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Treatment Results of Intensity-Modulated Radiotherapy for Head and Neck Cancer

Venla Loimu

DOCTORAL DISSERTATION

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Cover image: Mikko Tenhunen
This teleradium unit, designed by Rolf Sievert and manufactured in Sweden, was the first megavoltage external beam treatment unit in Finland. It was used between 1938-1962 in the old Radiotherapy clinic (Unioninkatu 38, Helsinki). The first curative radiation treatments in Finland for head and neck cancers were given with this device.

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Milloin sitä prokrastinoisi, jos ei eläessään
-H. J. Visapää

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List of original publications

This thesis is based on the following publications:

I Loimu V, Collan J, Vaalavirta L, Bäck L, Kapanen M, Mäkitie A, Tenhunen M, Saarilahti K. Patterns of relapse following definitive treatment of head and neck squamous cell cancer by intensity modulated radiotherapy and weekly cisplatin. Radiother Oncol 2011; 98(1):34-37

II Loimu V, Mäkitie A, Bäck L, Sintonen H, Räsänen P, Roine R, Saarilahti K. Health-related quality of life of head and neck cancer patients with successful oncological treatment. Eur Arch Otorhinolaryngol 2015; 272(9):2415-2423

III Loimu V, Seppälä T, Kapanen M, Tuomikoski L, Nurmi H, Mäkitie A, Tenhunen M, Saarilahti K. Diffusion-weighted magnetic resonance imaging for evaluation of salivary gland function in head and neck cancer patients treated with intensity-modulated radiotherapy. Radiother Oncol 2017; 122(2):178-184

Abbreviations

ADC	Apparent diffusion coefficient
ART	Adaptive radiotherapy
BNCT	Boron neutron capture therapy
CRT	Chemoradiotherapy
CT	Computed tomography
CTV	Clinical target volume
DW-MRI	Diffusion-weighted magnetic resonance imaging
ENE	Extranodal extension
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HRQoL	Health-related quality of life
ICT	Induction chemotherapy
IMRT	Intensity-modulated radiotherapy
LRC	Locoregional control
MLC	Multiple leaf collimator
MRI	Magnetic resonance imaging
OAR	Organ at risk
OPSCC	Oropharyngeal squamous cell carcinoma
ORN	Osteoradionecrosis
OS	Overall survival
PET	Positron emission tomography
PT	Proton therapy
PTV	Planning target volume
PORT	Postoperative radiotherapy
PROM	Patient-reported outcome measure
QoL	Quality of life
RT	Radiotherapy
SIB	Simultaneous integrated boost
TNM	Tumour, node, metastasis
VMAT	Volumetrically modulated arc therapy

Abstract

Intensity-modulated radiotherapy (IMRT) combined with concomitant chemosensitisation is the standard treatment of locally advanced head and neck squamous cell carcinoma. Despite providing improved disease control rates compared with radiotherapy alone, it is associated with substantial toxicity that can impair patients' quality of life.

With a decreased incidence of smoking- and alcohol-related carcinomas of the head and neck and an increased incidence of human papillomavirus-associated oropharyngeal carcinomas, more and more patients will survive the disease, thus having to cope with the long-term toxicities related to treatments. This stresses the importance of understanding the mechanisms behind radiotherapy-related toxicities and focusing on improving patients' quality of life.

Aims of the study

The first study of this thesis focused on assessing the local control and survival and patterns of relapse following definitive concurrent chemo-IMRT for head and neck squamous cell carcinoma.

The second study aimed at assessing the quality of life of patients treated with definitive IMRT for head and neck carcinoma during the first 12 months after initiation of the treatments, using the generic 15D instrument.

The third study focused on evaluation of the salivary gland function of head and neck cancer patients treated with IMRT during and after the treatments with diffusion-weighted magnetic resonance imaging.

Materials and methods

The studies included in this thesis consisted of a total of 167 patients treated with IMRT for head and neck cancer at Helsinki University Hospital between 2000-2013. Study I was a retrospective analysis including 83 patients, Studies II-III were prospective analyses including 64 and 20 patients, respectively. Clinical and tumour-related factors were collected from hospital registries. Health-related quality of life (HRQoL) in Study II was

assessed with the generic 15D instrument before and at 3, 6, and 12 months after the initiation of the radiotherapy course. In Study III, salivary gland function was assessed with diffusion-weighted magnetic resonance imaging and salivary gland scintigraphy prior to and at a mean of six months after completing the treatment.

Results

Definitive IMRT combined with concomitant weekly cisplatin resulted in excellent disease-control and survival rates. In Study I, the 2-year local control, overall survival, and disease-specific survival rates were 84%, 82%, and 89%, respectively. The corresponding 5-year Kaplan-Meier estimates were 79%, 69%, and 76%.

In Study II, a significant decrease in overall HRQoL was seen during the first 3 months after the treatment onset. At 6 and 12 months, gradual recovery was seen. Dimensions reflecting mental well-being showed gradual improvement throughout the follow-up but remained decreased compared with the general population. The mean HRQoL was lower among patients with pharyngeal carcinoma compared with other primary sites.

In Study III, apparent diffusion coefficient (ADC) measured with diffusion-weighted MRI increased as a function of RT dose absorbed by the salivary glands. A moderate statistical correlation between ADC-values of non-stimulated salivary glands and ejection fraction measured with salivary gland scintigraphy was found.

Conclusions

Definitive IMRT with concomitant weekly cisplatin provides excellent locoregional disease control in the treatment of patients with locoregionally advanced HNSCC.

Health-related quality of life declined during the first 3 months after the treatment onset but gradually improved during the 12-month follow-up. The 15D instrument is feasible for evaluation of health-related quality of life of head and neck cancer patients treated with IMRT and seems to detect differences among different patient groups.

Changes in ADC at 6 months after the treatment correlates with the RT dose absorbed by the major salivary glands as well as ejection fraction measured with salivary gland scintigraphy. Diffusion-weighted magnetic resonance imaging is a promising tool for detection of RT-induced salivary gland damage.

Summary in Finnish

Intensiteettimuokattu sädehoito (IMRT) yhdistettynä samanaikaisesti annettavaan sytostaattihoitoon (ns. kemosädehoito) on vakiintunut standardihoidoksi paikallisesti edenneessä pään ja kaulan alueen levyepiteelikarsinoomassa. Vaikka sen on osoitettu parantavan tautikontrollia pelkkään sädehoitoon verrattuna, siihen liittyy merkittäviä sivuvaikutuksia, jotka voivat heikentää potilaiden elämänlaatua.

Tupakointiin ja runsaaseen alkoholinkäyttöön liittyvien pään ja kaulan alueen syöpien ilmaantuvuuslukujen pienentyessä ja papilloomavirukseen liittyvien suunielusyöpien ilmaantuvuuden kasvaessa yhä useampi potilas paranee pysyvästi ja joutuu elämään hoitoon liittyvien pitkäaikaishaittojen kanssa. Tämän vuoksi on korostetun tärkeää ymmärtää paremmin sädehoidon sivuvaikutusten syntymekanismeja ja keskittyä parantamaan potilaiden elämänlaatua.

Tutkimuksen tavoitteet

Väitöskirjan ensimmäisessä osatyössä pyrittiin selvittämään paikalliskontrollia, elossaoloa ja taudin uusiutumistapoja pään ja kaulan alueen levyepiteelikarsinoomapotilailla, jotka oli hoidettu IMRT-pohjaisella kemosädehoidolla.

Toisessa osatyössä selvitettiin IMRT:llä hoidettavien pään ja kaulan alueen syöpäpotilaiden elämänlaatua ensimmäisen 12 kuukauden aikana sädehoidon alkamisesta käyttäen geneeristä 15D-kyselylomaketta.

Kolmannessa osatyössä tutkittiin pään ja kaulan alueen syövän sädehoitoa saavien potilaiden sylkirauhastoiminnan arviointia diffuusiopainotteisella magneettikuvantamisella.

Aineisto ja menetelmät

Tähän väitöskirjaan sisällytetyt osatutkimukset koostuivat yhteensä 167 pään ja kaulan alueen syöpäpotilaasta, jotka hoidettiin IMRT:llä Helsingin yliopistollisessa sairaalassa vuosina 2000-2013. Ensimmäinen osatyö oli retrospektiivinen analyysi ja se sisälsi 83 potilasta. Toinen ja kolmas osatyö olivat prospektiivisia tutkimuksia, ja näiden potilasmäärät olivat 64 ja 20. Potilaiden kliiniset ja kasvaimeen liittyvät tiedot kerättiin

sairaalan potilastietojärjestelmistä. Terveyteen liittyvää elämänlaatua arvioitiin toisessa osatyössä geneerisellä 15D-työkalulla ennen sädehoidon aloitusta sekä 3, 6 ja 12 kuukautta sen jälkeen. Kolmannessa osatyössä sylkirauhastoimintaa arvioitiin diffuusiopainotteisella magneettikuvantamisella ja sylkirauhasten skintigrafiatutkimuksella ennen sädehoidon aloitusta ja keskimäärin kuusi kuukautta sädehoidon päättymisen jälkeen.

