JÖNKÖPING UNIVERSITY
School of Health and Welfare

Doctoral Thesis

Radiation-Induced Xerostomia in Chinese Patients with Head and Neck Cancer

– An Explorative and Interventional study

Nan Jiang

Jönköping University
School of Health and Welfare
Dissertation Series No. 108 • 2021

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Abstract

Background: Radiation-induced xerostomia is a common oral complication of patients with head and neck cancer (HNC) undergoing radiotherapy (RT). This can lead to a series of functional oral disorders, particularly dental caries, and ultimately negatively affect their oral health and health-related quality of life (HRQoL).

Aims: The overall aim of this thesis was to understand the living experience of radiation-induced xerostomia and to determine the effects of an integrated supportive program based on multicomponent oral care strategies in Chinese patients with HNC.

Methods: A qualitative descriptive study was conducted to describe how patients (13 men and 7 women) with HNC experienced radiation-induced xerostomia (I). A cross-sectional study of patients (n=80) with HNC was conducted to accomplish the validation of the Chinese version of the xerostomia questionnaire (XQ) (II). A randomized controlled trial (n=79) was conducted to determine the effect of an integrated supportive program (with a combination of face-to-face health education and coaching sections) on xerostomia, saliva characteristics (III), oral health, and HRQoL (IV).

Results: Five categories emerged from the manifest content of the interviews: *communication problems, physical problems, psychosocial problems, treatment problems,* and *relief strategies*. The meaning underlying these categories formed a theme, which was the latent content of the interview: *Due to lack of information regarding xerostomia, patients had to find their own ways to deal with the problem* (I). The Chinese version of XQ was a unidimensional scale (1-factor solution explained 75.6 of the total variance) and had good psychometric properties with excellent internal consistency (Cronbach's α of 0.95), test-retest reliability (intraclass correlation coefficient of 0.92), and good criterion-related validity and content validity (II). The integrated supportive program showed significant inter-group differences in xerostomia (P=0.046), unstimulated saliva flow rate (P=0.035), plaque index (P=0.038), Oral Health Impact Profile-14 (P=0.002), and Functional

Assessment Cancer Therapy-Head & Neck (P=0.001) over the 12-month follow-up, with better outcomes in the intervention group (III & IV).

Conclusion: This thesis contributes knowledge regarding the experiences of living with xerostomia from a patient perspective, noting that xerostomia has a profound impact on a patient's physical, psychological, and social quality of life. There is lack of assessment tools for xerostomia in the Chinese population, and the Chinese version of XQ proved to be a valid and simple self-administered tool to measure and monitor the xerostomia level in patients with HNC. The integrated supportive program with multicomponent oral care strategies demonstrated positive effects on relieving xerostomia, increasing unstimulated saliva flow rate, and improving their oral health and HRQoL. These findings provide a basis for improvement in the management of xerostomia and oral health of Chinese patients with HNC through the integration of oral care in nursing.

Original papers

The following papers are enclosed as appendices.

Paper 1

Experiences of xerostomia after radiotherapy in patients with head and neck cancer: a qualitative study

Nan Jiang, Yue Zhao, Henrik Jansson, Xiaocen Chen & Jan Mårtensson. Journal of Clinical Nursing. 2018, 27(1-2): e100-e108.

Paper 2

Assessment of radiation-induced xerostomia: validation of the Chinese version of the xerostomia questionnaire in head and neck cancer patients

Nan Jiang, Siqi Wei, Yue Zhao, Henrik Jansson, Jan Mårtensson & Kristofer Årestedt. Cancer Nursing, 2019, 44 (2): e68-e75.

Paper 3

The effects of an integrated supportive program on xerostomia and salivary characteristics in patients with head and neck cancer undergoing radiotherapy: a randomized controlled trial. (Submitted)

Nan Jiang, Yue Zhao, Malin Stensson & Jan Mårtensson

Paper 4

The effects of an integrated supportive program on oral health and quality of life in patients with head and neck cancer undergoing radiotherapy: a randomized controlled trail. (Submitted)

Nan Jiang, Yue Zhao, Jan Mårtensson & Malin Stensson

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Abbreviations

CTCAE, Common Terminology Criteria for Adverse Events

CVI, Content validity index

DMFT, Decayed, missing, and filled teeth index

EORTC QLQ-H&N35, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head & Neck 35

FACT H&N, Functional Assessment Cancer Therapy-Head & Neck

GI, Gingival index

HNC, Head and neck cancer

HRQoL, Health-related quality of life

ICC, Intraclass correlation coefficient

KPS, Karnofsky performance scale

OHIP-14, Oral Health Impact Profile-14

PI, Plaque index

RT, Radiotherapy

SMT, Symptom management theory

XQ, Xerostomia Questionnaire

1. Introduction

Head and neck cancer (HNC) is a life-threatening disease with high incidence in many countries, including China. Radiotherapy (RT), which is considered as a standard treatment and often given in combination with surgery and chemotherapy, is effective in treating HNC (Sarris et al., 2013; Ratko et al., 2014). Xerostomia, described as the subjective feeling of oral dryness, is the main oral complication in patients with HNC undergoing RT (Dirix et al., 2006). Approximately 60%–90% of patients with HNC experience some degree of xerostomia months or years post-RT (Dirix et al., 2008; Jensen et al., 2010). Patients with xerostomia often experience hyposalivation (i.e., the objective finding of decreased salivary production), which can lead to functional oral disorders (Meurman & Grönroos, 2010; Sroussi et al., 2017). These problems ultimately affect their oral health and health-related quality of life (HRQoL) (Dirix et al., 2008; Almståhl et al., 2019; Bonzanini et al., 2020).

Several strategies have been used to manage xerostomia, including maintenance of oral hygiene care and use of refined radiation delivery techniques, salivary gland transfer, acupuncture, and pharmacotherapy (Chambers et al., 2004; Chambers et al., 2007); Nevertheless, not all patients have access to or benefit from these approaches owing to the high cost, short-term efficacy, specialized training needed for surgical procedure, drug interaction, etc. (Furness et al., 2013; Sood et al., 2014; Riley et al., 2017). Patients with xerostomia have described changes in the physical, psychological, and social aspects of food and the eating experience during and after RT (Ottosson et al., 2013; Ganzer, Rothpletz-Puglia, et al, 2015; Ganzer, Touger-Decker, et al., 2015). To our knowledge, no research has been conducted to describe the living experience of xerostomia from a patient perspective in China. Furthermore, no valid Chinese version of xerostomia assessment tool and intervention with multicomponent oral care have been used in irradiated patients with HNC. Thus, the overall aim of this thesis was to understand the living experience of radiation-induced xerostomia and to determine the effects of an oral care-based intervention in Chinese patients with HNC.

2. Background

2.1. Healthcare system in China

The healthcare system in China is a hospital-oriented service system. More than 90% of healthcare services are provided by public hospitals (Liu et al., 2017). These public hospitals are classified into primary, secondary, and tertiary levels based on the number of beds, professional healthcare force, diagnosis, treatment equipment, etc. (Zhang et al., 2017). A tertiary level hospital is the highest level of hospital in China, which has more than 500 beds, provides high-level specialized medical and health services to several regions, and performs tertiary education and scientific research tasks. Nearly all patients with HNC are treated with RT at tertiary oncology hospitals or tertiary general hospitals in China since there is no RT equipment in primary and secondary level hospitals. Patients with HNC experienced heavy financial burden since they had to pay for cancer treatment, medicine, dental treatment, and other related treatment (Jiang et al., 2020).

There are three major national health insurance systems in China, including medical insurance for urban workers, medical insurance for urban residents, and new rural cooperative medical care, which provide basic health insurance coverage for 95% of the whole population (Jin et al., 2016). The reimbursement rates for inpatient care range from 50% to 69% according to the resident's health insurance type (Jin et al., 2016; Munro et al., 2016). Apart from national health insurance, private health insurance plays an increasing role, important in filling the coverage gap and meeting the diverse health care needs of the population. It is estimated that approximately 6.9% of the Chinese population had private health insurance in 2013 (Center for Health Statistics and Information, National Health and Family Planning Commission, 2013). Although Chinese public health insurance schemes have gradually covered the majority of its population in rural and urban areas, the domestic migrants, the poor, and the vulnerable remained at the edge of the system due to the expensive cost for cancer treatment and the low insurance reimbursement rate (Jiang et al., 2020).

2.2. Head and neck cancer

HNC remains a major life-threatening disease. Approximately 300,000 people are newly diagnosed and 145,000 patients die from HNC annually worldwide (Torre et al., 2015). HNC is more prevalent in males and is observed in about 66%-90% of cases (Gao et al., 2009). The peak incidence of HNC occurs between the ages of 40 and 60 years old (Gao et al., 2009). The primary causes include tobacco and alcohol use and exposure to human papillomavirus and Epstein-Barr virus (Conway et al., 2018). Multidisciplinary approach in the treatment of HNC positively affects the survival (Lo Nigro et al., 2017).

2.2.1. Treatment options for HNC

RT alone, or in addition to surgery and chemotherapy, has an essential role in HNC treatment (Grégoire et al., 2010; D'cruz et al., 2013). For early-stage HNC, RT and surgery serve as standard treatments, achieving equally good long-term function, while for the locally advanced-stage, multidisciplinary approach with surgery followed by RT is required, with or without chemotherapy or concurrent chemoradiotherapy (Lo Nigro et al., 2017). The most common RT schedule for HNC is 2.0 Grey in a single fraction per day, five days per week, for six to seven weeks (Grégoire et al., 2010; D'cruz et al., 2013). Compared with conventional RT, the advanced radiation techniques, including three-dimensional conformal RT (intensity-modulated RT) allow precise delivery of radiation beam to the tumor while sparing and minimizing the radiation dose delivered to the surrounding organs (Mirestean et al., 2019). However, the normal tissues of these surrounding organs are very sensitive to radiation. There are many acute and late oral complications, including xerostomia, changes in saliva characteristics (i.e., salivary gland hyposalivation, decreased saliva pH, and low buffering capacity), and dental caries, which significantly affect the oral health and HRQoL (Dirix et al., 2008; Meurman & Grönroos, 2010; Almståhl et al., 2019; Bonzanini et al., 2020). Thus, managing these oral complications and ultimately improving the HRQoL have become a big challenge.

2.2.2. Routine care for patients with HNC receiving RT in China

Before the initation of RT for patients with HNC in China, patients are advised to visit a dentist to undergo dental examination. The infected teeth and periodontal disease are suggested to be treated to avoid future dental extraction and prevent osteoradionecrosis (Beech et al., 2014). Meanwhile, the ward nurses provide health education for patients regarding RT, common problems caused by radiation (i.e., mucositis, dermatitis, xerostomia, and dental caries), oral health education about management of these problems (i.e., oral hygiene instructions, pain care for mucositis, and skin care for dermatitis), and general health education (i.e., instructions for myelosuppression and dietary intake) (Feng, 2017). During RT, patients can seek help from physicians and nurses, especially for drugs for relief of dermatitis and pain caused by oral mucositis (Feng, 2017). After RT, patients are suggested to visit a physician regularly at the clinic to undergo re-examination for cancer recurrence.

Dental hygienists play a unique and important role in oral care. However, this profession has not yet been established in China (Liu, 2021). Thus, physicians, nurses, and dentist are responsible for oral problems of irradiated patients with HNC. Nurses in China only provide routine oral care for inpatients and routine telephone follow-up for discharged patients (Qian, 2012; Wang, 2016). However, patients rarely benefit from routine telephone follow-up due to poor communication and lack of targeted guidance (Wang, 2016). Due to the large number of patients followed up in the outpatient clinic and the short time for physicians to visit each patient, they may not prioritize the needs of patients for oral care and may rarely provide patients with information related to xerostomia. In addition, physicians and nurses have no direct communication and contact with dentists across cancer treatment (Yuan, 2015). If patients experience oral problems, they are advised to seek help from dentists in the dental hospital (Yuan, 2015). Thus, xerostomia and its related oral problems are not well resolved after patients discharge from the hospital.

2.3. Radiation-induced xerostomia

Radiation-induced xerostomia, which is the subjective feeling of oral dryness, is a common oral complication in patients with HNC during and post-RT. Nearly 40% of HNC survivors receiving intensity-modulated RT suffer from some degree of xerostomia (Vergeer et al., 2009). It is a permanent condition that seriously impairs the patient's well-being; however, the inconvenience decreases with time. Saliva becomes thick, sticky, and frothy, and saliva flow decreases after RT (Chambers et al., 2007). Generally, xerostomia is related to both altered saliva compositions and hyposalivation. Patients living with radiation-induced xerostomia experience decreased physical, social, and psychological aspects of the quality of life (Charalambous, 2014). To our knowledge, there has been no qualitative study regarding radiation-induced xerostomia in Chinese patients with HNC.

2.3.1. Xerostomia management strategies

Strategies used to manage radiation-induced xerostomia incorporate the application of salivary gland-sparing RT, surgical transfer of salivary glands, and administration of pharmacological and non-pharmacological interventions (Vissink et al., 2010; Furness et al, 2013; Sood et al., 2014; Riley, 2017). Intensity-modulated RT allows precise target determination and delineation, potentially minimizing the dose to salivary glands, and thereby reducing the incidence and severity of xerostomia and improving HRQoL (Li et al., 2012). However, reduction of radiation dose to the salivary glands might be difficult without compromising the treatment of the disease. Salivary gland transfer is a novel preventive approach for xerostomia (Jha et al., 2000). However, it is only practical for patients who intend to undergo postoperative RT (Jha et al., 2000). The main pharmacological interventions include cytoprotective agents, parasympathomimetic and parasympatholytic drugs, and saliva stimulants and substitutes. However, these interventions are somewhat limited owing to their high cost, short-term efficacy, drug interaction, and other side effects (Riley et al., 2017).

In China, it is popular to use Traditional Chinese Medicine (TCM) (i.e., Chinese herbal medicine, acupuncture, qigong, and gua sha) to treat radiation-induced xerostomia. Results from previous studies have shown that TCM

treatment during RT had positive effects in reducing the severity of xerostomia and improving salivary function (O'Sullivan & Higginson, 2010; Hsu et al., 2016; Rark et al., 2018; Wang et al., 2018; Lim et al., 2019). However, TCM treatment needs to be performed by certified professionals or in hospitals with qualifications for TCM. This hampers the application of TCM in routine nursing care since nurses need to acquire the qualifications of TCM or have rich knowledge and experiences on TCM (China Association of Chinese Medicine, 2016).

The non-pharmacological interventions to reduce xerostomia have been highlighted in previous studies (Ibayashi et al., 2008; Hakuta et al., 2009; Furness et al., 2013; Komulainen et al., 2015; Ohara et al., 2015). Application of oral care can reduce patients' oral dryness and increase saliva secretion in adults and elderly with xerostomia within the two-month to two-year follow-up period (López-Jornet et al., 2014; Komulainen et al., 2015; Ohara et al., 2015). Performing 3-month or 6-month oral functional exercise (i.e., facial and tongue muscle exercises and swallowing exercise) can relieve tongue dryness, increase salivary flow rate, and improve oral functions (Ibayashi et al., 2008; Hakuta et al., 2009; Ohara et al., 2015). Softly massaging the major salivary glands using fingers can increase blood flow in the surrounding areas of the salivary glands, alleviating oral dryness (Zelles et al., 1999; Weerapong et al., 2005). Along with the above measures, xerostomia can be alleviated though self-care strategies, including frequent sipping of water or sugarless drinks without caffeine, sucking on ice chips, often applying lonalin-based lip balm, consuming sugar-free chewing gum, sugar-free candy, and alcohol-free mouth rinse, using a humidifier at night, avoiding salty, sugary, or spicy foods and drinks, and quitting smoking habits (Edgar et al., 2012; Capaldi, 2018; Mark, 2019). However, to date, no integrated supportive programs, which combines the above strategies to determine its effects on xerostomia and HRQoL for patients with HNC undergoing RT, have been tested.

2.3.2. Xerostomia measurement

The available measurements for xerostomia include objective and subjective methods. Measurement of salivary flow rate and use of salivary gland imaging techniques are the common objective ways to assess xerostomia. However, the complexity in completing these objective assessments hampers its daily

use in clinical work. Observer-based measurements and patient self-reported measurements are the main subjective methods. Common Terminology Criteria for Adverse Events (CTCAE) (Department of Health and Human Services, 2017) and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer radiation morbidity scoring criteria (Cox et al., 1995) are based on physician observations, which permits possible influence from the examiner. Patient self-report evaluations based on specific questionnaires include the University of Washington Quality of Life questionnaire (Rogers et al., 2010) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head & Neck 35 (EORTC QLQ-H&N35) (Bjordal et al., 1999). However, the items on the xerostomia-related domain of these questionnaires are limited. Therefore, researchers developed and validated xerostomia-specific questionnaires, including the Groningen Radiotherapy-Induced Xerostomia Questionnaire (Beetz et al., 2010), Xerostomia Inventory (Putten et al., 2011), Xerostomia Questionnaire (XQ) by Eisbruch et al. (2001) and XQ by Dirix et al. (2008). However, no xerostomia-specific questionnaires have been validated in patients with HNC in Mainland China, which hampers the assessment and management of xerostomia in these patients.

