Fedele** at 020 3456 1004 or **Motaz Assas** at 02034567890 (Ext: 61193).

14. Who is organising and funding the research

The study is sponsored by UCLH

15. Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the South Central - Berkshire Research Ethics Committee [Ref 17/SC/0485]

16.Whom to ask questions regarding this study or to make a complaint to

You have the right to ask questions concerning this study at any time - please contact **Prof. Stephen Porter** at 020 3456 1142 or **Dr Richeal Ni Riordain** or **Prof Stefano Fedele** at 020 3456 1004.

Complaints

- To Study Investigators: please contact **Prof Stephen Porter** or **Dr Richeal Ni Riordain, or Prof Stefano Fedele**.
- To UCLH: please speak to the person in charge of the ward or clinic, or to our **Patient Advice and Liaison Service (PALS)** who will help with your problem quickly and informally. Contact PALS on 020 7380 9975.
- You can also make formal complaint. You can do this within 12 months of the events concerned, or within 12 months of becoming aware of the problem. Please write with full details to the **Complaints Manager** at: Governance Department, UCLH, 2nd Floor West, 250 Euston Road, London, NW1 2PG (Fax: 02073809595- email: complaints.officer@uclh.nhs.uk).

A copy of this information sheet and a signed consent form will be given to you.

APPENDIX F: Participant Information Sheet (PFI) Phase II

Participant Information Sheet

Lay Title of the Project: Patient Reported Outcome Measures in Radiotherapy Induced Xerostomia – Which Instrument Should We Use? Phase 2

[**Scientific title:** Measurement Properties Of Patient-Rated Outcome Measures In Radiotherapy Induced Xerostomia (REMIX)].

Please read this sheet carefully. Please ask if you do not understand or would like more information

1. Invitation to participate

We would like to invite you to take part in our research study. This study forms a part of an educational project (PhD). Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have.

You have been selected as a potential participant because you might have the appropriate condition that we are studying. The following information is provided so that you can make an informed decision regarding your willingness to participate. We encourage discussing with family and friends and ask us if there is anything which is not clear or if you would like more information.

2. What is the purpose of the study?

The majority of patients with cancer of the head and neck (e.g. cancer of the mouth or throat)

You would be asked to complete one or more dry mouth questionnaires at three different times as part of your hospital appointments (one questionnaire at study entry, one two weeks later and then the final questionnaire after 3 months). We will then analyse relevant data so to assess the validity of the questionnaire.

6. Expenses and payments
We will reimburse your travel expenses and refreshments will be present at each visit.

7. What will I have to do?
Attend the Hospital for three visits over 3 months and complete the designated dry mouth questionnaire. You do not have to attend outside their regularly scheduled appointments.

8. What are the possible disadvantages and risks of taking part?
There are no relevant risks related to completing the questionnaire.

9. What are the possible benefits of taking part?
There will be no direct benefits associated with your participation in the study. However, the study will help clinicians understanding which questionnaires is best suited to assess dry mouth symptoms after radiotherapy and the effects of the therapy they provide.

10. What happens when the research study stops?
On study completion, you will be offered the return to you usual NHS clinics.

11. Will my taking part in the study be kept confidential?
The Investigators (study doctors) will make every possible effort to keep your personal information confidential. All the information collected during the study will be anonymised and kept by the research team in a secured facility. The Chief Investigator is responsible for safety and security of the recordings and data. Anonymised study data, as well as your Hospital Medical records and the consent form you signed may be inspected by an Institutional Review Board or Ethical Review Committee. The results of this research project may be presented at meetings or in publications; however, any research data released or published will not identify study participants by name. All data and results will be completely anonymised and it will be impossible to identify you from them.

12. What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Contact numbers of study investigators are provided at the end of this document – as an alternative, you can also complain directly to UCLH.
If you are harmed by taking part in this research project, there are no special compensation arrangements – although the normal NHS complaints mechanisms will still be available to you where appropriate. If you are harmed due to someone's negligence, you may have legal grounds for compensation, but you may have to pay for it.
UCLH Patient Advice and Liaison Service (PALS) who will help with your problem quickly and informally. Contact PALS on 020 7380 9975.