Tulokset

Samanaikaisesti viikoittain annettavaan sisplatiiniin yhdistetty intensiteettimuokattu kemosädehoito johti erinomaiseen tautikontrolliin ja elossaololukuihin. Väitöskirjan ensimmäisessä osatutkimuksessa kahden vuoden paikalliskontrolli, kokonaiselossaolo ja tautispesifinen elossaolo olivat 84%, 82% ja 89%. Vastaavat 5-vuoden Kaplan-Meier -arvot olivat 79%, 69% ja 76%,

Toisessa osatyössä yleinen terveyteen liittyvä elämänlaatu laski merkittävästi kolmen kuukauden kohdalla sädehoidon aloittamisesta. Kuuden ja kahdentoista kuukauden kohdalla nähtiin kuitenkin elämänlaadun asteittaista palautumista. Henkistä hyvinvointia mittaavat elämänlaatu-ulottuvuudet paranivat asteittain seurannan aikana, mutta olivat koko seurannan ajan alhaisemmat kuin verrokkiväestöllä. Keskimääräinen elämänlaatu oli heikompi nielusyöpäpotilailla muihin potilasryhmiin verrattuna.

Kolmannessa osatyössä diffuusiopainotteisella magneettikuvantamisella mitattu diffuusiokerroin nousi sylkirauhasten saaman sädehoitoannoksen funktiona. Kohtalainen tilastollinen korrelaatio nähtiin ei-stimuloitujen sylkirauhasten diffuusiokerroinarvojen ja skintigrafialla mitattujen ejektiofraktioarvojen välillä.

Johtopäätökset

Definitiivinen IMRT yhdistettynä samanaikaisesti annettavaan viikoittaiseen sisplatiiniin johtaa erinomaiseen paikalliseen tautikontrolliin paikallisesti edennyttä pään ja kaulan levyepiteelikarsinoomaa sairastavilla potilailla.

Terveyteen liittyvä elämänlaatu heikkeni ensimmäisen kolmen kuukauden aikana sädehoidon aloituksen jälkeen mutta parani sen jälkeen asteittain kaksitoista kuukautta jatkuneen seurannan aikana. 15D-työkalu on käyttökelpoinen IMRT:llä hoidettavien pään ja kaulan alueen syöpäpotilaiden elämänlaadun arvioimiseen. Se myös näyttää löytävän eroja eri potilasryhmien välillä.

Diffuusiokertoimen muutokset kuuden kuukauden kuluttua sädehoidon päätyttyä korreloivat sylkirauhasten saaman sädeannoksen kanssa sekä sylkirauhasskintigrafialla

mitattavan ejektiofraktion kanssa. Diffuusiopainotteinen magneettikuvantaminen on lupaava työkalu sädehoidon aiheuttaman sylkirauhasvaurion arvioinnissa.

1. Introduction

Head and neck cancer (HNC), defined as a group of malignancies arising from the oral cavity, pharynx, larynx, or nasal cavity, is the 6th most common cancer worldwide with approximately 890 000 new cases and 450 000 deaths annually [1, 2]. In Finland, roughly 950 new cases of HNC are diagnosed each year, and these diseases are responsible for approximately 300 deaths annually [3]. The most common histological subtype of head and neck cancer is squamous cell carcinoma, comprising over 90% of the cases [4].

Head and neck squamous cell carcinoma (HNSCC) is two- to fourfold more commonly found in men than in women [2, 5]. The main risk factors for HNSCC are tobacco smoking and heavy use of alcohol [4, 6]. In addition, the importance of high-risk human papillomavirus (HPV) infection as an etiological factor in oropharyngeal squamous cell carcinomas (OPSCC) has emerged during the past decades [7-9]. Currently, up to 70% of the newly diagnosed OPSCCs in Western countries are related to HPV [10-12], primarily HPV type 16 [13, 14]. HPV-positive OPSCCs differ markedly from their HPV-negative counterparts in terms of their genetic and biological profiles and clinicopathological behaviour and are associated with a significantly better survival compared with the non-HPV-related OPSCCs [15-17].

Small and early stage HNSCCs, comprising approximately 30-40% of the newly diagnosed cases, can be successfully treated with single-modality RT or surgery [18, 19]. However, most of the patients are diagnosed at an advanced stage [20], and therefore, they often require multimodal treatment. The choice of the primary treatment modality depends on anatomical accessibility and expected functional outcome. E.g., for oral cavity tumours [19, 21] and advanced laryngeal tumours [22], upfront surgery is the standard of care. With the novel transoral robotic techniques, the role of surgery in the treatment of oropharyngeal carcinoma is increasing [23].

Definitive radiotherapy (RT) with concurrent chemosensitisation has been the mainstay in treatment of locally advanced HNSCC for two decades, offering equal survival rates compared with surgery with the advantage of organ preservation. Based on several clinical trials [24-27], meta-analyses supported by subsequent updates [28-31], and systematic reviews [32, 33] reporting significantly improved survival and locoregional control,

concurrent platinum-based chemoradiotherapy (CRT) established its status as the standard of care in locally advanced HNSCC in the early 2000s. Last updated in 2021, a meta-analysis of more than 100 randomised controlled studies and nearly 20,000 patients showed that the concomitant addition of chemotherapy to RT improves overall survival (OS) at approximately 6,5% and locoregional control (LRC) at 9,3% compared with radiotherapy alone [30]. However, despite the improvement in survival rates achieved with concomitant chemoradiotherapy, there are major disproportions in survival rates between different patient subgroups: while 5-year overall survival for patients with locoregionally advanced HPV-related oropharyngeal carcinoma is over 80% [15, 34, 35], the corresponding rate in patients with locoregionally advanced laryngeal carcinoma is only 40% [36].

The unique anatomical and functional features and distinct radiosensitivity of the healthy tissues in the head and neck region make the patients particularly prone to the side effects of radiotherapy. Introduction of intensity-modulated radiotherapy (IMRT) into the treatment of head and neck cancer in the early 2000s, followed by subsequent introduction of the volumetrically modulated arc therapy (VMAT), improved optimisation of the dose-distribution, helping to avoid excess irradiation of healthy tissues without compromising the RT dose to the target volume [37-40].

Despite the technical improvements due to modern treatment delivery techniques, RT of head and neck cancer is still associated with a high rate of toxicity, which can be partly irreversible. E.g., in a study of patients with p16-positive oropharyngeal carcinoma, RT-related toxicity rates were 50% and 32% for acute and late Gr 2-3 xerostomia, 37% and 4% for acute and late dysphagia, and 42% for acute Gr 3-4 mucositis [35]. Since social and emotional interactions are largely dependent on the structural and functional integrity of organs in the head and neck [41], treatment and/or tumour induced damage to these structures can have a crucial impact on patients' functional and psychosocial well-being, leading to reduction in HRQoL. Novel prognostic models on treatment response and late toxicity are needed to improve the therapeutic window of the treatments.

From this background, it is evident that in order to optimise the treatment results of head and neck cancer, it is important to know both the factors affecting treatment efficacy as well as patient experience and quality of life after the treatments. Quantitative

measurements for normal tissue complication assessment would be beneficial in order to enable tailoring the treatment on the basis of individual factors.

2. Review of the literature

2.1. General considerations for head and neck cancer

2.1.1. Clinical characteristics, histopathology, and diagnosis

Squamous cell carcinoma is the most common histological subtype of head and neck cancers, comprising over 90% of all cases [4]. Occasional cases of other histologies, such as adenocarcinoma, melanoma, and lymphoma may also arise. Head and neck squamous cell carcinomas show an infiltrating growth pattern into the adjacent tissues. Due to the wide lymphatic network in the head and neck region, lymph node metastases are often evident in most primary tumour locations. Around 60% of the cases are locally advanced at the time of diagnosis [20].

The symptoms of head and neck squamous cell carcinoma vary according to the stage and location of the disease. Symptoms related to the primary tumour may include a non-healing ulcer, dysphagia, hoarseness of voice, or airway obstruction. Lymph node metastases, particularly related to HPV-associated carcinomas, may present as a painless neck mass. The diagnosis is often delayed, as these symptoms can be assumed to be related to benign processes both by health care professionals and the patients [42]. Early recognition of the disease is crucial, as delayed diagnosis may lead to impaired survival [43]. The diagnostic process of head and neck cancer comprises thorough clinical examination including endoscopies and radiological imaging (CT/MRI/PET). Diagnosis must be established by biopsy of the primary tumour and/or neck metastasis [44].