2.4. Health-related quality of life

HRQoL pertains to a broad definition of the quality of life in clinical health research. It is defined as: *"A personal, evaluative statement summarizing the positivity or negativity of attributes that characterize one's psychological, physical, social, and spiritual well-being at a point in time when health, illness, and treatment conditions are relevant"* (Padilla et al., 1996). HRQoL in patients with HNC is a multi-dimensional concept based on the patient's own experiences, consisting of physical, functional, emotional, psychological, and social dimensions (List & Stracks, 2000). An increasing number of published studies have been conducted to explore how HNC and its treatment affect patients' HRQoL both physically and psychosocially (So et al., 2012; Loorents et al., 2016; Karimi et al., 2019). Results from these studies show an overall deterioration in patient's functional, emotional, and social dimensions of HRQoL, from the initiation until the end of RT. However, their global QoL gradually recovers between 3 and 6 months and reaches baseline levels at 12

months after treatment (So et al., 2012; Loorents et al., 2016; Bashir et al., 2020). However, a number of outstanding issues persist, resulting in the deterioration of physical functioning and symptoms of fatigue, pain, xerostomia, sticky saliva, speech, swallowing, and altered sense (So et al., 2012; Loorents et al., 2016; Bashir et al., 2020). Beyond the influence of clinical factors (i.e., site and stage of cancer and treatment modalities), the HRQoL is impacted by patients' demographic and socio-cultural characteristics (Sherman et al., 2005). Women are reported to have poorer quality of life outcomes than men (de Graeff et al., 2000; Howren et al., 2013). Younger patients have better physical functioning (de Graeff et al., 2000;) but poorer psychosocial aspects of HRQoL than the elderly (Bjordal et al., 2001). In terms of psychological variables, optimism is associated with better global quality of life and mental well-being (Llewellyn et al., 2007), while pessimism predicts worse physical and social well-being (Holloway et al., 2005). Furthermore, patients who have a stronger illness identity, more pronounced self-blame, or greater expectations that the illness will have a serious impact are more likely to experience poorer global quality of life at the two-year follow-up (Scharloo et al., 2010).

2.5. Oral health

Oral health is defined as *"a state of being free from chronic mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit an individual's capacity in biting, chewing, smiling, speaking, and psychosocial well-being"* (Petersen et al., 2003). Due to the complexity of oral health, a new definition with a wider perspective was created in 2016 by the Fédération Dentaire Internationale World Dental Federation. This states that *"Oral health is multifaceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow, and convey a range of emotions through facial expressions with confidence and without pain, discomfort, and disease of the craniofacial complex"* (Glick et al., 2016). This definition implies that oral health is a fundamental component of physical and mental well-being and an integral and essential part of general health and quality of life (Glick et al., 2016). The majority of patients with HNC often have suboptimal oral health before cancer

diagnosis (Lawrence et al., 2013). Their oral health status is further affected by prolonged oral complications post-cancer treatment.

Dental caries is "*the localized destruction of susceptible dental hard tissues by acidic by-products from bacterial fermentation of dietary carbohydrates*" (Fejerskov & Kidd, 2003). Dental caries is a common oral disease in irradiated patients with HNC (Palmier et al., 2018), which have profound negative effects on their oral health. Patient with HNC after RT often present a severe form of rapidly developing decay that results in loss of dentition (Deng et al., 2015). Saliva has essential functions in pH control, remineralization, antimicrobial, and tooth cleansing effects; therefore, it plays an important role in preventing dental caries (Dowd, 1999). It has also been found that there is an association between various components of saliva and dental caries (Hegde et al., 2019). Saliva helps in cleaning the accumulation of plaque and other debris on teeth and periodontal tissues, which can be beneficial in preventing gingivitis (Chambers et al., 2004). Gingivitis is a complex inflammatory disease which affect the tissues supporting the teeth - the periodontium (Wåhlin, 2017). Aside from the influence of hyposalivation and altered saliva composition, other associated factors of development and progression of dental caries and periodontal problems include increased carbohydrates or sugar consumption, use of tobacco and alcohol, and inappropriate exposure to fluorides and poor oral hygiene (Selwitz et al., 2007; Gomes-Silva et al., 2017; Madrid et al., 2017; Palmier et al., 2018). Therefore, management of these pathogenic factors becomes an essential part of oral care for patients with HNC.

2.6. Oral care

Oral care is required prior to, during, and after treatment to prevent and reduce the risk or severity of oral complications. Oral examination is advised before RT. However, nearly 66% of the Chinese patients with HNC do not undergo oral examination before RT (Luo et al, 2018). In addition, general preventive measures and necessary dental treatment pre- and post-cancer treatment are recommended to provide to ensure that oral problems are detected early and solved promptly (Tolentino et al., 2011; Kawashita et al., 2020). The general preventive measures include use of fluoride, treatment of active carious

lesions, repair of defective restorations, and supportive periodontal therapy (Tolentino et al., 2011; Kawashita et al., 2020). Furthermore, providing health education about potential oral complications, their prevention and/or amelioration, and necessary prophylactic information to patients is an integral part of oral care. It is also recommended to maintain good oral hygiene to minimize oral complications and provide greater comfort to patients. The strategies of oral hygiene include brushing teeth twice a day with fluoride toothpaste and daily interdental cleaning with floss (Capaldi, 2018; Mark, 2019). Previous studies also show that fluoride supplements support remineralization and prevent caries (Petersen, 2003; Jepsen et al., 2017) and diet modification (i.e., restriction of sugar consumption) is effective in preventing oral diseases (Petersen, 2003; Jepsen et al., 2017). Patients can implement most of the above oral hygiene strategies through self-care (Larson et al., 1998).

2.7. Self-care

Self-care is a complex and multidimensional topic receiving various amounts of attention. Several definitions of self-care have been proposed by researchers without reaching a clear consensus. In 2009, WHO claimed that self-care is *"the ability of individuals, families, and communities to promote health, prevent disease, and maintain health to cope with illness and disability with or without the support of a healthcare provider."* The concepts of self-care are impacted by different social, economic, and political factors and are implanted into different theoretical perspectives and paradigms. For patients with HNC treated with RT, oral hygiene strategies based on self-care do not only play an important role in preventing oral infections and relieving xerostomia, but also have positive effects in preventing dental caries and periodontitis. It is practical for patients to perform oral hygiene procedures as self-care. In addition, combining self-care into oral hygiene programs is beneficial in enhancing patient adherence to good oral hygiene habits for a longer time (Larson et al., 1998).

2.8. Health coaching

Health coaching is a patient-oriented and relationship-based process which focuses on increasing patient-intrinsic motivation and self-efficacy to promote behavior modifications and improve health status and medication adherence (Thomas et al., 2012). Health coaching effectively motivates behavior change through a structured, supportive partnership between the participant and the coach (Huffman, 2007). The coach helps the participant to clarify and set their goals and provide insight into goal achievement through inquiry, collaboration, and personal discovery (Huffman, 2007). It is often delivered via one-on-one face-to-face, telephone, or web-based coaching. Telephone coaching is considered the most popular method. It is recommended to use a combination of telephone and face-to-face coaching, as this is beneficial in obtaining good results (Kivelä et al., 2014). Health coaching emerged from the concept of motivational interviewing, which originated from Miller and Rollnick (1990). Motivational interviewing is a health coaching technique to activate patients' own motivations to explore and resolve ambivalence regarding behavior change (Rollnick et al., 2008). There are four guiding principles, including resisting the righting reflex, understanding and exploring the patient's own motivations, listening with empathy and empowering the patient, and encouraging hope and optimism (Rollnick et al., 2008). Motivational interviewing has been consistently demonstrated as causally and independently associated with positive behavioral outcomes regarding the prevention of dental caries and improvement of oral health and HRQoL (Gao et al., 2014).

3. Theoretical framework

3.1. Symptom management theory (SMT)

The original conceptual model of SMT was initially proposed in 1994 (Larson et al., 1994), and the updated version was published in 2001 (Dodd et al., 2001) and 2008 (Humphreys et al., 2008). In SMT, symptoms are viewed as subjective experiences reflecting changes in an individual's biopsychosocial function, sensation, or cognition. There are three essential concepts of SMT: symptom experience, symptom management strategies, and outcomes, which are nested within three domains of nursing science: person, environment, and health/illness (Figure 1).

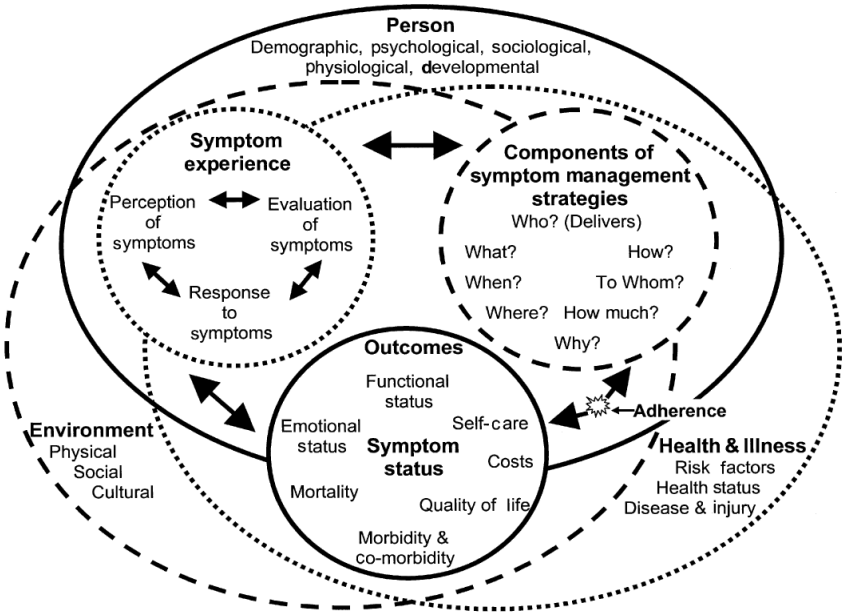

Figure 1. Revised Symptom Management Conceptual Model.

3.1.1. Symptom experience

Symptom experience is a dynamic interaction involving three components: the individual's perception, evaluation of the meaning of a symptom, and response to a symptom (Humphreys et al., 2008). The perception of symptom is viewed as an individual noticing a change from the way he/she usually feels or behaves. The evaluation of symptom is defined as the way people evaluate the characteristics of the symptoms by judgment of the severity, cause, treatability, and effects of symptoms in daily life. The response to symptoms refers to aspects of physiology, psychology, socio-culture, and behavior. Bi-directional relationships exist among these three components of symptom experience. When people notice the unusual sensation (perception), they evaluate the symptoms by assessing the characteristics of the symptom (evaluation) and proceed try to solve the problems using self-care strategies or effective interventions (response). These relationships are conceived to be repetitive and may occur simultaneously (Humphreys et al, 2008).

3.1.2. Symptom management strategies

This dimension aims to avert, delay, or minimize the negative outcome by biomedical, professional, and self-care strategies (Larson et al., 1994; Dodd et al., 2001; Humphreys et al., 2008). It includes *what* (the nature of the strategy), *where* (where the intervention strategy is used or tested), *why* (why the intervention is affected), *how much* (dose of intervention), *to whom* (recipient of intervention), and *how* (method of delivery), which serve as a guide for the clinician or investigator in selecting the appropriate intervention strategies (Dodd et al., 2001). Interventions are aimed at achieving one or more desired outcomes by influencing one or more of the components in the dimension of symptom experience. To fully realize a successful symptom management, it is important to form a patient-family-clinician partnership (Dodd et al., 2001; Humphreys et al., 2008).

3.1.3. Outcomes

In SMT, outcomes are viewed through eight multidimensional indicators: symptom status, functional status, emotional status, self-care, costs, morbidity & comorbidity, mortality, and quality of life (Dodd et al., 2001). Although no

relationships are specified within this dimension, the authors posit that each of the identified outcomes may be related to the symptom status and to each other (Dodd et al, 2001). Adherence is a critical factor in the relationship between symptom management strategies and outcomes, but patients may not always comply. When nonadherence occurs (i.e., intervention is too demanding or is not applied consistently), management of symptoms may be problematic (Dodd et al, 2001).

3.1.4. Domains of nursing science

The concept of person, health/illness, and environment, considered as the main domains of nursing science, were added in the updated model in 2001 and influenced all three dimensions of SMT (Dodd et al, 2001). The domain of person encompasses the demographic, physiological, psychological, sociological, and developmental factors (Dodd et al, 2001). It may be expanded or contracted based on an individual's symptom(s) (Dodd et al, 2001). The health and illness domain consists of variables that are unique to an individual's health or illness state (Dodd et al, 2001). The domain of environment is viewed as the aggregate of condition or the context where a symptom occurs (Dodd et al, 2001). It encompasses the physical environment (i.e., home, work, and hospital), social environment (i.e., social network or interpersonal relationships), and cultural environment (i.e., beliefs, values, and practices) (Dodd et al, 2001).

SMT, a middle range theory for nursing, illustrates a multidimensional process of symptom management. To date, SMT has been proved to be a useful framework for research in patients with cancer (Linder, 2010; Mathew et al., 2021). Findings gained from previous studies guided by SMT add a deeper understanding of the process of symptom management, which prompt development of testable interventions (Linder, 2010; Mathew et al., 2021).

4. Rationale for the thesis

Xerostomia, combined with hyposalivation, low saliva pH, and decreased buffering capacity, can increase the risk of oral diseases and affect oral health in patients with HNC undergoing RT. Oral health is an essential part of general health; therefore patients with xerostomia often experience decreased HRQoL. It is important to describe the experience of xerostomia from a patient's perspective since this can provide an insight regarding its impact on the patient's physical and psychosocial life. The experience of xerostomia has been described by patients who have a severe grade, but not from those with slight or mild xerostomia. Furthermore, there is a lack of knowledge regarding how Chinese patients with HNC experience xerostomia. To identfy xerostomia and the severity in individuals with HNC, various self-reported xerostomia-specific instruments have been developed. Despite Chinese being a common language, to our knowledge, there is no validated Chinese version of the xerostomia questionnaire (XQ). As translations and cultural adoptions of self-reported instruments can change the measurement properties, there is a need to test the psychometric properties of the Chinese version of the XQ. Non-pharmacological interventions can provide positive effects on relieving xerostomia and improving oral health in patients with HNC undergoing RT. However, no intervention combined with multicomponent oral care strategies has been designed to determine its effect on xerostomia, oral health, and HRQoL for patients with HNC.

5. Aims of the thesis

The overall aim of this thesis was to understand the living experience of radiation-induced xerostomia and to determine the effects of a multiple component oral care-based intervention in Chinese patients with HNC.

The specific aims of the four studies were as follows:

To describe the experiences of radiation-induced xerostomia in patients with HNC (I).

To evaluate the content validity and psychometric properties of XQ in Chinese patients with HNC undergoing RT (II).

To determine the effects of an integrated supportive program on xerostomia and saliva characteristics in patients with HNC within the 12-month follow-up post-RT (III).

To determine the effects of an integrated supportive program on oral health in patients with HNC within the 12-month follow-up post-RT (IV).

6. Methods

6.1. Study design

This thesis makes use of an explorative and interventional approach, including qualitative (I) and quantitative research methods (II-IV). Table 1 shows the overview of the methodological procedures of the four studies.

Table 1 Overview of the methodological procedures

Study	*Design*	*Participants*	*Data collection*	*Data analysis*
I	Inductive, descriptive	20 participants with HNC who experienced xerostomia	Individual semi-structured interviews	Qualitative, content analysis
II	Cross-sectional	80 participants with HNC who received RT	Questionnaire package	Descriptive, inferential statistics
III & IV	Prospective, randomized controlled trial	79 participants with HNC who received RT	Questionnaire package, saliva tests, and dental clinical examination	Descriptive, inferential statistics

Abbreviation: HNC, head and neck cancer; RT, radiotherapy

6.2. Participants

For study I, a purposive sampling method was used for the participant's age, sex, site and stage of tumor, severity of xerostomia, phase (i.e., acute vs. late), and treatment modalities by physicians and ward nurse managers between May 2015 and September 2015 from one tertiary hospital in Tianjin, China. The inclusion criteria were as follows: patients older than 18 years; histologically diagnosed with HNC; and had received RT. Patients with dementia or difficulty understanding Chinese were excluded.

Table 2 Demographic and clinical variables of 20 patients

No	*Sex*	*Age*	*Tumor site*	*Tumor stage*[a]	*Grade*[b]	*Phase*[c]	*Treatment*
1	Male	42	Nasopharynx	Ⅱ	1	Acute	CT+RT
2	Female	71	Nasopharynx	Ⅲ	2	Late	RT
3	Female	80	Nasopharynx	Ⅱ	2	Late	RT
4	Male	34	Nasopharynx	Ⅱ	3	Acute	CRT
5	Female	67	Parotid gland	Ⅱ	2	Late	Surgery+ CT+RT
6	Male	50	Nasopharynx	Ⅲ	1	Late	CT+RT
7	Male	66	Nasopharynx	Ⅲ	2	Late	CT+RT
8	Male	31	Nasopharynx	Ⅲ	2	Late	CT+RT
9	Male	50	Hypopharynx	Ⅱ	1	Late	RT
10	Male	58	Nasopharynx	Ⅲ	1	Late	RT
11	Male	50	Nasopharynx	Ⅲ	2	Acute	CT+RT
12	Female	54	Nasopharynx	Ⅲ	1	Late	CRT
13	Male	43	Nasopharynx	Ⅳa	1	Late	CRT
14	Male	29	Nasopharynx	Ⅳa	2	Acute	CRT
15	Male	63	Parotid gland	Ⅱ	3	Late	RT
16	Male	62	Larynx	Ⅲ	1	Acute	RT+ Surgery
17	Male	60	Parotid gland	Ⅱ	3	Late	Surgery+ CT+RT
18	Female	64	Larynx	Ⅱ	1	Late	RT+ Surgery
19	Female	45	Nasopharynx	Ⅲ	1	Acute	CT+RT
20	Female	49	Nasopharynx	Ⅳ	1	Acute	CRT

Abbreviation: CT, chemotherapy; CRT, concurrent chemoradiotherapy; CT+RT, induction chemotherapy and radiotherapy; RT, radiotherapy. [a] Based on tumor, node, and metastasis staging system (TNM); [b] Based on Radiation Therapy Oncology Group /European Organization for Research and Treatment of Cancer radiation morbidity scoring criteria of xerostomia grading; [c] Acute: within 3 months post-RT; Late: after 3 months post-RT.