13. Study results
The results of this research study may be presented at meetings and may be published in medical journals. No patient's identifiable data will be used. If you would like to receive the results of the study, please contact the Chief Investigator, Professor S. Porter, or Principal Investigators, Dr R Ni Riordain and Dr Stefano Fedele by phone, letter or email. **This study will form part of an educational project (PhD).**
You can contact the investigator team on: **Prof. Stephen Porter** at 020 3456 1142 or **Dr Richeal Ni Riordain** or **Prof Stefano Fedele** at 020 3456 1004 or **Motaz Assas** at 02034567890 (Ext: 61193).

14. Who is organising and funding the research

The study is sponsored by UCLH

15. Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the South Central - Berkshire Research Ethics Committee **[Ref 17/SC/0485]**.

16.Whom to ask questions regarding this study or to make a complaint to
You have the right to ask questions concerning this study at any time - please contact **Prof Stephen Porter** at 020 3456 1142 or **Dr Richeal Ni Riordain** or **Prof Stefano Fedele** at 020 3456 1004 or **Motaz Assas** at 02034567890 (Ext: 61193).

Complaints
- To Study Investigators: please contact **Prof Stephen Porter** or **Dr Richeal Ni Riordain**, or **Prof Stefano Fedele** or **Motaz Assas**.
- To UCLH: please speak to the person in charge of the ward or clinic, or to our **Patient Advice and Liaison Service (PALS)** who will help with your problem quickly and informally. Contact PALS on 020 7380 9975.
- You can also make formal complaint. You can do this within 12 months of the events concerned, or within 12 months of becoming aware of the problem. Please write with full details to the **Complaints Manager** at: Governance Department, UCLH, 2nd Floor West, 250 Euston Road, London, NW1 2PG (Fax: 02073809595- email: complaints.officer@uclh.nhs.uk).

A copy of this information sheet and a signed consent form will be given to you.

APPENDIX G: Consent form phase I

University College London Hospitals **NHS**

NHS Trust

Version 3.0, 08/09/2017
Study Number: IRAS [215186] JRO [17/0051]
Patient ID for this trial:

Eastman Dental Hospital
256 Grays Inn Road
London WC1X 8LD

EASTMAN CLINICAL INVESTIGATION CENTRE
Enquiries and Appointments: Tel: 020 3456 1276

CONSENT FORM

Lay Title of the Project: Patient Reported Outcome Measures in Radiotherapy Induced Xerostomia – Which Instrument Should We Use? Phase 1

[**Scientific title**: Measurement Properties of Patient-Rated Outcome Measures In Radiotherapy Induced Xerostomia (**REMIX**)].

Name of Chief Investigator: **Prof. Stephen Porter**
Names of Principal Investigators: **Dr. Richeal Ni Riordain, Dr Stefano Fedele**

Please initial box

1. I confirm that I have read and understood the information sheet Phase1, Version 3.0 dated 08/09/2017 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by the researchers and responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to my General Practitioner and General Dental Practitioner being informed of my participation in the study. ☐

5. I understand that I will be audio recorded for the focus group interviews for data analysis purposes. I understand that these recordings will remain anonymous. I am happy to be audio recorded. ☐

6. I understand that this study will investigate whether current dry mouth questionnaires explain patients' condition clearly and reliably. ☐

7. I understand that I should treat the contributions of fellow group members in confidence. ☐

8. I agree to take part in the above study. ☐

_____ _____ _____
Name of patient   Date   Signature

_____ _____ _____
Name of Person taking consent   Date   Signature
(if different from researcher)

_____ _____ _____
Researcher   Date   Signature

UCL HOSPITALS

UCL Hospitals is an NHS Foundation Trust incorporating the Eastman Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Heart Hospital, Hospital for Tropical Diseases, National Hospital for Neurology & Neurosurgery, The Royal London Homeopathic Hospital and University College Hospital.