Solid evidence shows that HPV-associated oropharyngeal squamous cell carcinoma is a distinct disease entity [45, 46] with significantly better prognosis and radiosensitivity than conventional smoking and alcohol-related head and neck carcinomas [15, 16, 47-49].

HPV-associated carcinomas typically arise from the crypts of lingual or pharyngeal tonsils [50], whereas in non-HPV-related OPSCCs, the malignant process usually

begins in the surface layer of the tonsillar epithelium or other subsites of the oropharynx [9]. Histologically, HPV-positive carcinomas are typically poorly differentiated, non-keratinising, and with frequent mitotic activity, whereas HPV-negative carcinomas are more often moderately to well differentiated, with preservation of keratinisation and stratification [51-53]. Compared with non-HPV-mediated head and neck carcinomas, HPV-associated oropharyngeal carcinomas affect typically younger patients (median 53 vs 66 years for HPV-positive vs HPV-negative OPSCC [54, 55]) with less alcohol or smoking exposure and thus less comorbidity, higher socioeconomical status, and more lifetime sexual partners [8, 15, 56-59].

HPV-testing of oropharyngeal carcinoma relies on detection of HPV DNA by in situ hybridisation or polymerase chain reaction, or detection of mRNA of the viral oncogenes E6/E7 [60-62]. Alternatively, p16 protein overexpression, as a consequence of the transcriptional activity of high-risk HPV, can be used as a surrogate marker of HPV-background [63].

Clinically, HPV-associated OPSCC usually presents with an early-stage primary tumour and extensive lymph node involvement [64-67]. Despite the markedly aggressive clinical behaviour of HPV-associated oropharyngeal carcinomas, they are associated with a significantly better survival compared with their HPV-negative counterparts irrespective of the disease stage or age of the patient: the risk of death is consistently less than 60% of that of HPV-negative tumours [15, 16], and even at very advanced stages, 85% of patients with HPV-associated OPSCC are alive at 5 years from chemoradiotherapy [35].

2.1.2. Staging

Stage and HPV status are recognised as the most important prognostic determinants of HNSCC [15]. Staging, based on UICC/AJCC TNM (tumour, node, metastasis) - classification, characterises the primary tumour size and possible invasion to the adjacent structures, extent of regional lymph node metastases, and presence or absence of distant metastases. Until 2017, the TNM-staging of HNSCC was based on anatomical subsites of the tumours, irrespective of HPV status. The recognition that HPV-associated oropharyngeal carcinoma is a distinct disease entity created a need to

develop a novel staging system for these diseases. Released in 2017, the 8th UICC/AJCC staging manual contained three major updates aiming at improving the characterisation of the diseases. The most notable update was the re-classification of HPV-positive oropharyngeal carcinoma towards less advanced stage based on nodal status (tables 1-4), supported by the findings in the ICON-S study [68]. Other updates included the depth of invasion of the primary tumour in oral cavity cancers and the addition of extracapsular spread to nodal staging in non-HPV-mediated HNSCC [69].

With the current TNM-classification for HPV-associated oropharyngeal carcinoma, it must be acknowledged that the purpose of this classification is to paint a picture of the clinical prognosis of the disease, not to function as a basis for treatment adjustments. In a retrospective analysis of National Cancer Database for 4443 patients, reduced OS was reported in patients treated with less intensive treatment modalities compared with standard multimodal therapies. Thus, the treatment choice still must be based on the clinical extension of the disease rather than the current staging system [70].

UICC 7.0		**UICC 8.0**	
T1	Tumour ≤2 cm in greatest dimension	**T1**	Tumour ≤2 cm in greatest dimension
T2	Tumour >2 cm and ≤4 cm	**T2**	Tumour >2 cm and ≤4 cm
T3	Tumour >4 cm or in extension to lingual surface of epiglottis	**T3**	Tumour >4 cm or in extension to lingual surface of epiglottis
T4a	Tumour invades any of the following: larynx, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, or styloglossus), medial pterygoid, hard palate, or mandible	**T4**	Tumour invades any of the following: larynx, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, or styloglossus), medial pterygoid, hard palate, mandible, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base; or encases carotid artery
T4b	Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base; or encases carotid artery		

Table 1. Clinical and pathological T categories for HPV-associated oropharyngeal carcinomas

UICC 7.0		**UICC 8.0**			
Clinical and pathological		Clinical		Pathological	
c/pN0	No regional lymph node metastasis	**cN0**	No regional lymph node metastasis	**pN0**	No regional lymph node metastasis
c/pN1	Metastasis in a single ipsilateral lymph node, ≤3cm	**cN1**	Metastasis in ipisilateral lymph nodes, all ≤6 cm	**pN1**	Metastasis in 1-4 lymph nodes
c/pN2a	Metastasis in a single ipsilateral lymph node, >3 cm and ≤6 cm	**cN2**	Metastasis in bilateral or contralateral lymph nodes, all ≤6 cm	**pN2**	Metastasis in 5 or more lymph nodes
c/pN2b	Metastasis in multiple ipsilateral lymph nodes, all ≤6 cm				
c/pN2c	Metastasis in bilateral or contralateral lymph nodes, all ≤6 cm				
c/pN3	Lymph node metastasis >6 cm	**cN3**	Lymph node metastasis >6 cm		

Table 2. Clinical and pathological N categories for HPV-associated oropharyngeal carcinomas

	T1	T2	T3	T4a	T4b
N0	I	II	III	IVA	IVB
N1	III	III	III	IVA	IVB
N2	IVA	IVA	IVA	IVA	IVB
N3	IVB	IVB	IVB	IVB	IVB

Table 3. UICC 7.0 Stage grouping for oropharyngeal carcinoma
Distant metastatic disease (M1) is considered Stage IVC

	T1	T2	T3	T4
N0	I	I	II	III
N1	I	I	II	III
N2	II	II	II	III
N3	III	III	III	III

Table 4. UICC 8.0 Stage grouping for HPV-associated oropharyngeal carcinoma
Distant metastatic disease (M1) is considered Stage IV

2.2. Treatment

Due to the functional and anatomical complexity of the head and neck region, optimal treatment of HNSCC requires a multidisciplinary approach. The choice of treatment should be based on primary tumour site and stage, tumour histology and, in oropharyngeal sites, the HPV-status [71]. Treatment should always be planned and given in specialised centres by a dedicated multidisciplinary team [72, 73] aiming at the highest possible cure rates with minimal acute and long-term morbidity.

2.2.1. Surgery

Upfront surgery, followed by postoperative radiotherapy in cases of adverse pathologic features, is the standard of care for all stages or oral cavity cancers [19, 21], locally advanced laryngeal cancers [22], and in some cases, early laryngeal cancers [18, 19]. In cases of extensive resections, reconstructions are often necessary to maintain the functional integrity. With the novel transoral techniques, the role of surgery in the treatment of oropharyngeal carcinomas is also emerging [23].

2.2.2. Definitive concomitant chemoradiotherapy

Concomitant chemoradiotherapy has been the mainstay of treatment for locally advanced HNSCC since early 2000s, and its efficacy has been proven in large meta-analyses [28-30]. According to a recent meta-analysis update comprising 19 805 patients and 107 randomised controlled studies, concomitant chemoradiotherapy improved 5-year and 10-year overall survival with 6.5% and 3.6%, respectively, and 5-year locoregional control with 9,3% compared with radiotherapy alone [30]. This OS benefit comes from a decrease in cancer deaths influenced by reduced rates of locoregional relapses; the effect on distant control remains non-significant. Due to the substantial toxicity related to concurrent chemoradiotherapy, this treatment modality is primarily recommended to nonelderly patients with no major coexisting conditions.

The treatment efficacy decreases with increasing patient age. For patients over 70 years, the addition of concomitant chemotherapy brought no significant benefit in terms of overall survival or event-free survival [30].

2.2.3. Postoperative concomitant chemoradiotherapy

Postoperative radiotherapy (PORT) is often required in cases with adverse pathological features, such as advanced T stage, high tumour grade, perineural or lymphovascular invasion, multiple positive lymph nodes, positive margins, or any other concerns of high recurrence risk [74]. The benefits of postoperative chemoradiotherapy in patients with positive margins and/or extranodal extension was established by large phase 3 trials, comprising mostly oral cavity cancer patients [75-77].

In the EORTC 22931 trial [75], 167 patients with resected high-risk carcinoma of the head and neck were randomised for postoperative radiotherapy alone (66Gy in 33 fractions) or postoperative radiotherapy with concomitant cisplatin 100mg/m^{2}x3. The high-risk features were defined as a T3-4 primary with positive surgical margins, extranodal extension in lymph node metastases, perineural or vascular invasion, or oral cavity/oropharyngeal tumours with lymph node involvement on levels IV-V. The results showed significant improvements in 5-year progression-free survival (47% vs. 36%), locoregional control (82% vs. 69%) and overall survival (53% vs. 40%) favouring concomitant chemoradiotherapy.