A total of 21 patients were invited to participate, and only one patient refused. The list of demographic and clinical variables is shown in Table 2.

For study II, 82 patients with HNC were invited by outpatient nurses to participate between May 2016 and April 2017 at a tertiary hospital in Tianjin, China. The inclusion criteria were as follows: 18 years of age or older; histological diagnosis of HNC; received RT; and able to read and speak Mandarin Chinese. Patients were excluded if they had cognitive dysfunction, psychiatric disorders, or Sjögren syndrome. Two patients refused to participate, and 80 patients were recruited into this study.

For study III and IV, a total of 176 patients with HNC were assessed by ward nurses for eligibility before the initiation of RT at a tertiary hospital in Tianjin, China between February 2019 and September 2020. The inclusion criteria were as follows: a histological diagnosis of HNC; age of 18 years or older; Karnofsky Performance Scale Index (KPS) of 80-100; primarily received definitive RT or surgery with postoperative RT for a curative approach (dose of $\geq$ 60 grey) with concurrent or induction chemotherapy or both; and the ability to attend regular re-examination during the 12-month follow-up. The exclusion criteria were as follows: patients with total edentulism; other cancers; other causes of xerostomia (i.e., Sjögren syndrome, diabetes mellitus, use of drugs that could interfere with salivary flow, removed bilateral salivary glands); or severe cognitive impairment (i.e., dementia) or psychiatric disorders that interfered with the ability to complete the questionnaire package.

Since no previous study has reported on the effect of oral care-based intervention on xerostomia and oral health, the sample size was calculated based on a pre-test study using a power analysis. Fifteen participants in each group were included in the pre-test. The sample size was calculated based on the XQ score at the 3-month follow-up, with a mean of 32.67 (standard deviation [SD] 5.55) and 36.41 (4.86) for the intervention group and control group, respectively, for study III, and the Oral Health Impact Profile (OHIP-14) score, with a mean of 23.40 (6.96) and 28.00 (6.22) for the intervention group and control group, respectively, for study IV. A sample size of 34 participants per group was required to detect significant inter-group differences at 80% power and at 5% significance level. Considering the

possible loss during follow-up, ten patients were added in each group. A simple online binomial randomization program was used by a statistician to assign participants to either an intervention group or a control group, stratified by sex, site, and stage of tumour. In total, 92 participants were recruited at baseline and thirteen (14.1%) participants dropped out after the 12-month follow-up.

6.3. Procedure

Participants in the intervention group received an integrated supportive program and usual care (Figure. 2), while participants in the control group received usual care only.

6.3.1. The integrated supportive program (III & IV)

The integrated supportive program was developed based on evidence from literature review and the research team's experience (Ohara et al., 2005; Ibayashi et al., 2008; Hakuta et al., 2009; Edgar et al., 2012; López-Jornet et al., 2014; Komulainen et al., 2015; Sakayori et al., 2016; Okuma et al., 2017; Miyoshi et al., 2019). The integrated supportive program includes three steps (Figure 2), with a combination of face-to-face health education and coaching sections during the 12-month follow-up post-RT. This program was conducted by one researcher (NJ, the first author and a trained coach).

Step 1: Face-to-face health education

A researcher (NJ) firstly introduced the cause of xerostomia and saliva alteration and their negative effects on oral health and HRQoL to the participants. She then provided the face-to-face education at the ward. It included four sessions: In the first session, the importance and benefit of having a good oral hygiene were introduced, and oral hygiene instructions were provided to the participants. In the second session, oral self-care strategies were given. In the third session, participants were taught how to do facial and tongue muscle exercises and guided on how to excute the exercises properly. The exercises were suggested to be performed three times a day after meals, repeating each step 10 times. In the fouth session, the salivary gland massage method was shown, and the participants practiced performing the

massage. This was suggested to be done three times a day after meals, repeating each step 10 times. A handbook on the integrated supportive program and a five-minute intructional video about the modified Bass tooth brushing technique, oral muscle exercises, and salivary gland massage were also provided. Patients were encouraged to discuss the involvement of their own care strategies with the researcher. The average time of the face-to-face education was around 20–25 minutes.

Step 2: Face-to-face coaching

Face-to-face coaching was conducted by a researcher (NJ) at the outpatient department at 1-month post-RT when patients first visited the hospital for follow-up after cancer treatment. The coaching started with listening to the participant's experience and assessing the adherence to the integrated supportive program over the past month using a self-designed adherence questionnaire. The researcher retrieved the patient's history by asking open questions, i.e., what has been your experience living with xerostomia? If poor adherence was identified, the researcher discussed the possible issues of non-adherence and the impact of adherence, reflected on possible reasons and barriers, and provided help to solve problems. Questions (i.e., What difficulties did you encounter upon performing the strategies that resulted in low adherence? What else are you capable of doing?) were asked to help the researcher collaboratively work with patients and to revise the plan and proceed with short-term realistic goals. The average time consumed was approximately 15–20 minutes.

Step 3: Telephone coaching

Telephone coaching protocols were performed by a researcher (NJ) at 2-, 3-, 6-, and 9-months post-RT with the same aim as that of face-to face coaching. The level of adherence to the integrated supportive program over the past month was assessed. A motivational interview was conducted to address the difficulties encountered during doing the integrated supportive program. The basic principles of motivational interviewing were as follows: expressing empathy, avoiding argument, supporting self-efficacy, rolling with resistance, and managing discrepancy. If the goals were not being met, the telephone coach and participants would modify the goals together to be more realistic

after addressing problems and identifying potential solutions. If the goals were being met, the telephone coach motivated the participant to maintain and sometimes even set higher goals. The coach kept track of the progress regarding the participant's goals through subsequent telephone coaching sessions. Each telephone coaching lasted for approximately 15–20 minutes.

STEP 1 Face-to-face education

- **Section 1**: **Oral hygiene instruction** Information about the importance of oral hygiene; Oral hygiene advises (i.e., daily brush teeth after meal by using modified Bass tooth brushing technique).
- **Section 2**: **Self-care instruction** Smoking/drinking alcohol cessation; Use of mouth-wetting agents, sugar-free chewing gum, sucking tablets; Frequently sip water or fluid; Intake adequate amount of water/fluid, fluid food or food with fluid; Decrease the frequency of sugar-use; Avoid irritating agents; Use of air humidifier.
- **Section 3**: **Facial and tongue muscle exercise** (1) Facial muscle: Breathe deeply, tightly close eyes and pull lips to both sides of the face (smile); Fully open eyes and mouth; Tightly close mouth, fill the mouth with air, and move the air in mouth right and left; (2) Tongue muscle: Extend tongue out far and retract; Hold tongue out as far as possible, move it left and right, and move it up and down to lick nose and chin; Turn tongue to lick around mouth; Push upper and lower lips with tongue; Alternately push the left and right cheeks with tongue.
- **Session 4**: **Salivary gland massage** (video) Check the position of major salivary glands and massage the glands softly with fingers.

STEP 2 Face-to-face coaching

- Listen to participants experience (retrieved the patient's story by asking open questions; i.e., what has been your experience living with xerostomia?)
- Assess the adherence by questionnaire
- Explore the possible issues that influence adherence and discuss solutions (What's your feeling to do XXX i.e., facial and mouth muscle exercises/salivary gland massage…? If I heard you correctly, this is what I think you are saying XXX; Given what you said, you might feel XXX; You are having trouble with XXX)
- Discuss possible reason, barriers and solution (What difficulties did you upon performing the strategies that resulted in low adherence? What else are you capable of doing?)
- Discuss health goals and revise plan

STEP 3 Telephone coaching

- Listen to participant's experience
- Assess the adherence
- Explore the possible reasons, barriers and solution
- Health goals discussion and set a revised plan

Figure 2. Contents of the integrated supportive program

6.3.2. Usual care

The usual care for participants at baseline included a 10–15-minute face-to-face group-based health education conducted by a ward nurse. The education included information about oral hygiene instructions: brushing teeth using toothpaste and soft hair toothbrush after meals, replacing toothbrush monthly, immersing dentures in antimicrobial solution for 10 minutes after being worn, ceasing consumption of cigarette and alcohol, avoiding irritating food, and gargling with lidocaine to relieve pain caused by mucositis.

6.4. Data collection

For study I, face-to-face, semi-structured interviews were performed by the first author (NJ) based on an interview guide in a room adjacent to the outpatient clinic, following a visit to a physician. The interview guide was developed according to five holistic dimensions: biophysical, socio-cultural, emotional, intellectual, and spiritual-existential (Sarvimäki & Stenbock-Hult, 1992). The reason for choosing the holistic dimensions as a guide was the importance of seeing a patient as a person who needs to be taken care of wholly and not just their disease, injury, or functional impairment.

The interview guide includes six questions: What is it like living with xerostomia in your daily life? How does xerostomia affect your physical life? How does xerostomia affect your emotional life? How does xerostomia affect your social life? How do you perceive the information about xerostomia? What is your outlook on the future considering your xerostomia? Follow-up questions (i.e., How do you mean? Can you explain that further?) were asked to help participants articulate their experience. Two pilot interviews were conducted to test the interview guide. There were no important changes in the interview guide; therefore, these two pilot interviews were included in the data analysis. All interviews were audiotaped and transcribed verbatim. Next, a bilingual researcher (a native Chinese and fluent with English) translated the interviews from Mandarin to English, and two bilingual team researchers (native Chinese and fluent with English) checked the translation accuracy. The duration of the interviews varied between 22 to 50 minutes.

For study II, data collection was conducted by a PhD student using a questionnaire package, including the Chinese version of the XQ, the EORTC QLQ-H&N35 (Yang et al., 2012). Approximately two weeks after the first administration, 40 patients were asked to fill out the Chinese version of the XQ for a second time to evaluate the test-retest reliability.

For studies III and IV, data collection was performed by a PhD student (who did not belong to the research group). Patients answered the questionnaires, including the Chinese version of XQ, WHO Oral Health Questionnaire for Adults (World Health Organization, 2013), OHIP-14 (Li et al., 2014), and Functional Assessment Cancer Therapy-Head & Neck (FACT H&N) (Meng et al., 2010) at baseline, at the end of RT, and at 3- and 12-month post-RT. Saliva test was conducted by a PhD student (the same student as in the questionnaire data collection) at baseline and after 3 and 12 months. Dental examination was performed by two trained and calibrated dental students at baseline and after 12 months. The adherence to the integrated supportive program was assessed by the researcher (N.J) using a self-designed questionnaire with 15 questions at the outpatient department during the 9-month follow-up (Figure 3). The questionnaire data collection, saliva test, and dental examination were conducted in a single-blind method, which implied that the PhD student and dental students were not informed whether the patient belonged to the control group or intervention group.

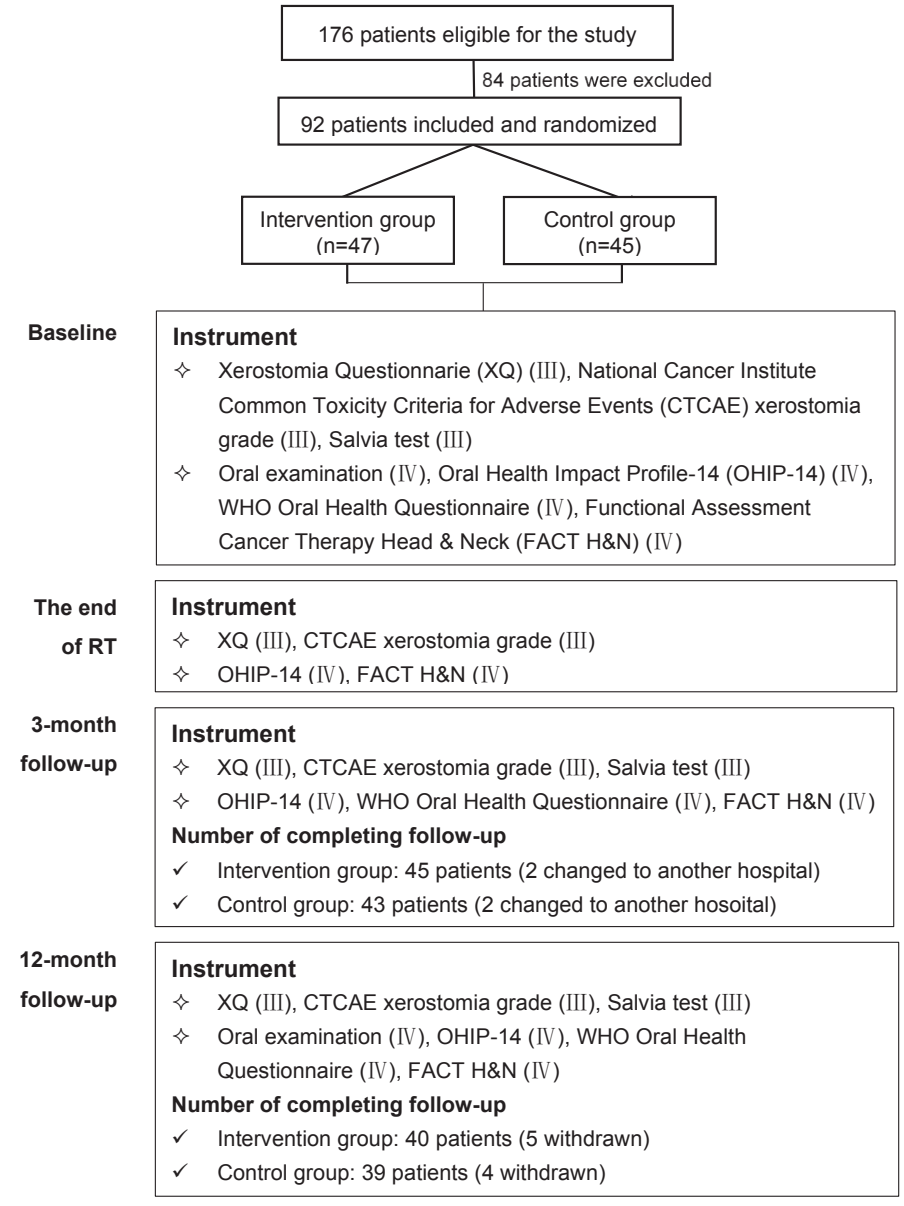

Figure 3. Flow chart describing data collection of study Ⅲ and Ⅳ.

6.4.1. Instruments (II-IV)

Demographic and clinical questionnaire (II-IV). Questions were asked regarding the marital status, living arrangements, current smoking status, employment status, comorbidities, etc. The clinical and pathological data, i.e., age, sex, site and stage of tumor, and treatment modalities, were obtained from the medical records.

The Chinese version of XQ (II, III). The XQ developed by Eisbruch et al. is an eight-item English instrument for patients with HNC to measure xerostomia (Eisbruch et al., 2001). Four items are about mouth dryness while chewing or eating and the other four items are about mouth dryness while not chewing or eating. Each question is rated on a numeric rating scale from 0 to 10. The total XQ score is calculated by the sum of the eight questions and multiplied by 1.25 to obtain a final summary score (0-100). Patients with higher scores represent those experiencing greater severity of oral dryness or discomfort. The XQ has shown good psychometric properties in different language versions.

The original version of XQ was translated into Chinese in accordance with the guidelines proposed by Guillemin et al. (1993) after acquiring permission from its developer. Two independent native Chinese speakers fluent in English were invited as bilingual translators to perform the primary forward translation. Subsequently, the translation was reviewed and revised by an oncology nurse and a radiation physician to achieve a good consensus on a single Chinese version. The back translation was performed by two other independent native English speakers proficient in Chinese who were unfamiliar with the original version of XQ. The research group (N.J. and S.W.) then compared the back-translated English version with the original XQ and revised the minor discrepancies based on consensus.

To test whether the instructions, items, and response options were relevant, clear, unambiguous, and easy to complete, cognitive interviews were conducted at an outpatient department on patients who experienced xerostomia. Cognitive interviews can enhance instrument content validity and reliability by assessing the relevance and clarifying the items for the respondents (Knafl et al, 2007). Cognitive interviews have multiple forms,

including verbal probing and thinking aloud, and these two forms can be used alone or combination (Collins et al, 2003). When performing verbal probing, to identify ambiguous or poorly worded questions, respondents were asked to verbalize their interpretation of the items and comment on the wording, which allows understanding of the questionnaire from the respondents' perspective rather than that of the researchers their response (Drennan et al, 2003; Knafl et al, 2007). Verbal probing can further clarify and refine questionnaire items (Knafl et al., 2017). When thinking aloud, respondents are asked to verbalize what they are thinking as they respond to each item in order to let investigators elicit data on the respondents' thought process regarding their response to items and gain useful insights into the respondents' decisions associated with what constitute an appropriate response (Knafl et al, 2007).