APPENDIX H: Consent form phase II

University College London Hospitals **NHS**
NHS Trust

Version 2.0, 08/09/2017
Study Number: 17/0051
Patient ID:

Eastman Dental Hospital
256 Grays Inn Road
London WC1X 8LD

EASTMAN CLINICAL INVESTIGATION CENTRE
Enquiries and Appointments: Tel: 020 3456 1276

CONSENT FORM

Lay Title of the Project: Patient Reported Outcome Measures in Radiotherapy Induced Xerostomia – Which Instrument Should We Use? Phase 2.

[**Scientific title**: Measurement Properties of Patient-Rated Outcome Measures in Radiotherapy Induced Xerostomia (**REMIX**)].

Name of Chief Investigator: **Prof. Stephen Porter**
Names of Principal Investigators: **Dr. Richeal Ni Riordain, Prof. Stefano Fedele**

Please Initial box

1. I confirm that I have read and understood the information sheet Phase 2, Version 2 dated 19/07/2017 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by the researchers and responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to my General Practitioner and General Dental Practitioner being informed of my participation in the study. ☐

5. I understand that I will be completing a questionnaire about dry mouth for data analysis purposes. I understand my information will remain anonymous. ☐

6. I understand that this study will investigate whether current dry mouth questionnaires explain patients' condition clearly and reliably. ☐

7. I agree to take part in the above study ☐

Name of patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

UCL Hospitals is an NHS Foundation Trust incorporating the Eastman Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Heart Hospital, Hospital for Tropical Diseases, National Hospital for Neurology & Neurosurgery, The Royal London Homoeopathic Hospital and University College Hospital.

APPENDIX I: Importance scale for GRIX

Participant ID:		Investigator		DOB:		Date	

Importance scale for *The Groningen Radiotherapy-induced Xerostomia questionnaire (GRIX)*

Items:

1. Have you had a dry mouth during the day?

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

2. Have you had a dry mouth outdoors?

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

3. Have you had difficulties with eating due to a dry mouth?

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

4. Have you had a dry mouth during activities?

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

Participant ID:		Investigator		DOB:		Date	

5. Have you had difficulties with talking due to a dry mouth?

① ② ③ ④ ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

6. Did you drink more during the day due to a dry mouth?

① ② ③ ④ ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

7. Have you had a dry mouth during the night?

① ② ③ ④ ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

8. Have you had difficulties with sleeping due to a dry mouth?

① ② ③ ④ ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

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9. Did you need to drink during the night due to a dry mouth?

①   ②   ③   ④   ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

10. Have you had sticky saliva during the day?

①   ②   ③   ④   ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

11. Have you had difficulties with eating due to sticky saliva?

①   ②   ③   ④   ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

12. Have you had difficulties with talking due to sticky saliva?

①   ②   ③   ④   ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

13. Have you had sticky saliva during the night?

①   ②   ③   ④   ⑤

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

Participant ID:		Investigator		DOB:		Date	

14. Have you had difficulties with sleeping due to sticky saliva?

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

APPENDIX J: Importance scale for XeQoLS

Importance scale for *Xerostomia Quality of life scale (XeQoLS)*
Items:

1. My mouth/throat dryness limits the kinds or amounts of food I eat

| ① | ② | ③ | ④ | ⑤ |
| Of no importance | Slight importance | Moderate importance | high importance | extreme importance |

2. My mouth/throat dryness causes discomfort

| ① | ② | ③ | ④ | ⑤ |
| Of no importance | Slight importance | Moderate importance | high importance | extreme importance |

3. My mouth/throat dryness causes a lot of worry or concern

| ① | ② | ③ | ④ | ⑤ |
| Of no importance | Slight importance | Moderate importance | high importance | extreme importance |

4. My mouth/throat dryness keeps me from socialising (going out)

| ① | ② | ③ | ④ | ⑤ |
| Of no importance | Slight importance | Moderate importance | high importance | extreme importance |