The RTOG 9501 trial [76] defined high-risk factors as positive resection margins, involvement of two or more metastatic lymph nodes, or extranodal extension. The treatment protocols were similar as in EORTC 22931 trial. In this study, the addition of concomitant chemotherapy improved 2-year locoregional control (82% vs. 72%) and disease-free survival (54% vs. 45%), but the overall survival benefit remained non-significant.

In the extended follow-up of RTOG 9501 at 10 years [78], combined chemoradiotherapy did not improve locoregional control, disease-free survival, or overall survival in overall population, but in a subgroup of patients with extranodal

extension or positive margins, chemoradiotherapy improved locoregional control (failure rate 33.1% vs. 21.0%) and disease-free survival (18.4% vs. 12.3%).

2.2.4. Selection and scheduling of concomitant chemotherapeutic agent

The most used and investigated chemotherapeutic agent in concomitant chemoradiation of HNSCC is cisplatin 100mg/m2 in a 3-weekly regimen [29, 30]. However, this regimen is associated with substantial morbidity, as it doubles the rate of Gr 3-4 acute mucositis compared with radiotherapy alone and increases the risk of other RT-related side-effects [24, 76, 79]. Furthermore, cisplatin is associated with several dose-dependent toxicities, such as ototoxicity, hematological toxicity, and nephrotoxicity [80-82]. The considerable toxicity associated with the three-weekly regimen has raised a concern about insufficient cisplatin delivery, with an adherence as low as 49% in clinical trials [75, 76, 80]. Weekly administered cisplatin is associated with fewer adverse events [83, 84] and it has proven to be active and well tolerated in prospective studies comparing concomitant chemoradiotherapy with weekly cisplatin with radiotherapy alone [85-87]. A randomised trial comparing weekly administered cisplatin 30mg/m^2 with 3-weekly high dose cisplatin failed to demonstrate non-inferiority in terms of locoregional control rates but enrolled mostly patients with a resected oral cavity cancer [84]. Another randomised trial comparing weekly 40mg/m^2 versus 3-weekly cisplatin 100mg/m^2 in patients with nasopharyngeal carcinoma showed noninferiority of the 3-weekly regimen compared with the weekly administration [88]. In this study, 3-weekly cisplatin was associated with more severe acute toxicities and late-onset auditory loss. Also, in a systematic review by Mohamed et al., no significant difference was found in locoregional control (58 vs 61%), 2-year overall survival (74 vs 67%), progression free survival (69 vs 62%), or Grade 3-5 adverse events (36 vs 40%) between the two regimens [89].

In patients uneligible to cisplatin-based concurrent chemoradiotherapy, other less toxic alternatives have been investigated. Carboplatin has not proved to be as effective as high-dose cisplatin [90]. Also cetuximab, despite having shown benefits when compared with RT alone [91], failed to show noninferiority when compared with 3-weekly cisplatin [35, 92], and definitely should not be used as a concomitant chemosensitising agent during RT.

2.2.5. Altered fractionation

The MARCH meta-analysis included individual patient data from 11 423 patients in 33 trials comparing standard fractionation with altered fractionation (hyperfractionated, moderately accelerated, and very accelerated) in the treatment of patients with HNSCC [93]. This meta-analysis showed that hyperfractionation was associated with significant improvements in OS with an absolute difference of 8.1% at 5 years and 3.9% at 10 years. When comparing altered fractionation alone with conventional fractionation given with concomitant chemotherapy, OS outcomes were significantly worse for altered fractionation, with absolute differences of -5.8% and -5.1% at 5 and 10 years, respectively.

Also, no improvements in outcomes have been shown in trials comparing conventional and accelerated RT schedules given with concomitant chemotherapy. The RTOG 0129 trial [94] randomised 721 patients with locoregionally advanced HNSCC for standard fractionated RT (70Gy in 35 fractions over 7 weeks) with 3-weekly concurrent cisplatin 100mg/m^{2}x3 or accelerated boost RT (70Gy in 42 fractions over 6 weeks) with concurrent cisplatin 100mg/m^{2}x2. The results showed no statistically significant difference in overall survival, progression free survival, locoregional failure or rate of distant metastases. Also, no differences in late toxicity were observed.

The GORTEC 99-02 trial [95], including 840 patients randomised for conventional concomitant chemoradiation (70Gy in 35 fractions over 7 weeks) with three cycles or carboplatin + fluorouracil, or accelerated chemoradiation (70Gy in 6 weeks) with two cycles of carboplatin + fluorouracil, showed the most favourable outcomes for conventionally fractionated chemoradiotherapy, suggesting that accelerated RT is probably not beneficial in concomitant chemoradiotherapy regimens.

2.2.6. Deintensification of treatments in HPV-associated oropharyngeal tumours

The favourable clinical behaviour of HPV-associated oropharyngeal carcinoma has led to an interest of RT deintensification with the aim at minimising treatment-related toxicities while still maintaining oncological efficacy. The main deintensification approaches in prospective trials have been RT dose-reduction or omission of concomitant chemotherapy in definitive setting; replacement of cisplatin to cetuximab as a concurrent agent in definitive RT; deintensification of RT in response to induction chemotherapy; or deintensification of adjuvant RT after surgical resection.

2.2.6.1. Deintensification of definitive chemoradiotherapy

Chera et al. performed two non-randomised studies with deintensified definitive chemoradiotherapy [96, 97]. In the first study of 44 patients with T0-3 N0-2 HPV-associated oropharyngeal carcinoma with no heavy smoking history [96], the patients were treated with deintensified chemoradiotherapy (60 Gy with weekly cisplatin 30mg/m^2). All patients underwent biopsy of the primary tumour and lymph node dissection at 6-14 weeks after the treatment. The pathological complete response rate was 86%, and the 3-year locoregional control and overall survival rates were 100% and 95%, respectively.

In a subsequent non-randomised phase II study by the same research group [97], 114 patients were treated with a similar chemoradiation protocol. In this study, response evaluation was made with PET-CT and surgery was not mandatory. Two-year locoregional control, progression-free survival, and overall survival were 95%, 86%, and 95%, respectively. In both studies, toxicity was acceptable and gastrostomy-dependence was less frequent than in previous trials [98]. The authors concluded that de-intensified concurrent chemoradiotherapy is associated with favourable outcomes in this patient group and no neoadjuvant chemotherapy or routine surgery is needed to obtain favourable results with de-escalation.

In the randomised phase II NRG-HN-002 study [99], the patients were treated with concomitant chemoradiotherapy (60Gy over 6 weeks with concurrent weekly cisplatin 40mg/m^2) or RT alone (60Gy over 5 weeks). 2-year PFS or OS did not differ between the treatment arms in a significant manner (90.5% for concomitant treatment arm and 87.6% for RT only arm), but 2-year locoregional failure rate was slightly higher in the RT only arm.

Further, two randomised phase III trials (RTOG 1016 and De-ESCALaTE) compared concurrent cetuximab with 3-weekly cisplatin [35, 92]. Both trials failed to show noninferiority in terms of survival or toxicity for cetuximab.

In conclusion, trials investigating reduced RT dose in a definitive setting showed good survival outcomes and low toxicity profiles for patients with no large tumour burden, but data from randomised trials are missing. Direct comparison with standard treatments is needed before a paradigm shift. Furthermore, the findings from HN002, RTOG 1016 and De-ESCALaTE confirm the role of concurrent cisplatin in the definitive treatment of locally advanced HPV-related oropharyngeal cancer.

2.2.6.2. Deintensification in response to induction chemotherapy

Four prospective trials investigating RT deintensification in response to induction chemotherapy (ICT) showed favourable survival outcomes. According to them, RT dose reduction to approximately 50-55Gy after good response to ICT was feasible.

In E1308 trial [100], the patients were given 3 cycles of induction chemotherapy with cisplatin, paclitaxel, and cetuximab. RT was given with concurrent cetuximab. Patients with complete response to induction treatment received RT up to 54Gy with 2Gy fractions whereas non-complete responders received 69.3Gy with 2.1Gy fractions. For patients treated with 54Gy, 2-year PFS and OS were 80% and 94%, respectively. Acute Grade 3-4 toxicity and swallowing difficulties were less common in the 54Gy RT dose group.

In a non-randomised study by Chen et al. [101], 44 patients were given two cycles of induction chemotherapy with paclitaxel and carboplatin. RT was given with

concomitant paclitaxel. RT dose was 54Gy in 27 fractions for patients with complete or partial response and 60Gy in 30 fractions for those with less than partial response. For all patients, 2-year progression free survival was 92%. Three patients had locoregional recurrence and one had distant metastasis. Grade 3-4 toxicity was uncommon and at 6 months, none of the patients were gastrostomy-dependent.