A total of 10 participants were invited to participate in a cognitive interview. They were asked to read the instructions and all the questions of the XQ and to fill out the instrument in a quiet place without family members. After completing the XQ, an interview based on the Participant View Form was conducted to evaluate the Chinese version of the XQ. The Participant Interview Form includes questions about the location and date of the test, participants' basic information (i.e., sex, age), and questions about whether the instruction, items, and response options were difficult to understand, relevant, clear, or unambiguous. The query regarding items that were difficult to understand, relevant, clear, or unambiguous, and the reason why patients found them so, as well as other suggestions for a better way to phrase these questions, were all gathered. The cognitive interview took approximately 20-25 minutes. Five patients did not understand the reference for the word "liquids" in items 7 and 8; therefore, modifications were made and added in items 7 and 8 as follows: "the examples of liquids, i.e., water, beverage, or soup."

EORTC QLQ-H&N35 (II) as a cancer-specific questionnaire is widely used to assess HRQoL for patients with HNC (Bjordal et al., 1999). The Chinese version of EORTC QLQ-H&N35, validated by Yang et al (2012), has good psychometric properties and has been used in Chinese patients with HNC. It consists of seven multiple-item scales and 11 single-item scales. The Head and Neck Swallowing Scale, Head and Neck Sticky Saliva Scale, and Head and Neck Dry Mouth Scale were used to measure swallowing, sticky saliva,

and dry mouth, respectively. The score of these three subscales ranged from 0 to 100, and high scores indicate a high burden of symptoms (Yang et al., 2012).

OHIP-14 (IV) is a commonly used international generic oral health-related quality of life (OHRQoL) instrument (Slade, 1997). It contains seven dimensions including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap (Slade, 1997). All items are answered on a 5-point Likert scale (0 represents never; 4 represents very often). The Chinese version of OHIP-14 has good psychometric properties (Li et al., 2014). The total OHIP-14 score is based on the summation of scores of all the responses, with a range from 0 to 56. A higher total OHIP-14 score represents the higher overall burden of oral problems.

FACT H&N (IV) is a multidimensional patient report outcome instrument designed for the assessment of functional performance status in patients with HNC and has been extensively used in Radiation Therapy Oncology Group trials (List et al, 1996). It includes the FACT-General scale, which contains 27 items encompassing four subscales: Physical Well-being, Social/Family Well-being, Functional Well-being, and Emotional Well-being. There is also a HNC Subscale specific for HNC signs and symptoms (11 questions). All items are answered on a 5-point Likert scale (0 represents not at all; 4 represents very much). A higher score indicates a better quality of life on all subscales and total scores (List et al, 1996). According to the FACT H&N scoring guidelines, items with negatively worded responses need to be reversed. The Chinese version of the FACT-H&N with good psychometric properties has been proven to be reliable, valid, and sensitive to the differences in functioning in patients with HNC (Meng et al, 2010).

WHO Oral Health Questionnaire for Adults (IV) is one of the instruments for basic oral health surveys which can provide a good basis to assess adults' oral health status (World Health Organization, 2013). This questionnaire provides reliable information about the oral health status and risk to oral health. It has been used in a range of countries across the world (World Health Organization, 2013). The Chinese version of WHO Oral Health Questionnaire

for Adults has been validated in 2017 and has been proven to be reliable for the Chinese population (World Health Organization, 2017).

Adherence Questionnaire (III & IV) was developed by the research team based on the content of the integrated supportive program. It contained 15 questions. The adherence questionnaire was filled in by the participants of the intervention group at the outpatient department during the 1-month face-to-face coaching. A researcher (NJ) assessed the adherence to the integrated supportive program using this questionnaire through telephone interviews at 2-, 3-, 6-, and 9-month coaching sessions.

6.4.2. Physician-based assessment criterion (III & IV)

KPS (Ⅲ & Ⅳ) is a measure of functional status that allows patients to be classified according to their functional impairment. KPS has been widely used as the gold standard tool for evaluating the performance status in oncology (Mor et al., 1984). Eleven qualifying items were measured, ranging from a score of 0 for death to 100 for normal function, with no complaints and no evidence of disease (Mor et al., 1984). The higher scores signified better functional status.

CTCAE v5.0 (III), a criterion for standardized classification of adverse effects in cancer treatment, is widely used in the HNC population (Department of Health and Human Services 2017). It consists of three grades: Grade 1, symptomatic (i.e., dry or thick saliva) without significant dietary alteration; Grade 2, moderate symptoms, oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); and Grade 3, inability to adequately aliment orally, tube feeding or total parental nutrition indicated.

6.4.3. Measurement (III & IV)

Saliva characteristics test (III)

Unstimulated saliva flow rate, saliva pH, and buffering capacity of unstimulated saliva were tested. A PhD student conducted the saliva test between 8 AM and 11 AM. Patients were instructed not to eat, drink, or brush

their teeth for at least two hours before saliva collection. Conscious movements of the oral musculature (i.e., sucking or swallowing) were not allowed during collection. Patients were invited to sit down and asked to swallow residual saliva present in the mouth. The unstimulated whole saliva samples were then collected for 5 min, and the secretion rate was calculated in ml/min. For patients with low salivary secretion rate, the unstimulated secretion was measured for 15 min. A normal range of the unstimulated saliva flow rate is considered to be at 0.3 ml/min to 0.4 ml/min, while a very low range is considered to be less than 0.1 ml/min (Edgar et al., 2012). The pH and buffer capacity of unstimulated saliva was performed according to the manufacturer's instructions (Shenzhen Kang Sheng Bao Bio-technology Co. LTD, China) immediately after saliva collection and judged by the color of the test strip. The pH values of 5.0 to 5.8, 6.0 to 6.6, and 6.8 to 7.8 indicate highly acidic, moderately acidic, and healthy saliva, respectively. The buffering capacity with a range of 0 to 5, 6 to 9, and 10 to 12 represent very low, low, and normal/high capacity, respectively.

Oral examination

Dental caries (IV) Two dental students, who have been trained and calibrated, conducted the clinical dental examination using a mirror and probe under optimal light condition in the ward at baseline and after 12 months. A dentist, serving as a standard examiner, provided a theoretical and clinical training for these two students before performing the examination. Duplicated examinations were conducted in three participants to compare the findings of the two students. The dentist reviewed the examination results of caries and periodontal conditions, and the results were used to calculate a Kappa value. The mean Kappa values were higher than 0.85 for the caries examination and higher than 0.80 for the periodontal examination. The two dental students were blinded to which group the individuals belonged to. All the teeth except for the third molars were registered using the Decayed, Missing, and Filling Teeth (DMFT) index.

Gingival and dental plaque (IV) Gingival condition and plaque amount were measured at the mesiobuccal, buccal, distobuccal, and lingual surfaces of six selected teeth (Sohn et al., 2021). The gingival index (GI) (Löe & Silness, 1963) and plaque index (PI) (Silness & Löe, 1964) are scored on a numeric

scale from 0 to 3; a higher score indicates poorer status. The gingival index (GI) (Löe & Silness, 1963) is used as follows: 0 represents healthy gingiva; 1 represents mild inflammation, slight change in color, mild edema, and no bleeding on probing; 2 represents moderate inflammation, edema with mild redness, and bleeding on probing; and 3 represents severe inflammation and edema, marked redness, ulceration, and a spontaneous bleeding tendency (Löe & Silness, 1963). Plaque index (PI) is scored as follows: 0, no plaque; 1, a film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen in situ only after application of the disclosing solution or using the probe on the tooth surface; 2, moderate accumulation of soft deposits within the gingival pocket or the tooth and gingival margin which can be seen with the naked eye; and 3, abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin (Silness & Löe, 1964).

6.5. Data analysis

For study I, the transcripts were analyzed using a qualitative content analysis (Graneheim & Lundman, 2004), where meaning units, condensed meaning units, codes, subcategories, and categories were identified. First, researchers carefully read the transcripts several times to get a sense of the whole data. Second, the text was divided into meaning units, which were condensed and labeled with a code according to the content. Finally, 18 subcategories were identified through comparing similarities and differences among various codes. Subcategories that were deemed to be related were abstracted, grouped, and constituted a total of five categories. The meaning underlying the categories ultimately formed a theme, which constituted the latent content (Folke et al., 2009). The results were illustrated by quotations for each subcategory.

For study II, the classical test theory was used to do psychometric evaluation of the XQ. Data completeness, item and scale score distributions, and ceiling/floor effects were evaluated using descriptive statistics. Data completeness was evaluated by calculating the percentage of the missing data of the total scores and each item among responders; the acceptable percentage should be less than 10% among responders (Hagell et al., 2017). Ceiling/floor effects are the percentages of people with the highest (ceiling) and lowest

(floor) possible scores, and the acceptable value is up to 15% or 20% (Hagell et al., 2017). Skewness and kurtosis statistics were calculated to explore the univariate normality of the items of the XQ. A normal distribution was supported by a skewness close to 0 and kurtosis close to 3 (Kirkwood & Sterne, 2003). The interitem and item-total correlations, based on the Pearson correlation coefficient, were used to evaluate homogeneity. Ideally, the mean interitem correlation should range from 0.2 to 0.4, (Cohen & Swerdlik, 2005), and the total correlations should range from 0.3 to 0.7 (Ware et al., 1980). The exploratory factor analysis, with principal components as the extraction method, was used to evaluate factorial validity. In the first step, the Bartlett's test of sphericity and Kaiser-Meyer-Olkin test were used to justify the factor analysis (Bartlett, 1950). Bartlett's test should be significant, and the Kaiser-Meyer-Olkin should exceed a value of 0.6 (Bartlett, 1950; Polit & Beck, 2006). Horn's parallel analysis, based on the 95th percentile and 1000 iterations, was used to decide the number of extracted factors (Glorfeld, 1995).

Internal consistency was evaluated by Cronbach's α and Cronbach's α if item deleted. When the value of Cronbach's α was above 0.70, the internal consistency of the Chinese version of the XQ was acceptable (Bland & Altman, 1997). According to results from previous studies (Beetz et al., 2010; Pellegrino et al., 2015), the criterion-related validity was evaluated by the Head and Neck Dry Mouth Scale, Head and Neck Sticky Saliva Scale, and Head and Neck Swallowing Scale of the EORTC QLQ-H&N35. For this purpose, the Pearson correlation coefficients were calculated between the XQ and the Head and Neck Sticky Saliva Scale, Head and Neck Dry Mouth Scale, and Head and Neck Swallowing Scale. We hypothesized that these scales would have moderate to strong correlations with the Chinese version of the XQ since they measure similar aspects of the same concept. Test-retest reliability was measured by the intraclass correlation coefficient (ICC; 2-way random-effects model of average measure). When ICC is above 0.75, the test-retest reliability is excellent (Rosner, 1995). $P<0.05$ was considered to be statistically significant. Stata 15.1 (StataCorp LLC, College Station, Texas) and SPSS statistics 22.0 (IBM Corp, Armonk, New York) were used to carry out statistical analyses.

For study III and IV, the demographic and clinical characteristics were reported as number, percent, means, and SD. The student's t-test and Chi-

square test/ Fisher's exact test were used to compare baseline data between the two groups (intervention and control). Repeated-measures analysis of variance was performed to compare differences in xerostomia, OHIP-14, and FACT H&N between the groups over time, and Chi-square test was used to compare differences of the CTCAE xerostomia grade between the groups. The Mann-Whitney U test was used to compare differences in saliva characteristics, DMFT, PI, and GI between the groups. $P<0.05$ was considered to be statistically significant. SPSS 22.0 (IBM Corp, Armonk, New York) statistical analysis software package was used to analyze the data.

6.6. Ethical considerations

This thesis was approved by the Ethics Committee of Tianjin Medical University (TMUHMEC 2015008) and adhered to the principles of the Declaration of Helsinki (World Medical Association, 2013). Ethical consideration of all participants was maintained throughout the research, including respect for autonomy, beneficence, non-maleficence, and justice (Buchanan, 2006)

Autonomy is considered to be related with an individual's ability to self-determination (Thompson et al., 2006). All the participants were given a written and verbal explanation regarding the purpose and procedure of the study. They were informed that their participation was voluntary and that they had the right to withdraw from the study at any time without negative outcomes (I-IV). Written consent forms were obtained from all the participants before data collection and were safely stored (I-IV).

Beneficence refers to the act of doing good things for people. The duty of beneficence generates obligations to act for the benefit of others and promotion of others' well-being (Cranmer, 2013). Patients were given an opportunity to share their experience and feelings with nurses who may otherwise have little time to listen to their narratives (I). The result of study II is beneficial to provide a valid tool to evaluate and monitor the level of xerostomia for future patients. Patients in the intervention group obtained oral health-related knowledge and strategies and received follow-up coaching, which were beneficial for them in maintaining long-term good oral hygiene habits, and ultimately, relieve symptoms and improve oral health (III & IV).

The principle of non-maleficence is concerned with the obligation not to cause harm to another person. It requires intentionally refraining from actions that may cause harm (Beauchamp & Childress, 2009). No sensitive questions were asked during interviews (I). All interview data was stored, protected, and accessed only by the researchers (I). Patient privacy was rigorously protected, wherein patient information was kept confidential, and no individual identifying information were shared or disclosed in presentations of the results (I-IV). Participants received the integrated supportive program without any predictable risk; the same was also applied to the standard care (III & IV).

Justice is defined as the obligation that we ought to treat each other equally (Cranmer, 2013). In our studies, patients who met the inclusion and exclusion criteria had an equal chance to be included (I-IV). Patients were equally allocated to an intervention group or a control group (III & IV). All patients in the intervention group had equal opportunities to access the integrated supportive program. Patients with HNC are part of the vulnerable group, and their economic situation may affect their willingness in using costly oral care measures. The intervention in studies III and IV consisted of self-care-based oral care, which involved patients in their own care and potentially reducing costs.

7. Results

7.1. Experience of living with xerostomia

Five categories and 16 subcategories emerged from the manifested content of the interviews (Table 3). Related to these categories, a theme was formulated from the latent content of the interviews: due to lack of information regarding xerostomia, patients had to find their own ways to deal with the problem.

Communication problems

Patients who had xerostomia experienced limited ability to speak in an articulate manner. The more they talked, the higher the severity of xerostomia. The common problems patients encountered when they spoke included hoarseness, nasal pronunciation, loss of voice, and poor pronunciation. Another aspect included in communication problems is the lack of information regarding xerostomia. As patients cannot gain adequate information about xerostomia from healthcare professionals, they had to seek help and receive information from their family, media, and other patients. Although patients were eager to learn more information regarding their condition, they were not made aware as to where they may gain authoritative information.

Physical problems

Most patients with xerostomia narrated difficulty swallowing as burdensome owing to the increased viscosity of saliva and decreased saliva secretion. Pain caused by oral sores and inflammation was intolerable, severely exacerbating the difficulty in swallowing. Difficulty in chewing was mostly caused by the deteriorated status of dental condition after RT. Eating has become an extreme time-consuming activity and may sometimes cause distressing problems, such as during times when swallowing food is done too quickly and food cannot smoothly pass, gets stuck in the throat, and may exit from the nasal cavity. Taste alteration was very common. As a result of loss of the tongue coating, the sensitivity of the tongue increased. Patients described as if they felt their tongue burning and tingling when consuming spicy, acidic, sweet, or salty

food. Both the taste alteration and extensive oral dryness contributed to loss of appetite. These problems aggregated the occurrence of weight loss in patients with HNC. In addition, patients often experienced disturbed sleep, causing them to feel annoyed or tired. This may be due to frequently waking up to sip water owing to their xerostomia or due to excessive nocturnal urination from drinking too much water before going to bed and throughout the night.

Psychosocial problems

Xerostomia adversely and profoundly affected patients' psychological state. Persistent and uncontrolled xerostomia caused them to feel deep sadness, fear, anxiety, and anguish. Some patients narrated that it was torturous to live with long-term xerostomia for the rest of their lives. Others attempted to keep a positive attitude since they thought that it was unhelpful to indulge in worries and fears. Patients also reduced their participation in social activities, such as parties and meetings, due to the fear of talking about their cancer with friends and difficulty speaking due to excessive dry mouth. Another reason was that people often drunk and smoked at parties, which they considered as harmful to their health. Most patients reported that they preferred to be alone in a quiet place and did not like being disturbed. Patients also narrated that they disliked the flavor of served food and were embarrassed about eating in an abnormal way. Patients viewed eating in public as a challenge. Xerostomia also had a significant negative influence on their work life. Some patients had to quit or change jobs due to difficulties in speaking and needing to keep a bottle of water nearby.

Treatment problems

Simple measures were ineffective for some patients in relieving dry mouth, such as chewing gum, doing oral exercises, and drinking water with honey. In addition, it was very expensive for patients to pay for xerostomia treatment. Thus, their family members had to provide financial support for them. Most patients did not receive treatment and information about xerostomia, leading them to believe that xerostomia was incurable, with no effective way of relieving it.

Relief strategies

Frequent sipping water was the most common and beneficial way used by patients to relieve xerostomia. They emphasized that they cannot survive without water. Due to this, patients made it a habit to carry a bottle of water with them throughout the day and night. Patients invariably indicated that they had to frequently sip water to aid in swallowing and speaking. In order to eat food, patients had to drink a large amount of water, which led to consumption of smaller amounts of food. As a result, they often felt very hungry after meal, but could not eat any more. Consuming plenty of fluids, such as tea, fruit juice, water with honey, and soup was another effective way to relieve xerostomia. Food rich in water, such as porridge, noodles, and fruit, were some of the favorite foods of the patients since these types of food were easy to swallow, helping them avoid swallowing problems. Some nutritious food, such as sea cucumber and beef broth, was encouraged to be consumed to alleviate xerostomia by improving the whole body function. Sucking on peanuts, strawberries, and candy was usually done by patients since they thought these foods can stimulate saliva production. In addition, traditional Chinese treatments such as qigong, gua sha, and traditional Chinese herb medicine were preferred by some patients to relieve xerostomia.