Participant ID:		Investigator		DOB:		Date	

5. My mouth/throat dryness makes me uncomfortable when eating in front of other people

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

6. My mouth/throat dryness makes me uncomfortable speaking to other people

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

7. My mouth/throat dryness makes me nervous

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

8. My mouth/throat dryness makes me concerned about the looks of my teeth and mouth

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

9. My mouth/throat dryness keeps me from enjoying my life

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

Participant ID:		Investigator		DOB:		Date	

10. My mouth/throat dryness interferes with my daily activities

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

11. My mouth/throat dryness interferes with my intimate relationship

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

13. My mouth/throat dryness has a bad effect on tasting food

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

15. My mouth/throat reduces my general happiness with life

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

16. My mouth/throat dryness affects all aspects of my life

①	②	③	④	⑤
Of no importance	Slight importance	Moderate importance	high importance	extreme importance

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Participant ID:		Investigator		DOB:		Date	

17. If you were to spend the rest of your life with your mouth/throat dryness just the way it is now, how would you feel about this?

① Of no importance   ② Slight importance   ③ Moderate importance   ④ high importance   ⑤ extreme importance

APPENDIX K: Importance scale for XI

Importance scale for *Xerostomia Inventory (XI)*

Items:

1. I sip liquids to help swallow food

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

2. My mouth feels dry when eating a meal

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

3. I get up at night to drink

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

4. My mouth feels dry

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

Participant ID:		Investigator		DOB:		Date	

5. I have difficulty in eating dry foods

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

6. I suck sweets or cough lollies to relieve dry mouth

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

7. I have difficulties swallowing certain foods

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

8. The skin of my face feels dry

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

Participant ID:		Investigator		DOB:		Date	

9. My eyes feel dry

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

10. My lips feel dry

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

11. The inside of my nose feels dry

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

APPENDIX L: Importance scale for XQ

Participant ID:		Investigator		DOB:		Date	

Importance scale for *Xerostomia Questionnaire (XQ)*

Items:

1. Rate the discomfort when wearing dentures

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

2. Rate the difficulty you experience in speaking due to dryness of your mouth and tongue

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

3. Rate the difficulty you experience in chewing food due to dryness

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

4. Rate the difficulty you experience in swallowing food due to dryness

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

Participant ID:		Investigator		DOB:		Date	

5. Rate the dryness your mouth feels when eating a meal

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

6. Rate the dryness in your mouth while not eating or chewing:

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

7. Rate the frequency of sipping liquids to aid swallowing food

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

8. Rate the frequency of fluid intake required for oral comfort when not

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

Participant ID:		Investigator		DOB:		Date	

9. Rate the frequency of sleeping problems due to dryness

Of no importance   Slight importance   Moderate importance   high importance   extreme importance

APPENDIX M: Supplementary Tables for Chapter two

Table on results of studies on measurement properties

PROM (ref)	Country (language) in which the PROM was evaluated	Structural validity			Internal consistency			Cross-cultural validity\ measurement invariance			Reliability		
		n	Meth qual	Result (rating)	n	Meth qual	Result (rating)	n	Meth qual	Result (rating)	n	Meth qual	Result (rating)
GRIX (Beetz et al. 2010)	The Netherlands (Dutch)				315	**Doubtful**	The Crohnbach's alpha for each subscale: xerostomia during the day 0.94 and night 0.88 and sticky saliva during the day 0.89 and night, 0.88. (? no evidence of unidimensionality)				315	**Inadequate**	(? Pearson correlation calculated)
GRIX Summary							**0.88-0.94 (?)**						**(? weighted Kappa not reported)**
XQ (Eisbruch et al. 2001)	The US (English)				84	**Doubtful**	The overall Crohnbach's alpha 0.86 (? no evidence of unidimensionality)				84	**Inadequate**	(? Pearson correlation

													calculated)
XQ-T (Lin et al. 2008)					50	**Doubtful**	The Crohnbach's alpha for each subscale range 0.56-0.90 (? no evidence of unidimensionality)				50	**Inadequate**	Based on the short interval (3 days). No remarkable change would be assumable. Pearson's correlation 0.96 (?)
XQ-IT(Pellegrino et al. 2015)	Italy (Italian)	102	Adequate	Exploratory factor analysis performed 1 principal component explaining 68% of the observed total variance (?)	102	**Very good**	The Crohnbach's alph 0.93 (CI 95%; 0.91-0.95) (+)				102	**Inadequate**	Measures ICC instead of weighted kappa (ordinal scale) ICC= 0.79 (CI95%; 0.67-0.87) (?)
XQ-G (Memtsa et al. 2017)	Greece (Greek)	100	Adequate	Exploratory factor analysis performed 1 principal	100	**Very good**	The Crohnbach's alph 0.971 (0.964-0.976) (+)				100	**Inadequate**	Measures ICC instead of