In the OPTIMA trial [102], patients were stratified into different risk groups depending on the TNM-stage of the tumours and smoking history. All patients first received three cycles of induction chemotherapy (carboplatin + nab-paclitaxel). Subsequent RT was based on the initial risk group of the patients and response to ICT. Low-risk patients with ≥50% response received RT up to 50Gy with 2 Gy daily fractions over 5 weeks, low-risk patients with 30-40% response or high-risk patients with ≥50% response received twice-daily RT with 1.5 Gy fractions up to 45Gy with concomitant chemosensitisation (paclitaxel, fluorouracil, hydroxyurea), and patients with less response received twice-daily RT with 1.5 Gy fractions up to 75Gy with concomitant chemotherapy. The overall response rate to ICT was 82%. Most (71%) low-risk patients received 50Gy RT, whereas 71% of the high-risk patients received 45Gy CRT. 2-year PFS and OS rates were 95% and 100% for low-risk patients and 94% and 97% for high-risk patients, respectively. Post-treatment biopsy/lymph node dissection was performed to most patients after oncological treatment. Grade 3 mucosal toxicity and need of feeding tube insertion were significantly less common in patients receiving de-intensified RT.

In the Quarterback trial [103], including not only oropharyngeal cancers but also p16-positive cancers arising from nasopharynx, supraglottic larynx, hypopharynx, and unknown primary, the patients first received three cycles of induction docetaxel/cisplatin/fluorouracil, whereafter clinical responders were randomised to receive RT with a reduced dose of 56Gy in 2 Gy daily fractions or standard dose if 70Gy in 2Gy daily fractions with weekly carboplatin. 3-year progression free survival or overall survival did not differ significantly between the treatment arms.

Despite the favourable outcomes reported by these studies, the heterogeneity between treatment protocols cause difficulty in interpretation of the findings. In poor responders, ICT leads to more intensive treatments than standard protocols and delays

the onset of the CRT. Further, as ICT is associated with considerable toxicity, it is debatable whether ICT is associated with less toxicity than a reduced RT dose.

2.2.6.3. Deintensification of postoperative RT after surgery

Surgical resection followed by postoperative RT can be used as an option for the treatment of oropharyngeal carcinoma if the expected postoperative functional outcome is acceptable. With this approach, the feasibility of modifications of postoperative treatment based on pathological features has been evaluated.

The non-randomised Phase II MC1273 [104] and subsequent randomised phase III MC1675 [105] investigated aggressive de-intensification of postoperative RT. Based on absence or presence of extranodal extension (ENE) in lymph node metastases, patients received de-intensified postoperative radiotherapy up to either 30Gy with 1.5Gy fractions twice-daily or 36Gy with 1.8Gy fractions twice daily, respectively, with concurrent docetaxel. In MC1675, 194 patients were randomised 2:1 to receive de-intensified RT according to the abovementioned protocol or standard treatment (60Gy with 2Gy daily fractions +/- weekly cisplatin 40mg/m^2). In MC1273, 2-year locoregional control among patients with ENE was 93%. Local recurrence occurred in patients who underwent multiple re-resections to achieve clear margins. This is why in MC 1675, a maximum of 2 resections were allowed. In this study, patients with ENE had significantly worse PFS in the de-intensified treatment arm (78.9% vs. 96.2%). The difference was most remarkable in patients with N2 and ENE; 2-year PFS among these patients was 42.9% vs. 100%. In patients with no extranodal extension, no significant differences between the treatment arms were recorded.

Based on these trials, RT dose reduction in an adjuvant setting seems feasible for low-risk patients with no extranodal extension. Further data with longer follow-up time are still needed to confirm these findings.

2.3. Adverse events following radiotherapy

2.3.1. Acute side effects

Acute side effects are defined as treatment-related symptoms occurring during or within a 90 days period from the onset of the treatment [106]. The most common acute adverse events related to RT of the head and neck include mucositis, taste disturbances and dermatitis [107]. Concomitant chemosensitisation [108], as well as altered fractionation [109], increase the risk of acute and late toxicity. Acute side effects, such as mucositis and consequential pain and dysphagia, are the main causes of treatment interruptions, which can translate to impaired disease control [110, 111].

2.3.2. Late side effects

Late side effects are defined as symptoms that occur more than 3 months from the initiation of the treatment [106]. The risk of late side effects depends on the dosing, volume and site of the primary treatment. The most important late adverse events following RT of the head and neck include xerostomia, dysphagia, and osteoradionecrosis. These symptoms have a detrimental effect on patients' everyday function and can have a significantly negative impact on patients' quality of life.

2.3.3. Grading scales for adverse events

In clinical trials, the toxicities are usually scored using the US National Cancer Institute (NCI) CTCAE scoring system, where the adverse events (AEs) are graded from 1-5 based on their severity (1= mild symptoms, 5=death related to AE). The limitation of CTCAE is its observer-reported nature, which may make it prone to lack of reliability [112] and under-reporting of the symptoms [113, 114]. Patient-reported outcomes can be used to improve the assessment of symptomatic adverse events and to better incorporate patients' subjective perspective. A complementary grading system (PRO-CTCAE) has been introduced [115]. Other, less often used toxicity grading measures include RTOG/EORTC Radiation Toxicity Grading scale [106] and LENT-SOMA[116].

2.3.4. Xerostomia

Dry mouth, or xerostomia, caused by radiation-induced damage of the salivary gland tissue, is one of the most distressing long-term adverse events following RT of the head and neck, and one of the main causes of reduction in quality of life (QoL) after HNSCC treatments [38, 117, 118]. Xerostomia has been defined as salivary flow reduction to 25% or less compared to the pre-treatment value [119]. The mean dose and irradiated volume of the salivary glands have been considered the most important factors related to RT-induced xerostomia [120-122]. In general, mean cumulative doses of less than 26-40Gy to the major salivary glands are associated with substantial preservation of salivary flow rates [119, 123]. Sparing of the minor salivary glands scattered in the oral mucosa is also considered to be effective in preservation of salivary flow [124, 125]. Parotid glands produce most of the stimulated saliva and their secretion is maximal while eating, whereas submandibular glands are responsible for up to 90% of the salivary output at rest. Thus, damage to the submandibular glands will lead to a subjective sensation of dry mouth [126-128]. Radiation-induced damage to the fluid-secreting acinar cells leads to decreased salivary flow, build-up of sticky saliva, discomfort, taste alterations, speech and swallowing difficulties, and increased risk of dental caries [129]. Clinical studies using IMRT have shown that radiation-induced xerostomia can partially recover during the first 2 years of the RT [38, 118]. Moreover, animal model data have suggested that radiation to the parotid gland subvolumes in proximity of the major ducts, containing the acinar cell progenitors, causes more xerostomia than radiation to other parts of the gland [130, 131]. In a clinical cohort, radiation dose delivered to these subsites correlated to the salivary flow at 12 months after treatment [132]. A recent double-blinded randomised controlled study failed to show improved post-RT parotid gland function in patients treated with IMRT with the aim at stem-cell preservation; however, dose to the stem cell rich regions was predictive of the development of clinical xerostomia [133].

2.3.5. Dysphagia

Dysphagia, or difficulty in swallowing, is considered as one of the most distressing side effects among patients with HNSCC [118, 134]. It increases the risk of aspiration and limits the oral intake, thus negatively impacting the patients' nutritional status, social well-being and quality of life[135] [136]. The most important anatomical structures related to radiation-induced dysphagia are pharyngeal constrictors and supraglottic larynx [137-139]. A dose-effect relationship between RT dose to these structures and clinical symptoms have been found in retrospective series [137, 139, 140]. For example, Levendag et al. concluded that every additional 10Gy to the pharyngeal constrictors increased the risk of dysphagia by 19% [137].

2.3.6. Mucositis

Oropharyngeal mucositis is one of the most common and clinically significant acute side effects following RT of the SCCHN. With conventional fractionation, it usually starts within a couple of weeks from the treatment onset and gradually progresses towards the end of the treatment [141]. Recovery occurs within 3 weeks from the completion of the RT, and at 1 month the mucosa is healed in 90-95% of the patients [141] [142]. Oropharyngeal mucositis is associated with pain, bleeding, infections, dysphagia, and impaired food intake, all of which can severely impair patients' quality of life [143-146] and lead to hospitalisations and treatment breaks [111]. Worsened nutrition status as a consequence of inadequate food intake caused by oral pain and dysphagia can worsen and prolong the duration of mucositis [147]. Concomitant chemosensitisation [29, 31], and altered fractionation increases the incidence of mucositis [109, 148].