Some patients struggled to overcome xerostomia but soon accepted the fact that xerostomia was an inevitable and incurable complication that is part of RT. In addition, patients distracted themselves from xerostomia by reading, playing games, and keeping busy, which made it easier for them to get through the uncomfortable situation. Some patients also adopted the strategy of attempting to ignore xerostomia.

Table 3 Quotations, subcategories, and categories describing the experience of xerostomia in patients with HNC

Quotations	*Subcategory*	*Category*
“I was unable to speak and open [my] mouth because it was too dry. There was no sound when I spoke. My voice changed and became hoarse and weak. I tried to speak less and listened more” (Patient 9).	Difficulty speaking	Communication problems
“I hoped that the physicians and nurses could give patients some information by using a booklet, e.g., what were radiation-induced side effects, how to handle these complications and so on” (Patient 6).	Lack of information	
“I could not consume dry food because I developed serious mouth ulcers during RT. My mouth was full of bubbles and white patches. My gums have receded, and in the future, my teeth may fall out, making it even harder to eat” (Patient 3).	Difficulty swallowing	Physical problems
“The desire and will to eat vanished completely because it was difficult for me to swallow. No matter what types of food I ate, I only sensed sourness on my tongue and mouth. The food did not taste the way it used to” (Patient 5).	Loss of appetite	
“I lost about 15 kg body weight from the start of RT to 6-month post-RT since I have had a bad appetite and inability to swallow” (Patient 10).	Loss of weight	
“I woke up to drink water every 2 hours at night, but it was difficult to get back to sleep. Also, sleep deprivation makes me upset” (Patient 3).	Loss of sleep	
“I have become irritable since undergoing RT. I used to be very kind and easy-going, but now there is a fire burning in my heart because of the extreme dryness in my mouth” (Patient 14).	Impaired psychological state	Psychosocial problems
“I knew some potential radiation-induced side effects would persist for a long period of time, [for] example, xerostomia, loss of taste, and stiff neck, but I told myself not to be bothered and worried. I must cherish what I have had” (Patients 6).	Preserved psychological state	
“I stopped attending New Year’s [Eve] parties because it was so smoky. My friends often questioned why I quit smoking and drinking. I was not willing to tell them the reason—my cancer” (Patient 16).	Decreased participation in social activities	
“I tried to chew gum and do mouth exercise to relieve my dryness, but it does not work” (Patient 7).	Lack of effect	Treatment problems

Quotations	*Subcategory*	*Category*
“I have accepted xerostomia as a normal side effect of RT, and there is nothing I can do” (Patient 5).	Lack of treatment options	Treatment problems
“The expense of traditional Chinese herbal medicine is nearly 5000 to 6000 yuan each month. It really costs too much. My children provide us with money to pay for the medicine” (Patient 3).	Excessive cost	
“I needed to be continuously sipping water 24 hours a day to deal with xerostomia. I woke up and drank some water several times every night. After drinking, I definitely felt better” (Patients 4). “After drinking a little water, my tongue became more flexible, and I could talk in an articulate way” (Patient 16).	Intake of fluid	Relief strategies
“If I suck on a peanut at night, I will not feel dry for almost the whole night or half a night” (Patient 18). “I was trying to eat spicy noodles, little by little. While eating, I felt that it was spicy, and there was no salivary gland secretion. But later, when the spiciness disappeared gradually, it really increased saliva production. The symptom of dry mouth was getting better” (Patient 1).	Intake of food	
“The level of dry mouth obviously decreased after I did qigong. There is one theory in Chinese traditional medicine that when people do qigong, it can generate body fluid, including saliva” (Patient 1).	Use of traditional Chinese treatments	
“There are many things that you cannot change, no matter how hard you struggle. It is just like how you cannot have another oral cavity. What I can do is to endure and get used to xerostomia” (Patient 15).	Accept the situation	

7.2. Validation of the Chinese version of XQ

Eighty patients participated in the psychometric evaluation. The mean age was 55 (SD, 11.0) years, and 25% were females. Nearly 34% of participants were non-smokers. Nasopharyngeal cancer was the most common cancer, with 64% of the population. More details on the demographic and disease-related characteristics of the participants are presented in Table 4.

The item level content validity index (CVI), scale level CVI/universal agreement, and scale level CVI/average agreement were used to evaluate the

content validity of the XQ. To support content validity, the item level CVI should be 0.78 or higher; scale level CVI/universal agreement, 0.70 or higher; and scale level CVI/average aggreement, 0.90 or higher (Spitz, 1994). Seven experts (five physicians and two nurses) with special field of symptom assessment and management of HNC were invited. The item level CVI values of the Chinese version of the XQ items ranged from 0.86 to 1. The scale level CVI/universal agreement and scale level CVI/ average agreement values were 0.88 and 0.98, respectively. Thus, there was satisfactory content validity from the perspective of healthcare professionals.

For data completeness and score distributions, problems with missing data for items ranged between 0%-2.5%. The number of computable scores, without imputation of missing data, was satisfactory (n = 76 [95%]). The ceiling/floor effect of items was less than 20%, except for items 1 and 4. The skewness of the items ranged from -0.28 to 0.14, and the kurtosis ranged from 1.68 to 2.40 (Table 5). There were no ceiling or floor effects for the total XQ score. The skewness and kurtosis of the total XQ score were -0.09 and 1.68, respectively. No strong deviation from normality was found, but the distribution was somewhat platykurtic. The interitem correlations varied between 0.64 and 0.83 (mean, 0.72), and the item-total correlations were between 0.79 and 0.85 (Table 5).

Based on the Kaiser-Meyer-Olkin (0.94) and Bartlett's test (χ^2_{28}= 571.04, P <0.001), a factor analysis was considered to be appropriate. The parallel analysis suggested a 1-factor solution, with adjusted eigenvalues of 5.76 for the first factor and 0.14 for the second factor. The 1-factor solution explained 75.6% of the total variance. The factor loadings of all the items varied between 0.84 and 0.91. All communality values ranged between 0.70 and 0.82. With this, the one-dimensionality was supported (Table 6).

There was excellent internal consistency of the Chinese version of XQ (Cronbach's α of 0.95). Cronbach's α varied between 0.94 and 0.95 if item deleted (Table 6), which indicated that all items equally contributed to the internal consistency of the XQ. As expected, the XQ correlated with the Head and Neck Sticky Saliva Scale, Head and Neck Dry Mouth Scale, and Head and Neck Swallowing Scale, which supports criterion-related validity. The strongest correlation was between the XQ and Head and Neck Swallowing

Scale ($r = 0.80$, $p < 0.001$), followed by the XQ and Head and Neck Dry Mouth Scale ($r = 0.78$, $p < 0.001$), and the XQ and Head and Neck Sticky Saliva Scale ($r = 0.78$, $p < 0.001$).

The test-retest reliability was excellent, as the ICC of the total XQ was above 0.75 (ICC = 0.92; 95% confidence interval [CI] = 0.82-0.96), and the ICC among the XQ items varied between 0.73 and 0.84 (Table 6), which indicate that all item ratings of the XQ were well consistent between the two occasions.

Table 4 Demographic and disease-related characteristics of participants, n (%) (n=80)

Characteristics		
Age (years), mean ±SD		54.7±11.0
Sex	Male	60(75)
	Female	20(25)
Marital status	Married	72(90)
	Others	8(10)
Smoking status	Former	44(55)
	Current	9(11)
	Never	27(34)
Tumor site	Nasopharynx	51(64)
	Larynx	14(18)
	Oropharynx	7(9)
	Hypopharynx	4(5)
	Oral cavity	4(5)
Tumor node metastasis staging system	I-II	28(35)
	III-IV	52(65)
Treatment modality	RT and CT	60(75)
	RT	20(25)

Abbreviation: CT, chemotherapy; RT, radiotherapy

Table 5 Item and scales score statistics of the Chinese version of XQ

Items[a]	*Mean (SD)*	*Min/ Max*	*Floor effects, %*	*Ceiling effects, %*	*Skewness*[c]	*kurtosis*[d]
1	3.3 (2.2)	0-8	21	0	-0.08	2.02
2	3.5 (2.2)	0-9	16	0	0.01	2.40
3	4.3 (2.8)	0-10	14	3	0.09	2.06
4	3.4 (2.8)	0-9	31	0	0.14	1.82
5	4.5 (2.6)	0-10	9	3	0.11	2.09
6	4.7 (2.7)	0-9	5	0	0.06	1.79
7	5.1 (2.7)	0-9	6	0	-0.28	1.89
8	5.3 (2.5)	0-10	5	3	-0.28	2.32
XQ score[b]	42.5 (22.4)	2.5-80	0	0	-0.09	1.68

[a] Each item is rated on a numeric rating scale from 0-10 (10=worse); [b] Calculated by adding the responses and then multiply the sum with 1.25 to obtain a score ranging between 0 and 100 (100=worse); [c] Values close to 0 support a normal distribution; [d] Values close to 3 support a normal distribution.

Table 6 Homogeneity, internal consistency, test-retest reliability, and factorial validity of the Chinese version of XQ

Items	*Inter-item correlation*								*ITC*[a]	*α*[b]	*ICC*[c]	*Factorial validity*[d]	
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*				*Factor loadings*	*Communality values*[e]
1	*1.00*								*0.85*	*0.94*	*0.80 (0.63-0.90)*	*0.89*	*0.79*
2	*0.79*	*1.00*							*0.83*	*0.95*	*0.76 (0.54-0.87)*	*0.87*	*0.76*
3	*0.69*	*0.70*	*1.00*						*0.82*	*0.95*	*0.84 (0.70-0.92)*	*0.86*	*0.74*
4	*0.77*	*0.71*	*0.71*	*1.00*					*0.83*	*0.95*	*0.80 (0.63-0.90)*	*0.87*	*0.76*
5	*0.67*	*0.71*	*0.75*	*0.71*	*1.00*				*0.80*	*0.95*	*0.73 (0.49-0.86)*	*0.85*	*0.72*
6	*0.83*	*0.76*	*0.71*	*0.78*	*0.76*	*1.00*			*0.87*	*0.94*	*0.83 (0.67-0.91)*	*0.91*	*0.82*
7	*0.70*	*0.65*	*0.74*	*0.67*	*0.64*	*0.72*	*1.00*		*0.79*	*0.95*	*0.83 (0.68-0.91)*	*0.84*	*0.70*
8	*0.72*	*0.74*	*0.70*	*0.71*	*0.67*	*0.74*	*0.71*	*1.00*	*0.82*	*0.95*	*0.78 (0.56-0.88)*	*0.86*	*0.74*
XQ (total)										*0.95*	*0.92 (0.82-0.96)*		

The 1-factor solution explained 75.6% of the total variance; [a]Item-total correlations adjusted for overlaps; [b] Cronbach's alpha if item deleted; [c] Intraclass correlations and its 95% confidence interval; [d] Exploratory factor analysis with principal components as extration method; [e]Spearman's rank correlations; all significant at a level of $P<0.001$. XQ, xerostomia questionnaire

7.3. Effects of the integrated supportive program

Participant characteristics

A total of 92 patients were included at baseline, and 79 (86%) completed the 12-month follow-up. The mean age was 50 (SD 10.93) years, and 21 (22.8%) of the participants were female. Patients with carcinoma in the nasopharynx, oral cavity, and oropharynx accounted for 40.2%, 20.7%, and 15.2%, respectively. Only 17.4% of the participants had early-stage cancer, and 54.3% of the participants were treated with RT and chemotherapy. No statistically significant inter-group differences were found at baseline with respect to the demographic, lifestyle, and clinical characteristics of participants (Table 7).

Xerostomia

The interaction effect between the time and group showed that the intervention group improved significantly compared with the control group (P=0.049). The difference was statistically significant in total XQ score at the 3- and 12-month post-RT (P=0.027 and P<0.001, respectively) (Figure 4). No significant inter-group differences were found in the grade level of xerostomia assessed by CTCAE at baseline, at the end of RT, and after the three-month follow-up, but the CTCAE xerostomia grade was significantly lower in the intervention group than in the control group after 12 months (P=0.046) (Table 8).

Saliva characteristics

A total of 79 unstimulated saliva samples were analyzed at baseline, 53 after the 3-month and 79 after the 12-month follow-up (Figure 5). No inter-group significant differences in the unstimulated saliva rate, saliva pH, and buffering capacity were reported at baseline, at the end of RT, and at the three-month follow-up; however, there was a statistically significant difference in unstimulated saliva flow rate between the groups after 12 months (P=0.035) (Figure 5), with better recovery in the intervention group. There were no significant inter-group differences in pH values and buffering capacity at the 12-month follow-up.

Oral health

After the 12-month follow-up, 22.5% of participants in the intervention group and 28.2% in the control group developed new dental lesions, with no significant differences between the two groups (P=0.56). Compared with the mean DMFT at baseline, the mean DMFT in both groups increased after 12 months. However, no significant inter-group differences were found (Table 9).

There were no significant differences in the mean value of PI and GI between the two groups at baseline (Table 9). After 12 months, PI decreased and GI increased in both groups. A statistically significant inter-group difference in PI (P=0.038) (Table 9) was encountered; however, no statistically significant inter-group differences in GI were found after 12 months.

There were no statistically significant differences between the two groups in the questions from the WHO oral health questionnaire at baseline. However, significant inter-group differences in state of teeth and gums after 12 months were reported, with better state of teeth and gums in the intervention group. The percentages of brushing teeth twice or more a day and use of fluoride toothpaste were higher in the intervention group than in the control group after the 3- and 12-month follow-up. The frequency of difficulty chewing and dry mouth in the intervention group was lower than in the control group during follow-up. Patients in the intervention group reported lower frequency of consumption of sweet foods and drinks than the control group after the 3- and 12-month follow-up. Patients in the intervention group had lower consumption of cigarettes and alcoholic drinks than the control group at 12-month after RT.

OHRQoL was lowest in all patients at the end of RT and improved slowly during follow-ups. Significant changes occurred over time between groups, which showed that patients in the intervention group had a significantly better OHRQoL than those in the control group (P=0.002) (Figure 4). The inter-group difference in the total OHIP-14 score was statistically significant at the 3- and 12-month post-RT.

HRQoL

Patients in the two groups had the lowest HRQoL at the end of RT, as the total FACT H&N score and its subscales were lowest, except for Emotional Well-being. The interaction effect between time and group showed that the intervention group experienced significantly better outcomes compared with the control group regarding the FACT H&N (total) (P=0.001) (Figure 6) and subscales of Physical Well-being (P=0.003), Functional Well-being (P=0.030), and HNC Subscale (0.042).

Adherence to the integrated supportive program

There was generally good adherence to the integrated supportive program, especially during the first 3 months, with a slight decrease during the follow-up. The percentage of performance of facial and tongue muscle exercises and salivary gland massage three times or more a day were 22.5%-40% and 50%-65%, respectively. Participants had better adherence to strategies such as frequently sipping water/fluid (52.5%-75%) and decreasing the intake of sweet foods and soft drinks (62.5%-77.5%), while they had lower adherence when it comes to strategies such as using mouth-wetting agents (5%-12.5%) and sugar-free chewing gum and sucking tablets (5%-15%).

Table 7 Baseline demographic and clinical characteristics, n (%) (n=92)

Characteristics		*Intervention group (n=47)*	*Control group (n=45)*	X^2/t^a
Age (years)	mean ±SD	48.11±10.7	51.9±10.8	-1.696
Karnofsky performance scale	80	14(29.8)	12(26.7)	1.175
	90	32(68.1)	30(66.7)	
	100	1(2.1)	3(6.6)	
Education level	Primary or below	8(17.0)	7(15.6)	0.779
	Secondary	23(48.9)	26(57.8)	
	Tertiary	16(34.1)	12(26.6)	
Economic situation	Very good/ Good	23(48.9)	23(51.1)	0.043
	Problematic/Very problematic	24(51.1)	22(48.9)	
Tumor site	Nasopharynx	20(42.6)	17(37.8)	2.037
	Larynx	7(14.8)	6(13.3)	
	Hypopharynx	6(12.8)	3(6.7)	
	Oropharynx	6(12.8)	8(17.8)	
	Oral cavity	8(17.0)	11(24.4)	
Tumor node metastasis staging system	Ⅱ	8(17.0)	8(17.8)	1.918
	Ⅲ	29(61.7)	22(48.9)	
	Ⅳ	10(21.3)	15(33.3)	
Treatment modality	Radiotherapy and chemotherapy	25(53.2)	25(55.6)	0.074
	Radiotherapy, chemotherapy, and surgery	18(38.3)	16(35.5)	
	Radiotherapy	4(8.5)	4(8.9)	

[a]*P* values of X^2/t test were >0.05.