				component explaining 83.69% of total variance (+)									weighted kappa (ordinal scale) ICC= 0.995 (CI 95%; 0.992-0.996) (?)
XQ Summary				**EFA performed and evidence of unidimensionality overall (+)**			**2? 2 + overall (? Less than 75% of results are +)**						**4? overall (?) no evidence of weighted kappa only ICC**
XI (Thomson 2007)					95	**Very good**	The Crohnbach's alph (0.7-0.9) (+)				95	Inadequate	**ICC (0.92) calculated instead of weighted kappa (ordinal scale) (?)**
XI summary							**Overall (+)**						**Overall (?)**
XeQoLS (Henson et al. 2001)					20	**Doubtful**	Four domains were tested for statistical						

							significance: physical (r=0.85), personal/psychological (r=0.87), social (r=0.86), pain/discomfort (r=0.89). Total (r=0.96, P<0.001) (? No evidence of unidimensionality)).						
XeQoLS (Lastrucci et al. 2018)					35	**Doubtful**	Overall Cronbach α = 0.937), study states α was acceptable in three of the four subscales (Physical functioning: α = 0.786; Pain/discomfort: α = 0.791; Social functioning: α = 0.736) and good in Personal/psychological functioning (α = 0.858) (? No evidence of unidimensionality)						
XeQoLS summary							Overall (?)						

Summary of Findings Tables

Structural validity	Summary or pooled result	Overall rating	Quality of evidence
XQ	EFA performed and evidence of unidimensionality	+	High (Two study results of adequate methodology)

Internal consistency	Summary or pooled result	Overall rating	Quality of evidence
GRIX	Alpha 0.88-0.94 with lack of evidence for unidimensionality (?)	?	Low (Very serious risk of bias one study results of doubtful methodology)
XQ	2? 2 + overall (+ More than 75% of results are +) two doubtful studies and two very good studies, decided to score sufficient because of very good studies included.	+	High
XI	The Cronbach's alpha (0.7-0.9) (+) with a very good methodology	+	Moderate (Imprecision sample n 95 > 100)
XeQoLS	?	?	Very low (Extremely serious risk of bias and serious inconsistency only one inadequate study result)

Reliability	Summary or pooled result	Overall rating	Quality of evidence
GRIX	(? weighted Kappa not reported)	?	Very low (Extremely serious risk bias only one inadequate study result)
XQ	4? overall (?) no evidence of weighted kappa only ICC	?	Low (Very serious risk of bias multiple inadequate study results)
XI	ICC (0.92) calculated instead of weighted kappa (ordinal scale) (?)	?	Very low (Extremely serious risk of bias only one inadequate study result)

Hypotheses testing	Summary or pooled result	Overall rating	Quality of evidence
GRIX	(?) No defined hypothesis	?	Low (Very serious risk of bias only one doubtful methodology study result)
XQ	5 + overall (+)	+	Moderate (Serious risk of bias 3 inadequate / 2 adequate methodological study results)
XI	overall (+)	+	Very low (Extremely serious risk of bias only one Inadequate methodology study result)
XeQoLS	Overall (+)	+	Very low (Very serious risk of bias one doubtful methodology study result, imprecision sample < 50)

Responsiveness	Summary or pooled result	Overall rating	Quality of evidence
GRIX	Comparing before and after intervention (Rx dose) against mean score of 4 subscales of GRIX no scores reported only figure (+)	+	Very low (Extremely serious risk of bias only one inadequate methodology study result)
XQ	3 + overall (+)	+	Low (Very serious risk of bias 3 studies of inadequate methodology study results)
XI	2 (+)	+	Low (Very serious risk of Bias two inadequate methodology study results)
XeQoLS	Overall (+)	+	Very low (Extremely serious risk of bias only one study of inadequate methodology study results)