2.3.7. Mandibular osteoradionecrosis

Osteoradionecrosis (ORN) is defined as a condition where the bone within the radiation field becomes devitalised and exposed through the overlying skin or mucosa and fails to heal within a period of 3-6 months [149-151]. ORN presents as a chronic, often painful ulceration, and often has a detrimental impact on quality of life of the

patients [152]. Risk factors associated with ORN include tumour-related factors (tumour location, size, presence of bone invasion), treatment-related factors (total RT dose, RT technique, volume of mandible irradiated), and patient-related factors (tobacco/alcohol use, oral hygiene, dental infections, dental extractions, comorbidities) [153-156]. The maximum mandibular dose of >70Gy and a mean mandibular dose of >40Gy are associated with increased risk of ORN [157].

2.4. Advances in radiotherapy delivery techniques

The particular radiosensitivity of healthy tissues in close proximity to the tumour site in the head and neck region poses therapeutical challenges. Former conventional RT delivery techniques, such as 2D-radiotherapy, and 3D conformal RT, led to high doses to remarkable healthy tissue volumes, with consequential severe late normal tissue toxicity such as xerostomia and dysphagia [158]. These conventional techniques were replaced in the early 2000s by intensity-modulated radiotherapy (IMRT), which is currently the standard RT technique for HNSCC. With the use of multiple beams with varying shapes and non-uniform intensities, IMRT provides a highly conformal dose distribution, allowing for more precise sparing of organs at risk while targeting the tumour volumes [159, 160]. This technique has further been developed with the introduction of volumetrically modulated arc therapy (VMAT) (fig.1), which utilises an arrangement of single or multiple coplanar arcs with continuous adjustments of the beam shape as a function of gantry angle [161]. Further, image-guidance [162] has enabled safe and accurate[163] treatment setup, and also enabled treatment re-planning [164] and adaptative techniques [165].

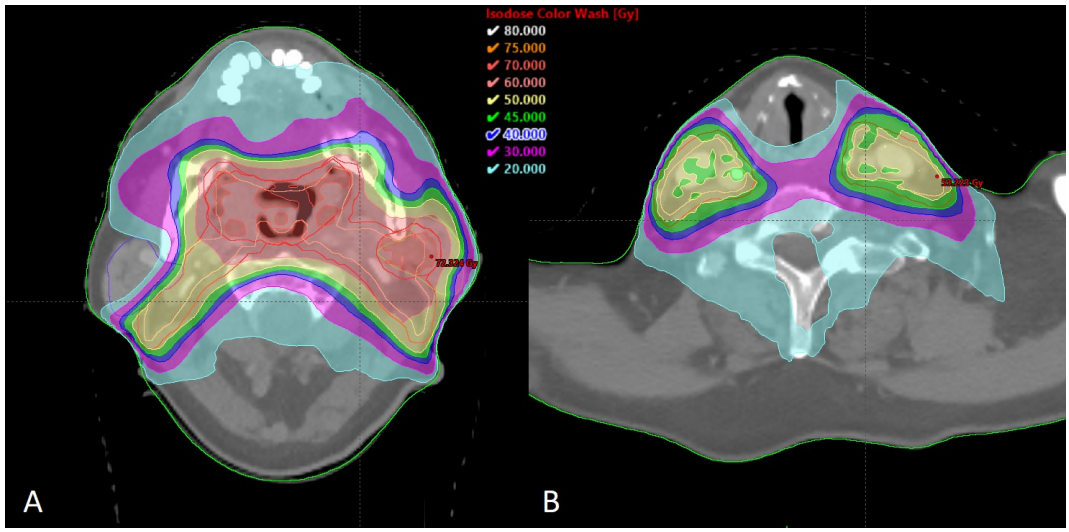

Fig.1 The dose distribution of a treatment plan for a patient with T2 N2a carcinoma of the soft palate. RT is delivered with the VMAT technique using two 6MV arcs. The contralateral parotid gland (A) and vocal cords (B) are being spared.

2.4.1. Locoregional control following IMRT

With more precise dose distribution achieved by IMRT, there is little space for error and thus theoretically an increased risk for marginal failure. Errors in delineation of target volumes, inappropriate margins, inadequate immobilisation, and anatomical changes during RT, can increase the risk of a so-called geographical miss [166-168].

However, high-quality comparative studies have reported on no increased risk of locoregional failure related to IMRT. On the contrary, several randomised [37-40] trials comparing IMRT and conventional RT delivery techniques have shown that IMRT provides similar or even better locoregional outcomes. In a review of 5 prospective randomised trials, 1 prospective phase II trial, and 10 retrospective comparative studies aiming at analysing patterns of treatment failures among HNSCC patients treated with (IM)RT [169], the 2-year locoregional control rates for IMRT were between 59% and 98.7%.

In several institutional analyses, the vast majority of locoregional recurrencies following IMRT for HNSCC have been recorded in the high-dose volume. In a large retrospective single-institution cohort study conducted at MSKCC [170], 1000 St III-IVB HNSCC patients treated with definitive (n=875) or postoperative (n=125) IMRT with or without concurrent chemosensitisation were reviewed. During the median follow-up time of 65.1 months, 147 locoregional relapses were recorded, with no marginal failures or isolated out-of-radiation-field failures. Distant metastases were recorded in 143 patients. Locoregional failure occurred most commonly among patients with oral cavity carcinoma and least commonly among patients with HPV-positive oropharyngeal carcinoma. Of all regional nodal recurrencies, 87.3% occurred in the sites of treated gross disease, and only 0.9% in the elective neck alone. Salvage surgery and Karnofsky performance score over 70 were associated with improved overall survival after locoregional failure.

In another retrospective study of 385 patients with pharyngeal, laryngeal, and oral cavity tumours treated with IMRT or VMAT at the University Hospital of Leuven [171], 22.1% of the patients developed a locoregional failure during a median of 6.4-year follow-up. The estimated 2-year and 5-year locoregional control was 78.2% and 74.2%,

respectively. In this series, local and regional recurrence outside the high-dose volumes were recorded in one and five patients, respectively. Four recurrencies were recorded in the electively irradiated neck and two outside the electively irradiated neck. Marginal failures were not observed in this patient cohort.

Several smaller single-institutional analyses have reported on similar patterns of locoregional recurrence. In a study conducted by De Felice et al. [172], 56 patients with locoregional failure following RT for HNSCC were reviewed. 95.6% of the recurrencies were classified as in-field. Patients receiving salvage surgery had a significantly improved median PFS compared with those receiving palliative treatments. Further, Bayman et al. [163] reported on a series of 136 HNSCC patients treated with IMRT, 7 of whom developed locoregional recurrence at 2-year follow-up. Five of these recurrencies were in-filed, one marginal to the high-dose CTV, and one out of field.

2.4.2. Reducing toxicities with IMRT

The benefits of IMRT compared with former conventional techniques in terms of reducing toxicities have been evaluated in prospective randomised and non-randomised studies. The most randomised evidence favouring IMRT is about xerostomia.

2.4.2.1. Xerostomia

Multiple randomised controlled trials have shown that with salivary gland-sparing IMRT, RT dose to the salivary glands can be significantly reduced, leading to less post-RT salivary flow decline and less patient-reported and investigator-assessed xerostomia without compromising locoregional control and overall survival [38-40, 158, 173]. In the landmark PARSPORT study [38] comparing IMRT and conventional 3DRT for the treatment of head and neck carcinoma, Nutting et al. found a significant reduction in Grade 2 or worse patient-reported xerostomia (38% vs. 74% at 12 months, and 29% vs. 83% at 24 months) and improved absolute salivary flow rates in favour of IMRT. Similarly, Gupta et al. [39] reported significantly less observer-reported acute and late (up to 36 months) xerostomia in patients treated with IMRT compared with 3DRT. In a

meta-analysis of four prospective phase 3 randomised trials, IMRT showed to be significantly better than conventional RT techniques in terms of salivary gland function sparing [174]. Further, a cross-sectional study of head and neck carcinoma survivors treated with conventional or intensity-modulated radiotherapy showed improved QoL for the IMRT group especially for dry mouth and sticky saliva [175].

2.4.2.2. Dysphagia

So far, no randomised trials have shown a benefit of IMRT in reducing dysphagia. PARSPORT study, without a specific attempt to spare these structures, reported significantly less Grade 3 or worse dysphagia at 12 months among patients treated with IMRT. In a prospective non-randomised study of patients with St III-IV oropharyngeal cancer [176], the patients were treated with an attempt to spare the pharyngeal constrictors, supraglottic larynx and esophagus. In this study, post-RT long term dysphagia score worsened only slightly compared with pre-treatment values. An ongoing prospective randomised DARS study with the attempt to investigate the benefits of IMRT in terms of reducing post-treatment dysphagia will provide more insight to this subject [177].