Table 8 The effects of an integrated supportive program on CTCAE, n (%) (n=79)

Variable		*Intervention group (n=40)*	*Control group (n=39)*	X^2	*P*
Baseline	Grade 0	37(92.5)	35(89.7)	0.186	0.666
	Grade 1	3(7.5)	4(10.3)		
	Grade 2	0(0)	0(0)		
	Grade 3	0(0)	0(0)		
End of RT	Grade 0	0(0)	0(0)		
	Grade 1	0(0)	0(0)		
	Grade 2	32(80.0)	33(84.6)	0.288	0.591
	Grade 3	8(20.0)	6(15.4)		
3-month	Grade 0	0(0)	0(0)	2.942	0.086
	Grade 1	14(35.0)	7(17.9)		
	Grade 2	26(65.0)	32(82.1)		
	Grade 3	0(0)	0(0)		
12-month	Grade 0	7(17.5)	6(15.4)	6.176	0.046
	Grade 1	23(57.5)	13(33.3)		
	Grade 2	10(25.0)	20(51.3)		
	Grade 3	0(0)	0(0)		

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events; RT, radiotherapy

Table 9 The effects of an integrated supportive program on DMFT, PI, and GI

Variables	*Follow-up time*	*Group*	*Mean±SD*	*Z*	*P*
DMFT	Baseline	Intervention (n=40)	8.10±4.92	-0.069	0.945
		Control (n=39)	8.00±4.93		
	12-month	Intervention (n=40)	9.73±7.01	-0.334	0.738
		Control (n=39)	10.13±6.58		
PI	Baseline	Intervention (n=40)	1.38±1.23	-0.128	0.898
		Control (n=39)	1.41±1.19		
	12-month	Intervention (n=40)	0.93±0.89	-2.080	0.038
		Control (n=39)	1.38±1.02		
GI	Baseline	Intervention (n=40)	1.08±0.97	-0.083	0.934
		Control (n=39)	1.13±1.17		
	12-month	Intervention (n=40)	1.20±1.04	-1.041	0.298
		Control (n=39)	1.46±1.14		

Abbreviation: RT, radiotherapy; GI, gingival index; PI, plaque index

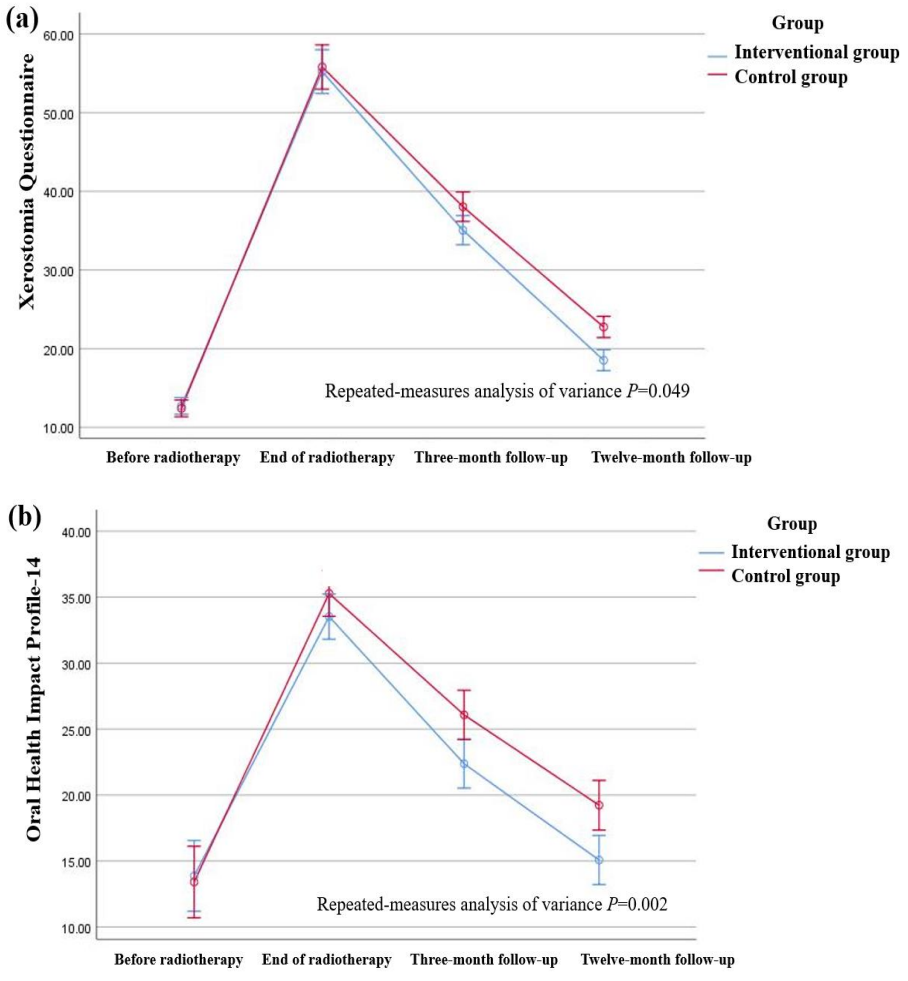

Figure 4. Longitudinal changes in xerostomia and oral health related-quality of life and significant differences per each time interval.

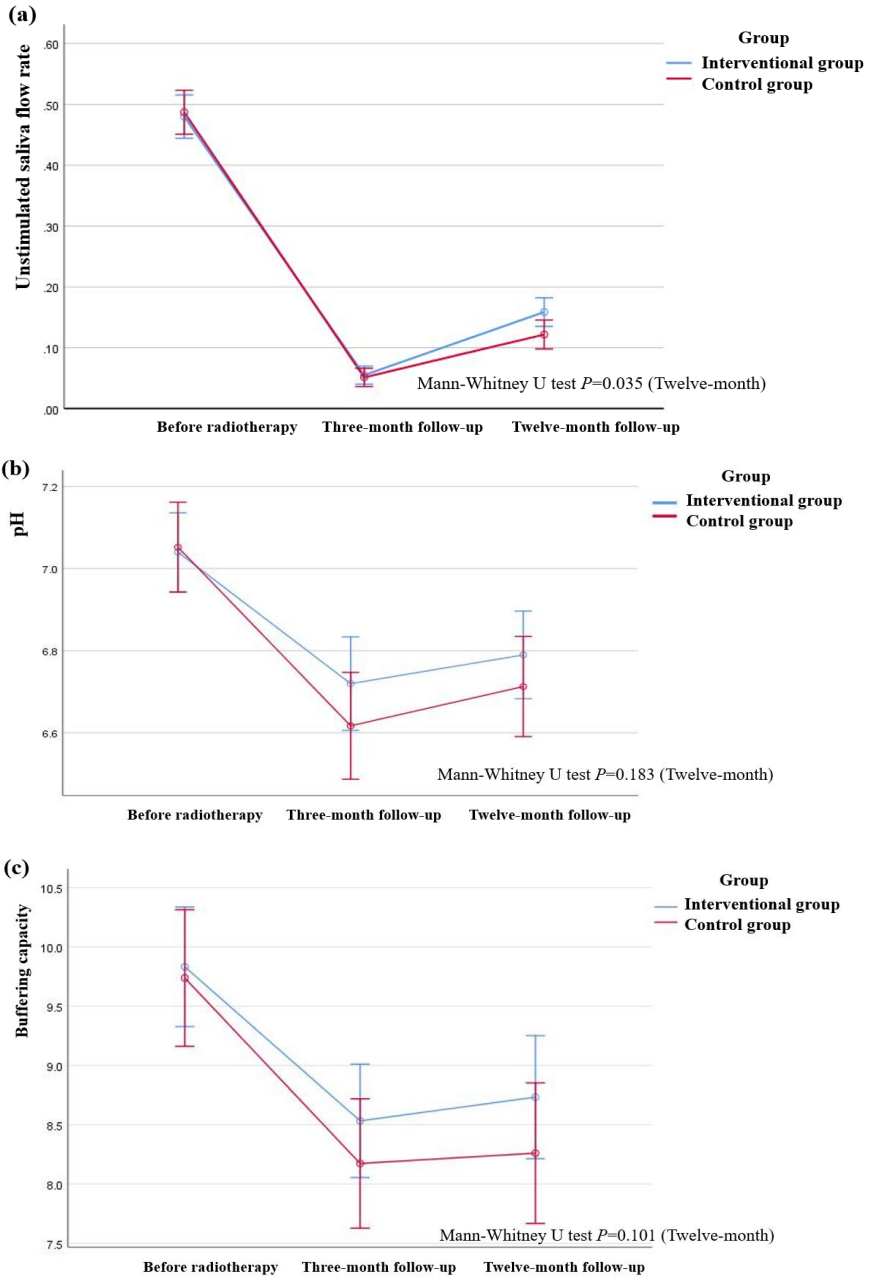

Figure 5. Longitudinal changes in saliva characteristics and significant differences per each time interval.

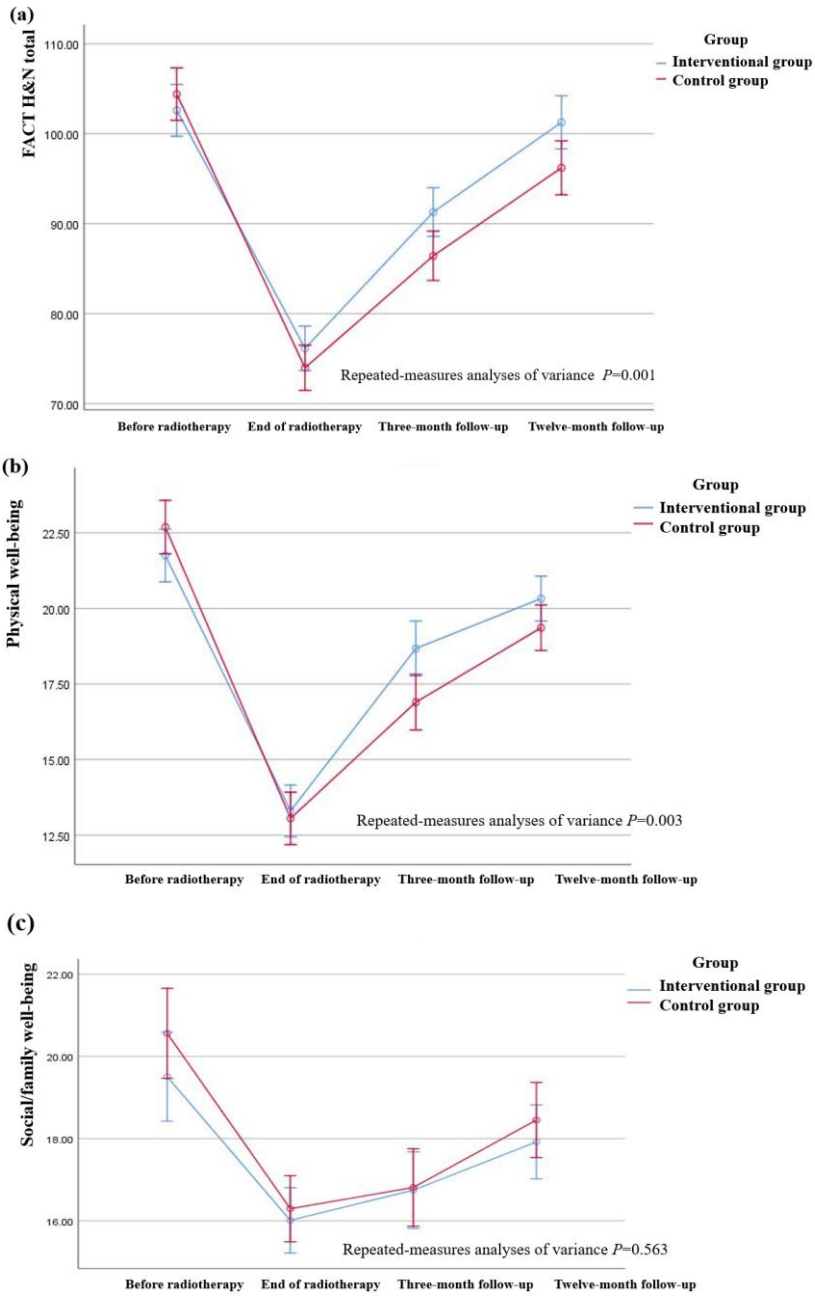

Figure 6. Longitudinal changes in health-related quality of life and significant differences per each time interval.

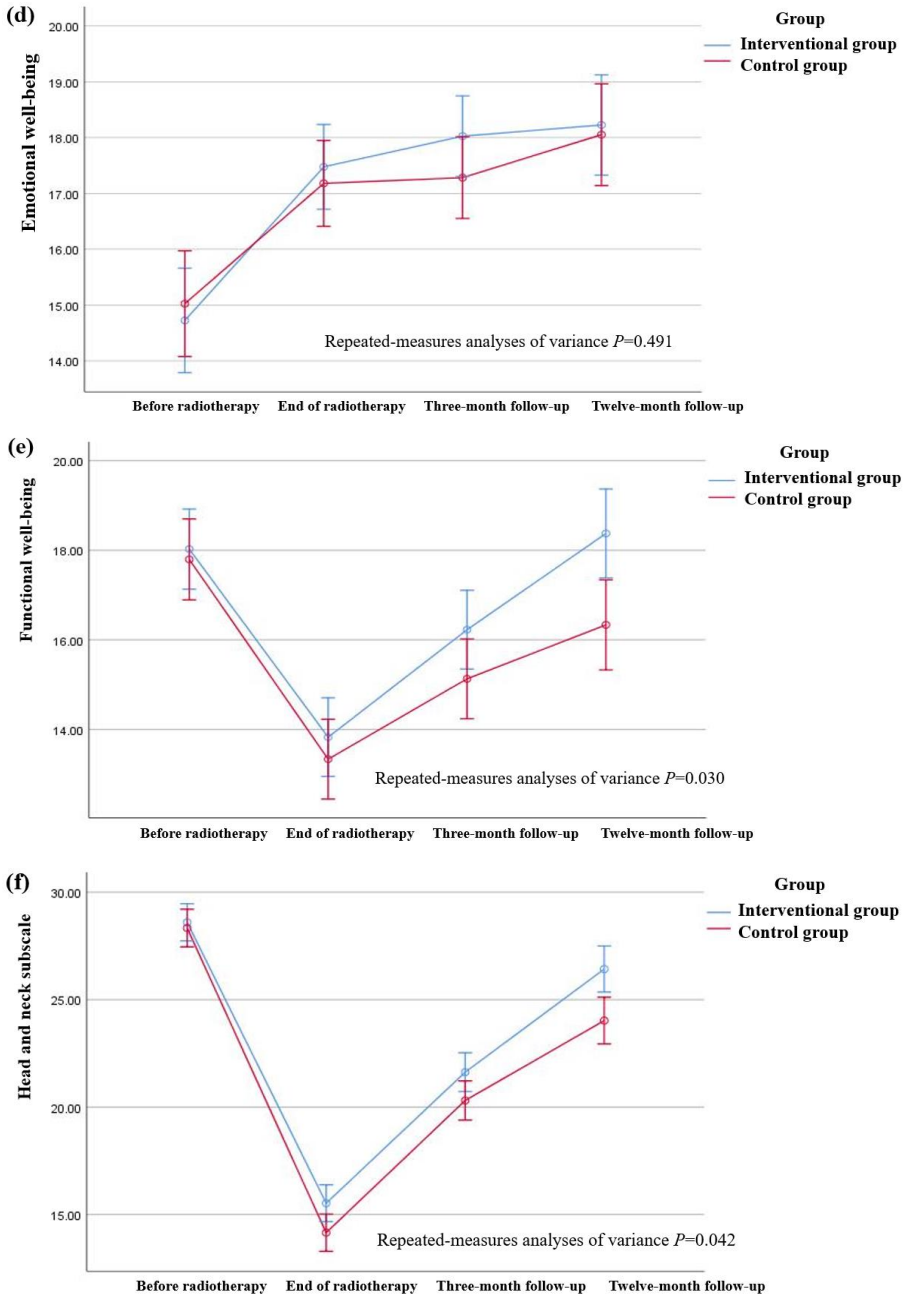

Figure 6. Longitudinal changes in health-related quality of life and significant differences per each time interval.

8. Discussion

8.1. Issues relating to the results

Xerostomia is a complex and multifactorial symptom. The choice of SMT was the theoretical framework for this thesis since it includes all parts that have been of interest for this thesis, including patient perspective, evaluation of symptoms, development of symptom management strategies and effects/outcomes of an intervention, etc. Another reason is that SMT is based on the individual's perception of the symptom and is recognized as a dynamic and multidimensional process where the impact of symptoms depends on the individual and the nursing domains: person, environment, and health/illness (Dodd et al., 2011). Xerostomia is analyzed from the perspective of the dimensions of symptom experience, symptom management strategies and outcomes, and the domains of nursing science: person, environment, and state of health /illness of the SMT.

8.1.1. Symptom experience

Xerostomia was far more than a biophysical symptom for the patients; it also had a profound and wearing effect on the sociocultural, emotional, and intellectual dimensions of the patients' lives (study I). **Perception of symptoms** is influenced by the domains of person, environment, and health/illness (Dodd et al., 2001). Patients with xerostomia experienced exacerbated physical problems, i.e., loss of voice, hoarse and nasal speech, pain in the mouth and throat, difficulty in swallowing, and loss of appetite, (study I), which negatively influenced their ability to eat and drink and increased the risk of inadequate intake of food and fluid. This result is confirmed by a previous study (Farhangfar et al., 2014) reporting that short- or insufficient long-term water or fluid intake can aggravate xerostomia. Thus, xerostomia and its related physical problems are encouraged to be simultaneously managed in patients with HNC. Furthermore, patients with persistent and uncontrolled xerostomia experienced psychosocial problems, such as impaired psychological state and decreased participation in social activities (study I). The perception of xerostomia is strongly associated with

their psychosocial states, especially stress, anxiety, depression, and social withdrawal (Folke et al., 2009; Gholami et al., 2017; Rech, 2019). The influence of a patient's psychological state on perception of xerostomia also should be noted. Thus, the strategies focusing on both physical and psychological aspects for xerostomia should be provided.

Patients with head and neck irradiation describe that the persistent xerostomia pushes them to learn how to accept the situation (study I). Some hold the view that xerostomia was an inevitable complication of treatment and might be a fair price to pay for survival, which is consistent with results reported by previous studies (Larsson et al., 2003; Ottosson et al., 2013; Charalambous, 2014; Ganzer, Rothpletz-Puglia, et al., 2015; Ganzer, Touger-Decker, et al., 2015). This hindered patients from disclosing their xerostomia and seeking help from healthcare providers, which made rehabilitation more difficult after RT (Larsson et al., 2007; Molassiotis & Rogers, 2012).

According to the SMT, the environment can influence the perception of symptoms (Dodd, 2011). Patients with xerostomia prefer a quiet and isolated environment because talking with others particularly aggravated their condition. Patients tried to talk as little as possible and avoided being disturbed (study I). However, this may have increased communication problems and resulted in feelings of isolation and loneliness. Eating in public was also viewed as a challenge for patients since they felt embarrassed that they are not able to eat like normal people due to difficulty in chewing and swallowing caused by excessive xerostomia (study I). Working environment can also aggravate xerostomia, wherein patients always need to talk or are not allowed to drink or sip water conveniently. Patients faced with these challenges tend to quit or change jobs due to difficulty with speech and excessive dryness (study I). The perception of xerostomia affects different aspects, such as communication, eating, and working environment. Therefore, it is very important to provide a relatively comfortable living and working environment for the patients.

Evaluation of symptoms can be done in terms of changes in frequency, severity, or distress associated with the symptom (Dodd et al., 2001). It is recommended that xerostomia is self-reported by patients rather than assessed by physicians since physician assessments seem to be too imprecise, biased

due to the examiner's influence, and tend to underestimate the level of xerostomia (Al-Nawas et al., 2006; Meirovitz et al., 2006; Memtsa et al., 2017). Compared with the xerostomia assessments made by physicians, the way patients reported by themselves is more beneficial in assessing the true level of xerostomia and its effects (Meirovitz et al., 2006). Therefore, it is important to select a reliable self-reported instrument to measure xerostomia. Previous studies reported that the single item for assessing xerostomia included in the self-reported quality of life scales was limiting since these scales contained very few items for proper assessment, which cannot reflect the full range of the problem (Bjordal et al., 1999; Rogers et al., 2010). Thus, XQ, a self-reported xerostomia-specific instrument was selected in study II. The XQ is a promising short self-reported instrument for xerostomia assessment since it only has eight items of high clinical relevance and is easy for patients to complete and for clinicians to evaluate (Eisbruch et al., 2001). As translations and cultural adoptions of self-reported instruments can change the measurement properties, the psychometric evaluation was done in the new translations of the XQ.

The Chinese version of XQ showed to be an easily administered instrument due to the low percentage of missing data. According to parallel analysis, one-factor model with strong factor loadings, small communality values, and high variance was found. This is supported by previous studies (Eisbruch et al., 2001; Pellegrino et al., 2015; Memtsa et al., 2017) and indicates that XQ is a stable unidimensional measurement xerostomia scale. In addition, the Chinese version of XQ had excellent internal consistency and high inter-item and item-total corelation. This may be related to the unidimensional nature of XQ. However, the strong inter-item and item-total correlations, together with a high α value, address a potential risk of redundancy (Streiner et al., 2015). Further studies are suggested to be conducted to determine whether a revision of the items of XQ is warranted. The criterion-related validity of the Chinese version of XQ was supported by fair correlations between the XQ total scores and other self-reported measures of xerostomia: the Head and Neck Swallowing Scale, Head and Neck Dry Mouth Scale, and Head and Neck Sticky Saliva Scale. This is in line with the results of the Italian version of XQ (Pellegrino et al., 2015). Furthermore, studies using saliva flow rate and grading system made by physicians as criterion variables to validate the criterion-related validity for other language versions of XQ also yield similar

results (Lin et al., 2008; Memtsa et al., 2017). These results from the present and previous studies have well strengthened the criterion-related validity of XQ (Lin et al., 2008; Pellegrino et al., 2015; Memtsa et al., 2017). The ICC on the item and scale score was high in study II , which indicates that the Chinese version of XQ had satisfactory test-retest reliability and had an adequate temporal stability and a sufficient reliability with limited measurement errors. The results of study II provided sufficient evidence that the Chinese version of the XQ with good psychometric properties is a valid and reliable instrument to evaluate xerostomia level in Mandarin-speaking patients with HNC.

Response to symptoms relates to physiological, psychological, socio-cultural, and behavioural aspects (Dodd et al., 2001). The majority of patients frequently increased the intake of fluid or water rich food to relieve xerostomia as it is convenient and saves money. This is persistent with previous studies that sipping water as a prime remedy is the most popular practice during the day and at night (Rohr et al., 2010; Ganzer, Rothpletz-Puglia, et al., 2015; Ganzer, Touger-Decker, et al., 2015). Sipping water have positive effects, such as moistening the mouth, relieving sticky saliva, and allowing swallowing (Rohr et al., 2010; Ottosson et al., 2013; Ganzer, Rothpletz-Puglia, et al., 2015; Ganzer, Touger-Decker, et al., 2015); however, frequent water or fluid consumption only temporarily relieves xerostomia and may cause inconvenience, such as nocturia, notably. (Kusler & Rambur, 1992). Patients are advised to decrease the frequency of sipping water before going to bed and use other methods, such as utilizing a humidifier at night.

The treatment problems with the methods that patients have used for xerostomia include lack of effect, lack of treatment options, and excessive cost (paper I). Patients described the use of relief strategies to manage xerostomia, including oral function exercise, chewing gum, and Traditional Chinese Medicine. Patients stated that doing oral function exercises and use of chewing gum are not effective (paper I). On the one hand, this may be related to their way of doing oral exercises or poor adherence to oral exercises. To enhance adherence, follow-up coaching needs to be provided to ensure doing oral exercises correctly (Kivelä, et al., 2014). On the other hand, there are no more residual salivary glandular function caused by severe damage to the salivary glands. Patients described that Traditional Chinese Medicine relieved

xerostomia but with excessive cost. Although the health insurance can reimburse a proportion of the cost of Traditional Chinese Medicine in China, patients still have to pay the higher out-of-pocket expense and may even need to seek financial support from their families. In addition, salivary substitutes with some effect to improve xerostomia were seldomly used in patients in study I. This may be due to the fact that health insurance does not cover the cost of saliva substitutes in China, and patients are reluctant to pay for measures with short duration of effects and high cost (Chambers, 2007). The additional financial burden and the experienced ineffectiveness of these methods were the main problems of these patients in managing xerostomia. Thus, health insurance needs to cover the cost of products to relieve xerostomia, such as artificial saliva and saliva substitutes, and increase the reimbursement rate of TCM. Researchers should consider how to reduce the economic burden on the patients to a minimum and integrate multiple oral care strategies to enhance the short-term effects of relieving xerostomia.

8.1.2. Symptom management strategies

This dimension includes strategies or efforts to reduce, minimize, or relieve symptoms. Performing professional and self-care strategies are effective approaches to avert or delay a negative outcome of the symptom. It needs to specify who, what, when, where, and how to deliver the strategy (Dodd et al., 2001). An integrated supportive program based on considering these specifications was developed by the research team. This is the first that combined face-to-face education, face-to-face coaching, and telephone coaching in an integrated supportive program for patients with HNC. It is based on a patient-nurse collaboration and aims to provide patients with education, self-care skills, and support.

Previous studies found that the adults and the elderly who regularly perform systematic oral hygiene, oral muscle exercises, and salivary gland massage can successfully reduce the incidence of xerostomia (Ibayashi et al., 2008; Hakuta et al., 2009; López-Jornet et al., 2014; Komulainen et al., 2015; Ohara et al., 2015). Furthermore, self-care skills and support based on oral care have positive effects on the relief of xerostomia (Edgar et al., 2012; Capaldi, 2018; Mark, 2019). With this knowledge, the integrated supportive program includes a face-to-face education which focuses on providing basic oral

hygiene instructions and oral self-care strategies, such as the proper method of performing the facial and tongue muscle exercises and salivary massage.

The occurrence of xerostomia is related with decreased salivary output and may be experinced after the initiation of radiation. Thus, face-to face health education was provided to patients a week prior to RT. The researcher carried out the baseline health education in the wards of the hospital, as most of the patients with HNC require hospitalization for RT in China due to the higher insurance reimbursement rate for hospitalization than outpatient treatment. Furthermore, the baseline health education was performed through the face-to-face approach as it is more effective than online health education in modifying health-related behaviors through better self-monitoring, more feasible goal setting processes, and more timely feedback (Araki et al., 2006).

Adherence is an important factor that influences the outcome of the intervention. It is important to enable follow-ups over a longer period of time. Studies using health coaching for six to eight months achieved significant multiple behavior changes (Prochaska et al., 2008; Olsen & Nesbitt, 2010). Meanwhile, the combination of face-to-face and telephone coaching can increase adherence motivation and obtain good results (Kivelä et al., 2014). Thus, the face-to-face coaching was conducted at 1-month post RT, and four telephone coaching sections, combined with motivational interviewing techniques, were performed at 2-, 3-, 6-, and 9-month post-RT (study III & IV). The researcher (NJ), a trained coach with rich experience of clinical cancer nursing practice, performed this program for patients in the intervention group. This meant that she was competent as an educator at baseline health education and an effective coach during coaching sections; it was also not possible to find another suitable person to perform this program as no Chinese researchers in our team had been trained as a coach. In addition, it is challenging to involve nurses in a hospital into research, explained by their burdensome workload and lack of coaching training experience.

8.1.3. Outcomes

The dimension of outcomes includes eight indicators (Dodd et al., 2001), which included the symptom status, functional status, emotional status, quality of life, and self-care as results in studies III & IV. These studies (III &

IV) were the first ones to be conducted to determine the effect of the integrated supportive program in this specific population.

Xerostomia

In the present study (III), xerostomia was described to be most severe at the end of RT, slightly relieved after 3 months, and largely relieved after 12 months in patients with HNC. This trend has been reported by previous studies (Lin et al., 2008; Memtsa et al., 2017) and is in line with the changed dysfunction level of salivary glands at different periods of RT that salivary flow decreases nearly 50% to 60% during the first week of RT and continues to decline throughout a typical course of treatment and may become barely measurable by the end of a 6-8-week course (Franzén et al., 1992). It is not surprising that the total XQ score in both groups did not decrease to their baseline levels after the 12 months, which is consistent with the results reported by Memtsa et al. (2017) and Jensen et al. (2019). However, the total XQ score in the intervention group was significantly lower than in the control group after the 3- and 12-month follow-up, and the interaction effect between time and group showed that the intervention group was more relieved significantly than the control group. This was also supported by the results assessed by observer-based CTCAE scoring system, showing that the grade of xerostomia was significantly lower in the intervention group than in the control group after 12 months. These results are reasonable as strategies such as oral function exercise and salivary gland massage included in the integrated supportive program can increase muscular and occlusal masticatory stimulation and increase saliva secretion, resulting in relieved xerostomia (Ibayashi et al., 2008; Cho et al., 2012; Edgar et al., 2012; Oral and Dental Expert Group, 2012; Komulainen et al., 2015; Pinna et al., 2015; Okuma et al., 2017). Therefore, nurses should encourage patients to adhere to this integrated supportive program until several years after RT.

There is usually a relationship between xerostomia and hyposalivation; however, some patients with xerostomia report that they do not experience hyposalivation (Shahdad et al., 2005). It is interesting to note that patients in the intervention group had a significantly higher mean value of unstimulated saliva flow rate than patients in the control group at the 12-month follow-up (III). This might be due to the fact that the patients' residual salivary gland

function was influenced by the dose and range of radiation (Jensen et al, 2010). Future studies are recommended to examine the effect of the integrated supportive program on unstimulated saliva flow value in patients with HNC in a specific region, such as nasopharyngeal carcinoma, where salivary glands are affected by similar ranges and dose of radiation. Another reason may be related to long-term salivary gland massage and oral muscle exercise, as both can stimulate residual salivary gland function, promoting saliva secretion (Zells et al., 1999; Weerapong et al., 2005; Ibayashi et al., 2008; Hakuta et al., 2009; Ohara et al., 2015). However, the results are questionable partly due to the difference between two groups being too small. The output of unstimulated saliva is measured by volume in this study. As the unstimulated saliva secretion is very low (less than 1 ml in 5 min) in patients after RT, the volume method may cause measurement errors. Weight measurement is better recommended in patients with reduced salivary secretion (Johansson et al., 2012). Future studies are suggested to measure saliva output by weight. Duplicating measurement at different time-points is also recommended as it can produce more reliable results. Furthermore, only unstimulated saliva flow rate was evaluated (III), as it can better represent patients' daily symptoms and best reflect basic saliva production. Stimulated saliva is important in determining the risk for caries and is also commonly used in research since it is easier to collect and compare. Further study is suggested to determine the effects of the integrated supportive program on both the unstimulated and stimulated saliva flow rate. The current treatment options for the management of xerostomia and hyposalivation include local therapies (i.e., salivary stimulants and artificial saliva/saliva substitutes). However, many patients do not have the capacity to avail them. As a result, self-care strategies, which are free-of-charge and with equally good results (i.e., regular sips of water), are more likely to be favored by patients (Edgar et al., 2012). Therefore, health professionals should consider the impact of financial burden of options of management strategies for patients.

Oral health

Oral health is an integral and essential part of general health and quality of life (Glick et al., 2016). Xerostomia with or without hyposalivation can cause difficulty speaking, chewing and swallowing, altered taste, and dental caries, which significantly impact patients' oral health (Dirix et al., 2008; Jensen et

al., 2010; Loorents et al., 2016). In our study, oral health was measured through OHIP-14 and dental examination (IV). The combination of these two was intended to evaluate both the objective and subjective oral health outcomes.

In study IV, the prevalence of caries in the intervention group was slightly lower than in the control group at 12 months. However, no significant inter-group differences were found. This indicated that the integrated supportive program did not provide significant effects in preventing caries. Dental caries is a multifactorial disease affected by physical and biological risk factors (e.g., radiation-induced dental hard tissue alteration, inadequate salivary flow, high number of cariogenic bacteria, and insufficient fluoride exposure), lifestyle-related and behavioral factors (e.g., high consumption of dietary sugars and poor oral hygiene), and other factors (e.g., lower socio-economic status and education level) (Selwitz et al., 2007; Liang et al., 2016). Modifiable factors in the development of caries should be fully considered and effectively controlled when implementing prevention strategies and treatment of dental caries (Jepsen et al., 2017). Thus, patients are encouraged to adhere for a long term to limited consumption of dietary sugars and maintain good oral hygiene with fluoride agents and antimicrobials to prevent dental caries and oral infection. In addition, the level of education may be related to the ability of the patient to acquire the knowledge and skills provided by health education. Nearly 16% participants had primary or below education level, and 50% experience problematic/very problematic economic situations in studies III and IV. These patients are at high risk of developing dental caries since they tend to have poor oral health behaviors, i.e., cigarette smoking, intake of cariogenic foods, lack of periodic dental visits and professional oral hygiene care, and poor oral hygiene habits (Selwitz et al., 2007; Singh et al., 2019).

To prevent oral diseases, dental professionals can contribute. As there are no dental hygienists in China, nurses are responsible for providing oral care for inpatients with HNC. However, nurses do not always perform regular follow-ups for discharged patients since it is not included in routine care. Therefore, it is suggested to have regular follow-up health coaching after discharge in routine nursing care to evaluate patients' adherence to oral hygiene behavior and discuss what difficulties or doubts they may have.

The follow-up of study IV is relatively short. In general, the caries disease progress is slow, but in this population, it can be rapid (Silva et al., 2009). Thus, the effect of the integrated supportive program on the prevention of caries may be difficult to evaluate at short periods of time. It is recommended to do follow-ups for a longer time, possibly two to three years, to observe the long-term effect of the integrated supportive program on caries prevention.

In study IV, only a significant inter-group difference in mean value of PI was observed, which indicated that the integrated supportive program had positive effects in decreasing plaque level but no effect on gingival inflammation. This may be related to better oral hygiene habits in the intervention group than in the control group. One explanation for that could be a higher percentage of patients use the modified Bass brushing methods and brushing teeth twice or more a day in the intervention group compared to the control group (IV). It is well known that the modified Bass brushing technique has positive effects on removing plaque and maintaining good dental hygiene (Janakiram et al., 2020; Qiao et al., 2020). Therefore, patients should be taught to use modified Bass brushing method correctly and to brush teeth at least twice a day.

Surprisingly, there was no significant difference in the mean value of GI between the groups. As the decline of GI value is not easy to achieve by only brushing teeth carefully, additional interdental brush or dental floss is needed. However, interdental brush with dental floss was used sparingly in patients for both groups in this study. This may be due to a lack of knowledge and skill on interdental brush and floss. Therefore, it is recommended for nurses to explore the different methods that participants adhere to good oral hygiene habits and practices and motivate them to maintain adequate plaque control throught periodic dental visits prior to, during and post-RT.

This integrated supportive program had significantly more positive effects on improving OHRQoL, indicated by lower OHIP-14 total, physical pain, physical disability, and psychological disability scores in the intervention group compared to the control group. OHRQoL is a multidimensional construct, which is influenced by the effects of oral health conditions, socio-cultural factors, emotional well-being, access to oral health care, satisfaction and expectations of dental care (Sischo et al., 2011). Strategies included in the integrated supportive program are known to be beneficial in preventing oral

problems and improve oral function, which directly decrease oral function limitation and disability (Jham et al., 2008; Edgar et al., 2012; Turner et al., 2013; Sakayori et al., 2016; Miyoshi et al., 2019; Janakiram et al., 2020; Kawashita et al., 2020). OHRQoL is important for patients with HNC undergoing RT due to its implications for oral health disparities and access to care. Therefore, oral health programs based on self-care should be widely used in this population.