2.4.2.3. Mucositis

Mucosal sparing with any RT technique can often be difficult because of the tumour location in or near the oral cavity. IMRT's potential in reducing mucositis has not been proven in randomised controlled trials. A prospective trial of oral cavity cancer patients receiving postoperative IMRT reported Grade 2 or more acute mucositis in 66% of the patients [178]. A randomised trial of 60 patients with HNSCC comparing 3DCRT and IMRT with concomitant chemotherapy reported less Grade 2 (71% vs 78,5%) and Grade 3 (6 vs 14.5%) mucositis in patients treated in the IMRT arm, but this was not statistically significant [39]. Another prospective non-randomised trial including 241 patients with HNSCC reported a significant difference in Grade 3 mucositis in favour of IMRT [179], which, by the authors, was explained by the use of a simultaneous integrated boost with lower dose per fraction to the electively treated areas. Moreover, studies investigating mucosal-sparing IMRT techniques [180-182] have shown that

IMRT could be a useful tool to reduce the volume of oral mucosa irradiated with doses higher than 30-32Gy, which seems to be related to a lower incidence of high grade oral mucositis.

2.4.2.4. Quality of life

Several randomised and non-randomised studies have reported on improved quality of life following IMRT when compared with conventional techniques. In a randomised prospective trial of 45 patients with an early-stage nasopharyngeal carcinoma [173], IMRT proved to be significantly better in terms of QoL and parotid sparing. Also, the prospective randomised PARSPORT trial [38] aiming at parotid gland sparing in patients with oropharyngeal/hypopharyngeal carcinoma, showed improved QoL in patients treated with IMRT compared with the conformal techniques. In a prospective randomised trial of 60 HNSCC patients assigned for 3DRT or IMRT showed consistently better QoL scores and more rapid recovery in patients treated with IMRT [183]. Improvements in QoL in patients treated with IMRT have also been seen in non-randomised studies [179, 184, 185].

2.5. Diffusion-weighted MR-imaging in the treatment of HNSCC

Magnetic resonance imaging (MRI) is an increasingly used imaging modality both in the diagnostical process and RT planning of head and neck cancers. Compared with computed tomography (CT), it enables superior soft tissue contrast and better assessment of tumour infiltration to adjacent tissues. It also provides molecular, metabolic, and physiological information of the tissues [186]. Diffusion-weighted imaging (DWI) is a form of functional magnetic resonance imaging based upon measuring the random thermal molecular diffusion of the water molecules in biological tissues, i.e., the Brownian motion [187]. Diffusion leads to signal attenuation, which can be quantified as the apparent diffusion coefficient (ADC) [187]. In high-density tissues, such as tumours, the cellular structures limit the free molecular movement, leading to decrease of ADC, whereas in hypocellular tissues, such as necrosis or fibrosis, the diffusion is high, which can be detected as an increase in ADC.

2.5.1. DWI in predicting RT-induced xerostomia

Traditionally, RT-induced changes in salivary glands have been assessed with quantitative salivary flow rate measurements or salivary gland scintigraphy. Salivary gland scintigraphy has shown to be feasible for predicting salivary gland function after radiotherapy, but its usefulness is limited by the low spatial resolution, complex procedure, and radiation exposure related to it [188]. Quantitative salivary flow rate measurements are feasible for evaluating the severity of the salivary gland damage but do not give any information on morphological or physiological changes in salivary glands [127].

Recently, diffusion-weighted imaging has gained increasing interest in evaluation of RT-induced salivary gland damage.

The salivary gland is an acutely responding tissue, showing significant loss on clinical function within just a couple of weeks after the treatment onset [126]. Irreversible xerostomia is often evident as a long-term complication. By measuring changes in ADC over the RT course, Diffusion-weighted MR-imaging can provide anatomical and functional information about the salivary glands, thus functioning as a potential biomarker for early prediction of RT-related toxicity [189, 190].

According to small prospective studies, all performed on patients with nasopharyngeal carcinoma, ADC of the salivary glands has been showed to increase during and after the RT [191-194], reflecting functional changes followed by RT damage. This increase has been shown to correlate with clinical saliva secretion and patient-assessed grade of xerostomia after RT [192, 193].

Moreover, in a prospective analysis of patients with nasopharyngeal carcinoma treated with radiotherapy, the rate of ADC changes in parotid and submandibular glands at 2 weeks from the treatment onset was associated with the grade of xerostomia at 6 months post-RT [194]. This early ADC increase following RT to the salivary glands has been postulated to be due to an increase of molecular flow in functional cells undergoing apoptosis, which is subsequentially followed by clinical xerostomia, driven by chronic inflammatory response [195].

2.5.2. Other indications of DWI in RT of the head and neck

Since hypocellular environments such as necrotic tissue exhibit high cellular diffusion, it has been speculated whether ADC changes during the treatment course could be useful in the detection of tumour response to radiotherapy. In a study by Kim et al. [196] , lower ADC values before treatment were associated with favourable disease control, and significantly higher ADC-increases during treatment were seen in those patients who achieved a complete response. Similarly, Matoba et al. showed that the increase in primary tumour ADC at 3 weeks from the RT onset correlated with the locoregional control [197]. On the contrary, in a study by King et al. [198], no prognostic value from individual measurements of ADC in pre- and intra-treatment scans was found; instead, low post-RT ADC values were associated with a high risk of locoregional failure at 6 months. A systematic review of twelve studies concluded that high pre-treatment ADCs and low rise in mid- and post-RT ADCs were predictive of locoregional failure following chemoradiotherapy for HNSCC [199].

2.6. Quality of life

2.6.1. Definition of QoL and HRQoL

Quality of life is a subjective, multidimensional construct that aims at providing a comprehensive picture of patients' own appraisal of themselves in the world [200]. According to WHO's definition, QoL is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [201]. Health-related quality of life (HRQoL) represents the individual's subjective perception of the impact of the medical condition or its treatments to their physical, social and emotional well-being [202].

2.6.2. Importance of measuring QoL in patients with HNC

Due to the anatomically complex and functionally important nature of the head and neck region, HNSCC along its treatments tends to have a huge impact on emotional, functional, and social well-being of the patients as well as their caregivers [203, 204] [205]. With the improved survival outcomes related to HNSCC, an increasing number of patients are living with long term side effects of the treatments and consequential impairment of daily functioning [206]. The importance of QoL as an individual endpoint has been increasingly recognised in clinical cancer research. Further, in clinical setting, awareness of the symptom burden can help to find patients in need of early palliative interventions and rehabilitation.

2.6.3. Measuring the QoL

Standardised tools have been developed to measure both general QoL aspects (i.e., "generic") and specific symptoms and conditions related to certain disease and its treatments (i.e., "disease specific"). However, there is no golden standard for measuring QoL or HR-QoL [200]. During the past decades, patient-reported outcome measures (PROMs), as opposed to observer-rated measures, have generally become the mainstay of evaluating the QoL [207, 208]. The most commonly used PROMs among HNSCC patients include the EORTC Quality of life questionnaires (QLQ-C30, QLQ-HN35, QLQ-HN43) [209, 210] and the Functional assessment of cancer therapy – Head&Neck cancer (FACT-H&N) [211, 212]. A widely used HRQoL tool in Finland is the generic 15D instrument [213]. The wide range of different measures evaluating different symptoms and aspects of QoL may make comparisons between studies difficult.

2.6.3.1. 15D

15D is a standardised, self-administered generic HRQoL instrument. The questionnaire consists of 15 questions comprising mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. For each of these dimensions, there

are five different answer options scored from 1 to 5 where 1 represents the best option and 5 the worst. The 15D instrument yields both a profile of the 15 separate HRQoL dimensions values on a scale 0-1 (1= no problems on the dimension, 0 = being dead) as well as a single index quality of life score (15D score) on a scale 0-1 (1 = full health, 0 = being dead). The valuation system for 15D score is elicited from general population-based utility or preference weights [213].

The 15D tool has been validated in multiple conditions and it is widely utilised in Finland. As a generic instrument it is used for comparison between different patient populations and assessment of cost-effectiveness of the treatment.

2.6.4. QoL during and following radiotherapy for HNSCC

Several studies have shown that overall QoL scores decline from the baseline after RT and generally return to the baseline levels after one year[214].

In a large analysis of 859 patients treated with definitive radiation therapy with or without concomitant chemotherapy, the patient-reported quality of life, measured with EORTC-QLQ-30, QLQ-H&N35, and QLQ-C30 questionnaires, showed increasing scores during treatment, with the highest symptom scores being reported at the end of treatment, followed by a gradual recovery during the first 2 years [215]. Early-stage laryngeal cancer had milder symptoms compared with patients classified to have an infrahyoideal of suprahyoideal tumour.