HRQoL

In this study, we found that patients with HNC in both groups had the lowest level of HRQoL at the end of RT and had better levels of HRQoL at the 3-month and 12-month follow-up. This is consistent with findings reported by previous studies that an overall deterioration was observed in patient function and symptoms of HRQoL from the baseline until the end of RT and gradually recovered during the follow-up months and years (So et al., 2012; Ringash et al., 2015; Loorents et al., 2016). As the largest HRQoL changes for patient with HNC are observed within the first year and the significant problems with xerostomia and teeth after treatment are constant over time (Hammerlid et al., 2001), it is important to provide an intervention aiming to improve HRQoL for irradiated patients with HNC within the first year after cancer treatment.

In this study, the integrated supportive program had positive effects on improving HRQoL, particularly in the physical and functional dimensions and HNC specific symptoms and signs. Patients in the intervention group adhered well to the strategies of xerostomia relief, oral hygiene, and function improvement, which may have been fundamental in improving oral residual function for eating, drinking, speaking, and communication and further increased their physical and functional aspects of HRQoL. In addition, health coaching is a candidate intervention for improving HRQoL self-care behavior in patients with chronic disease (Long et al., 2019). Moreover, the regular follow-up coaching protocols may increase participants' awareness of oral health and adherence to the integrated supportive program and help them become more proactive in managing the potential radiation-induced side effects, making it possible to achieve benefits for HRQoL.

Unfortunately, the effect of the integrated supportive program on social/family and emotional aspects of HRQoL was not observed. Other

studies have described that patients commonly experience psychological distress and social isolation due to physical handicaps caused by cancer disease and its treatment (Sawada et al., 2012; Aoki et al., 2018). It is also reported that there are no improvements in psychological and social functions observed in short-term periods post-RT in patients with HNC (Howren et al., 2013; Lohith et al., 2017). Future studies are recommended to incorporate the psychological supportive care and social/family support into this integrated supportive program to improve the psychosocial aspects of HRQoL.

Adherence

Good adherence to symptom management strategies can increase the likelihood of good outcomes (Dodd et al., 2001). In studies III and IV, adherence to the integrated supportive program was good, especially the first three months. The reason for good adherence to the integrated supportive program in this study may be because motivational interviews were conducted during follow-up coaching sections, where positive feedback, barriers and solutions of the impact of the adherence were discussed, which might increase the adherence to program. This is persistent with results reported by a previous study showing that motivational programs positively improve attendance at exercise-based clinic sessions (Friedrich et al., 2005). However, the adherence to the integrated supportive program slightly decreased during the last six months' follow-up (Ⅲ & Ⅳ). Strategies need to be taken to improve long-term adherence to program (especially three months to years post-RT). Due to the multifactorial nature of non-adherence, it is suggested to use combined strategies to improve adherence (Mclean et al., 2010). Follow-up health coaching lasted up to nine-month post-RT in this study. This may be too short and prolonged coaching might be needed to facilitate adherence; however, prolonged coaching may increase the workload of healthcare professionals. mhealth technology is often used in clinical practice to reduce the burden of physically present interactions (Loeckx et al., 2018). mhealth provides convenience and care opportunities to patients and minimizes the barriers of distance, time and cost (Hamine et al., 2015). In a previous study, mHealth and health-coaching interventions showed benefit from each other (Obro et al., 2021). Thus, combining follow-up health coaching with mhealth in the integrated supportive program is suggested to expect good adherence after the first three-month post-RT. Family support is an effective strategy to enhance

adherence (Ormel et al., 2018). Supervision or coaching in the home‐based setting can stimulate family support, which may provide long-term encouragement to patients and motivate them to adhere to management strategies (Ormel et al., 2018). Future studies are encouraged to add family support in the integrated supportive program to form a patient-family-clinician partnership to implement successful symptom management.

8.2. Methodological considerations

8.2.1. Research approach

Different research methods were used in this thesis, including qualitative content analysis, cross-sectional design, and randomized controlled trial. These methods provide a deeper understanding for this specific population. To our knowledge, there is a lack of qualitative studies on xerostomia in Chinese patients with HNC. As the aim of study I was to describe the experiences of living with xerostomia, inductive research method and qualitative content analysis were considered the most appropriate approaches. This was confirmed through the results, which led to categories, and a theme, which described various aspects of living with xerostomia. A cross-sectional design was used in study II since it was suitable for questionnaire validation. In addition, to our knowledge, studies III & IV were the first to determine the effects of the integrated supportive program on xerostomia, saliva characteristics, oral health, and HRQoL in patients with HNC. A randomized control trial was considered to be the most appropriate approach for evaluating the effects of the intervention. Participants were randomly assigned to receive either the usual care or the integrated supportive program to guarantee equality between the two groups at baseline. A control group was set up in the study to eliminate the influence of confounding variables and to produce results that are comparable and reliable.

8.2.2. Trustworthiness in qualitative method

To establish trustworthiness in a qualitative analysis, credibility, dependability, confirmability, and transferability were presented (Lincoln & Guba, 1985).

Credibility refers to the *"confidence in how well data and processes of analysis address the intended focus"* (Polit & Hungler, 1999). Credibility was strengthened by the use of strategic sampling, which allowed a diverse sample (study I). The interviewees' age, sex, and severity and phases of experiencing xerostomia increased the possibility of providing knowledge on the research question in several aspects (study I). Choosing the most appropriate data collection method and the amount of data to be collected are also important to establish credibility (Graneheim & Lundman, 2004). The face-to-face, semi-structured interviews were conducted until the data were saturated (study I). The rich and vivid descriptions obtained from the interviews, illustrated by representative quotations from the transcribed text, strengthened the credibility (Creswell & Miller, 2000). By having all interviews conducted and analyzed by the first author (NJ), credibility was achieved by prolonged engagement with participants (Lincoln & Guba, 1985). Meanwhile, seeking agreement among co-researchers and experts with regard to symptom management were done to reach a consensus on how data were labeled and sorted, which also aided in streghthening the credibility of this study (Catanzaro, 1988).

Dependability can be regarded as *"the degree to which data change over time and alteration made in the research decisions during the analysis process"* (Graneheim & Lundman, 2004). It is essential for researchers to take note of all the activities that happen during the research process, i.e., describing the inclusion criterion and the processes of conducting research (Shenton, 2004). To ensure dependability, two pilot interviews were conducted by the first author and were reviewed by all the authors before the remaining interviews were conducted. The first author's previous clinical experience and understanding of the patients' context might have affected the pre-understanding with regard to the analysis and interpretation of the data and presentation of findings; however, attention to the impact of preconceptions throughout the whole process, along with open dialogue with other authors,

helped reduce potential bias. Frequent and extensive discussions among authors allow them to reach a consensus on sampling, data collection, and analysis. The theme and categories were discussed with and agreed upon by the authors who are all highly experienced. These enhanced the dependability of the qualitative research.

Confirmability refers to *"the researcher's ability to demonstrate that the data represent the participants' responses and not the researcher's biases or viewpoints"* (Cope, 2014). Researchers can validate the criticality and thoroughness of data by detailing and describing the data analysis in-depth and repeatedly reviewing transcript to provide a process for achieving data saturation (Cope, 2014). They can also demonstrate confirmability by describing how to establish the conclusion and interpretations and illustrate the research findings that come directly from the data. (Cope, 2014). In study I, all the interviews were audiotaped and transcribed verbatim. The interviews were translated from Mandarin to English by a bilingual researcher, and the accuracy of the translation was verified by two bilingual researchers from the team. All the researchers followed the steps of qualitative content analysis and rigorously compared and discussed the meaning units, codes, subcategories, categories, and theme until an agreement was reached. Moreover, to strengthen confirmability, thick and rich quotations from the participants were presented in the findings to depict each emerging theme (Cope, 2014).

Transferability can be considered as *"the extent to which the findings can be transferred to other settings or groups"* (Polit & Hungler, 1999). The transferability was supported by providing a rich and detailed description of the context, location, participants studied, sampling process, data collection and analysis, and trustworthiness (Connelly, 2016). To strengthen transferability, a purposive sampling of patients with diverse backgrounds and a rich presentation of findings with appropriate quotations were used in study I. All of the interviews (I) were translated from Chinese to English by a bilingual researcher. Although the accuracy of the interview translation was checked by another two bilingual researchers from the team, the trustworthiness of the analysis might still be influenced. Thus, the findings might be useful in other patients and settings with a similar culture.

8.2.3. *Validity and reliability*

External validity determines the extent of generalizability of the inferences from the findings of this research that can be applied to a broader population and other settings (Creswell, 2005). The external validity can be threatened when the results are not applicable in a real-world setting (Surbhi, 2017). In the present studies, the data was collected in a tertiary cancer hospital where nearly 500 patients with HNC from all over the country were admitted annually. However, these studies were delimited to one cancer hospital located in a big city in Tianjin, China, which limited the sample selection and had an effect on the external validity and reproducibility of the results beyond this specific site. Future research should explore whether these findings can be replicated in a large multicenter context with larger sample sizes. It should be warned that errors in sample size impact the external validity of the research (Sproull, 2003). It is recommended to use a formula to calculate the sample size (Creswell, 2005). As there were no previous studies conducted to evaluate the effects of a multiple component oral care intervention on xerostomia and oral health, the sample size could not be calculated based on data from previous studies. Therefore, a pre-test was carried out and a power analysis was performed to determine the sample size according to the results of the pre-test. Patients included in this study was from one hospital where a small number of patients met the inclusion annually. This may impact the generalizability of the results outside this setting. A control group was used and attempted to control confounding variables (III and IV), which contributed in strengthening the external validity. The risk of contamination or dissemination may have occurred during the first step of the integrated supportive program since the participants in both groups were in-patients in one hospital (III &IV). However, contamination or dissemination of intervention was unlikely to happen during the second and third step of the integrated supportive program since patients were out-patients with little risk of meeting again.

Internal validity refers to the identification of the extent that a study may support inferences about covariation, causality, and whether the experiment treatment makes a difference to the outcome (Christensen et al., 2014; Chong-ho, 2015). The internal validity of the data was ensured by addressing the details of instrumentation, data collection, and data analysis (Creswell, 2005;

Neuman, 2006). Internal validity in the cross-sectional study (II) and the randomized control trial (III-IV) were partly controlled through the selection of valid instruments to collect data. To assure validity of the study, the data utilized in study II-IV was collected using validated questionnaires (XQ, OHIP-14, FACT H&N35, etc.) with good psychometric properties in the Chinese population. These questionnaires used a Likert scale, where respondents could specify their level of agreement or disagreement on a symmetric agree-disagree scale (Alvin & Ronald, 2008). The range captures the intensity of the respondent's feelings (Alvin & Ronald, 2008), which provides an easy interpretation and decreases the risk of misinterpretation of the data. In studies II-IV, questionnaires were filled in by the participants themselves, and the researcher provided help when needed. This made it possible for the researcher to clarify misunderstandings, aiding in fewer missing data. Different validated indexes of plaque, gingival status and dental caries were used in the oral examination (Löe & Silness, 1963; Silness & Löe, 1964), which might assure the validity of the results of study IV. Studies III and IV were randomized control trials, which is considered as the best method to test the link between cause and effect in clinical interventions. The use of a control group could decrease the risk of internal validity by preventing misinterpretation of meaning of pre-/post-measures (Marsden & Torgerson, 2012). Meanwhile, the validity of research may be assured through the use of a pretest to evaluate the time to complete the measure and to assure that the participants fully understood the items of the questionnaire (Dillman, 2007). Threats to internal validity included the limited selection of participants and selection bias. Proper randomization can minimize and eliminate selection bias (Hu et al., 2011). Randomized assignment was done after the participants were recruited according to the inclusion and exclusion criteria before performing the intervention (III & IV), which can effectively avoid selection bias and ensure that the differences between and within groups are not systematic (Hu et al., 2011). These study designs provided greater rigor and validity to the results.

Reliability refers to the dependability or consistency of a measure, including whether the instrument provides the same results under identical or highly similar conditions (Kimberlin & Winterstein, 2008). Study II has shown that the Chinese version of XQ had good psychometric properties with excellent internal consistency and test-retest reliability. Other instruments used to assess

oral health and HRQoL in studies III & IV have been validated in the Chinese population as well. Data were collected using a questionnaire package at four time points (III & IV), where too many items might increase the nonresponse error (Dillman, 2007). To decrease the effects of lengthy data collection (III & IV), the print layout of the questionnaire package was designed to be clear, concise, and aesthetic. A pre-test study (III & IV) was conducted to acquire feedback related to the ease of filling in questionnaires; feedback was adopted to revise the print layout to increase response rate in questionnaires. The potential threat to reliability of study contained errors of data entry (Neuman, 2006). To ensure the correctness of data, the data (II-IV) were entered by one researcher into SPSS and checked separately by another experienced researcher, which enhanced the reliability of the study. However, the same researcher who performed the intervention also assessed the patient adherence which might threaten the reliability as no Chinese researcher in our research team, except for NJ, had any experience of being a coach. Thus, it is important to train health professionals as a coach to participate in similar follow-up intervention studies in the future.

9. Conclusion

This thesis contributes to the understanding of the experiences of living with xerostomia from a Chinese patient's perspective, noting that xerostomia has a profound impact on a patient's physical, psychological, and social life. There is lack of assessment tools for xerostomia in the Chinese population, and the Chinese version of XQ proved to be a valid and simple self-administered tool to measure and monitor the xerostomia level in patients with HNC. The integrated supportive program demonstrated positive effects on relieving xerostomia and improving patient oral health and HRQoL. These findings provide a basis for improvement in the management of xerostomia and oral health through the integration of oral care in nursing for patients with HNC.

10. Implications

10.1. Clinical implications

Information regarding xerostomia and oral care needs to be provided for patients with HNC receiving RT. A platform can be developed to provide a holistic, interdisciplinary approach that adequately supports patients' physiological, psychological and social well-being to help them, their families, and the healthcare professionals obtain information about oral care.

Oral health is integrated in general health and can affect the situation of patients with HNC. Therefore, it is recommended to collaborate with dental professionals, as well as with physicians and nurses in the integrated supportive program. In addition to that, there is a need to establish a dental hygienist profession to promote oral care in China.

Coach training should be provided for healthcare professionals for them to achieve qualifications and experiences to perform follow-up coaching. In addition, physicians and outpatient nurses are encouraged to combine health coaching with mhealth to relieve xerostomia and improve oral health, possibly every 3 or 6 months within five years.

The Chinese version of XQ had good psychometric properties. It can be used as a short-term and valid instrument to screen for problems encountered due to xerostomia, monitor the xerostomia level, and determine the effects of treatment and interventions in both clinical practice and research. In addition, as XQ is available in many languages, it is possible to compare the study results across different countries.

10.2. Research implications

All the data of the four studies were collected from patients at one hospital. A study with a sample from multiple centers is suggested to be conducted to strengthen the trustworthiness of the results.

Patients with KPS below 80 are suggested to be included to evaluate whether this integrated supportive program is suitable for those with low functional performance.

The one-year follow-up period may be too short to determine the effect of an integrated supportive program on dental caries. Thus, a study with a longer follow-up is suggested to be conducted in further research.

Costs as an outcome of the integrated supportive program are suggested being evaluated in further studies. In addition, a valid symptom-based cost measurement is recommended to be developed to assess the impact of symptom management on cost.

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Radiation-Induced Xerostomia in Chinese Patients with Head and Neck Cancer

– An Explorative and Interventional study

Radiation-induced xerostomia is a common oral complication of patients with head and neck cancer (HNC) undergoing radiotherapy (RT). This can negatively affect their oral health and health-related quality of life (HRQoL). The overall aim of this thesis was to understand the living experience of radiation-induced xerostomia and to determine the effects of an integrated supportive program based on multicomponent oral care strategies in Chinese patients with HNC.

A qualitative study was conducted to describe how patients (n=20) with HNC experienced radiation-induced xerostomia (I). A cross-sectional study of patients (n=80) with HNC was conducted to accomplish the validation of the Chinese version of the xerostomia questionnaire (XQ) (II). A randomized controlled trial (n=79) was conducted to determine the effect of an integrated supportive program on xerostomia, saliva characteristics, oral health, and HRQoL (III & IV).

Patients with radiation-induced xerostomia experienced communication problems, physical problems, psychosocial problems, treatment problems, and relief strategies (I). Due to lack of information regarding xerostomia, patients had to find their own ways to deal with the problem (I). The Chinese version of XQ was a unidimensional scale and had good psychometric properties (II). The integrated supportive program showed significant inter-group differences in xerostomia, unstimulated saliva flow rate, plaque index, Oral Health Impact Profile-14 and Functional Assessment Cancer Therapy-Head & Neck over the 12-month follow-up, with better outcomes in the intervention group (III & IV).

This thesis contributes knowledge regarding the experiences of living with xerostomia from a patient perspective, noting that xerostomia has a profound impact on a patient's physical, psychological, and social quality of life. There is lack of assessment tools of xerostomia in Chinese population, and the Chinese version of XQ proved to be a valid and simple self-administered tool to measure and monitor the xerostomia level in patients with HNC. The integrated supportive program demonstrated positive effects on relieving xerostomia, increasing unstimulated saliva flow rate, and improving their oral health and HRQoL. These findings provide a basis for improvement in the management of xerostomia and oral health of Chinese patients with HNC through the integration of oral care in nursing.

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