A cross-sectional analysis on 50 patients treated with bilateral neck IMRT for HNSCC showed that at five years after treatment completion, 84% of the patients reported their quality of life being “much better” or “somewhat better” than at the time of the diagnosis [216], measured with the University of Washington Quality of life questionnaire, with 84% rating their overall quality of life as “outstanding” or “very good”.

In a prospective cohort study of 164 patients with head and neck cancer scheduled for concomitant chemoradiotherapy, quality of life was assessed with the EORTC QLQ-C30 and QLQ-H&N35 questionnaires 1 week before and ad 6, 12, 18, and 24 months after

the treatment [203]. The study showed a different course of HRQoL among survivors and non-survivors: in survivors, improvement over time was observed in both global quality of life and several specific domains, whereas in non-survivors, HRQoL scores stayed the same or worsened. In both survivors and non-survivors, emotional functioning improved after treatment but deteriorated long-term.

2.6.5. QoL and survival

Quality-of life is also associated with survival [217-219], and moreover, the baseline HRQoL has a significant impact on OS after treatments [219, 220]. In an analysis of 106 patients scheduled for curative-intent treatment for HNSCC, pretreatment QoL, measured with the EORTC QLQ-30 and the EORTC Head and Neck cancer module, showed to be an independent prognostic factor for survival [220]. An analysis of 495 head and neck cancer patients showed that the physical component score, measured with SF-36, and pain, eating, and speech domain, measured with the Head and Neck Quality of life scores, were associated with survival [221]. In addition, it must be noted that head and neck carcinoma survivors have high rates of depression and suicide, which further stresses the importance of rehabilitation after the treatments [222].

3. Aims of the Study

This thesis focused on evaluation of treatment results and quality of life following IMRT of HNSCC, and evaluation of salivary gland function during the treatment.

The specific aims of the studies were to
1. Assess the treatment outcomes and patterns of relapse following definitive concurrent chemo-IMRT in the treatment of head and neck cancer,
2. Evaluate the quality of life of patients treated with definitive IMRT during the first 12 months after the initiation of the treatments, and
3. Evaluate the feasibility of diffusion-weighted magnetic resonance imaging in the assessment of RT damage to the salivary glands.

4. Materials and methods

4.1. Patients and study design

All patients in Studies I-III had Stage I-IVb HNC and were treated at the Comprehensive Cancer Centre of Helsinki University Hospital with IMRT, which was adopted into clinical practice at our department in 2000. The treatments were given between 2000-2013. All patients had a histopatholgically cofirmed carcinoma of the head and neck, and staging was based on endoscopies and imaging (CT or MRI and PET/CT if necessary). The tumours were staged according to the UICC 7.0 TNM classification (Table 5).

Study I was a retrospective analysis on the first eighty-three HNSCC patients treated with definitive concomitant chemo-IMRT with weekly cisplatin between 2000-2007. The aim of the study was to assess the local control, survival, and patterns of relapse, as well as evaluate acute and late toxicity related to this treatment.

Study II was a prospective study on 64 HNC patients treated with either definitive chemoradiotherapy or radiotherapy whose quality of life was assessed with a generic 15D instrument before and up to 12 months after the treatment.

Study III was a prospective trial on 20 HNSCC patients receiving definitive or postoperative bilateral neck irradiation between May 2012-July 2013. The aim of the study was to evaluate the feasibility of DW-MRI for the assessment of post-RT salivary gland function at rest and in a stimulated state by matching the changes in ADC to RT dose absorbed by the salivary glands and comparing the results with salivary gland scintigraphy.

Study	No of pts (F/M)	Age of pts range (mean)	Year of dg	Clinical stage	Histology	Type of RT	Scheduled concomitant medication
I	83 (14/69)	26-77 (58)	2000-2007	I-IVb	Squamous cell carcinoma	Definitive with concomitant weekly cisplatin	Cisplatin
II	64 (16/48)	40-81 (62)	2007-2012	I-IVb	SCC (n=62), AC (n=1), Lymphoepithelioma (n=1)	Definitive RT (n=10), Definitive CRT (n=54)	Cisplatin (50), Cetuximab (2), Cisplatin + Panitumumab (1), Paclitaxel (1), None (10)
III	20 (4/16)	42-72 (60)	2012-2013	II-IVb	Squamous cell carcinoma	Definitive CRT (n=19), postoperative CRT(n=1)	Cisplatin

Table 5. Patient and treatment characteristics in Studies I-III

4.2. Imaging for treatment planning

A thermoplastic head and neck immobilisation device was used in 89 patients (Studies I-III) and a stereotactic head and neck immobilisation device in 78 patients (Study I). The treatment planning in all studies based on planning CT scans with the slice thickness of 5.0mm until the year 2000, and 2.5mm from there on. In most cases, the planning CT scan was made with intravenous contrast enhancement. Since 2011, all patients scheduled for definitive IMRT for HNC also went through a planning MRI scan of the head and neck; and in Study III, the pre-RT scans also included EPI DW-MRI series with the b values of 0 and 700.

4.3. Treatment

Treatments are summarised in Table 5.

All patients in Studies I-III (n=167) received IMRT, and for all but one of the patients (in Study III) it was given as a definitive treatment. The remaining patient received RT in a postoperative setting. For all patients, irradiation was performed with a 6MV beam from a linear accelerator using dynamic multileaf collimation (MLC) with the sliding window principle (IMRT) or dynamically moving MLC as a function of gantry angle (VMAT, since 2010 together with IMRT). The Clinical Target Volume (CTV) 1 typically encompassed the primary tumour with a 5-10mm margin and the draining lymph node areas, and a 3-5mm margin was used to obtain the Planning Target Volume (PTV). For all patients but one, RT was given with 2Gy daily fractions so that PTV1 was irradiated up to 50Gy, whereafter the RT volume was reduced (once or twice) based on new planning CT scans, and the high risk/macroscopic tumour areas were boosted up to the total dose of 60-70Gy. In addition, one patient (in Study II) received 50Gy with 2Gy daily fractions to the elective areas and 62.5Gy with 2.5Gy daily fractions to the primary tumour area as a simultaneous integrated boost (SIB). Most patients (n=157) received concomitant chemotherapy, and the most usual planned chemotherapeutic agent was weekly cisplatin (n=153). Four patients received another concomitant medication (cetuximab n=2, cisplatin + panitumumab n=1 and paclitaxel n=1). Ten patients, all in Study II, did not receive concomitant chemotherapy.

4.4. Evaluation of Health-Related Quality of Life (Study II)

All patients in Study II were asked to fill in the 15D questionnaire prior to and at 3, 6 and 12 months after the treatment onset. Completed questionnaires were available for all of the 64 included patients at baseline and at 12 months; 51 (79.7%) patients filled in all of the four questionnaires and the remaining 13 (20.3%) patients filled in three questionnaires. 15D results at different time points were compared with the baseline results of the patients themselves as well as with the scores of the age-standardised general population, which was obtained from the National Health 2000 Health Examination Survey. The sample of the general population was weighted to reflect the age distribution of the present patients.

The minimal clinically important change in the 15D score was estimated at 0.018 for improvement and -0.045 for deterioration.

4.5. Evaluation of Salivary Gland Function (Study III)

All patients went through MRI imaging and salivary gland scintigraphy prior to and at a mean of 6 months after completing the radiotherapy.

The pre-treatment MRI scans included the routinely used fast recovery fast spin echo T2-weighted and contrast-enhanced T1-weighted images, which were obtained with the patient wearing the head&neck immobilisation mask. For the purposes of this study, T2- and DWI sequences were thereafter obtained with 32-channel head-neck-spine coil with the patient's head supported with the vendor's cushions. The post-RT scan included only the T2 and DWI sequences with the 32-channel HNS coil.

DWI images were obtained with b factors of 0 and 700. Salivary stimulation was performed with two 500mg tablets of ascorbic acid, which the patients were advised to bite. The first two DWI series were acquired at rest, and after the salivary stimulation, the DWI sequence was repeated a mean of ten times.

ADC was measured on ADC maps using regions of interest placed over each of the salivary glands. For this purpose, all of the salivary glands, excluding large vessels, were manually delineated on DWI sequences, and for anatomical reference, also on T2-weighted images. DWI scans were manually registered to each time series to minimise the interpretation bias caused by the geometric distortion in EPI DWI images.

For salivary gland scintigraphy, dynamic 99mTc-pertechnetate (185MBq) imaging was performed, and a lemon juice bolus was used to stimulate salivary excretion at 15 min from the onset of the imaging. Parotid and submandibular glands on each patient were segmented in the dynamic image series, resulting in four time-activity curves. An additional ROI was used for background correction. The salivary ejection fraction (sEF) was calculated using the equation (Cmax-Cmin)/(Cmax-Cbg), where Cmax and Cmin are the detected counts in the salivary gland ROI immediately before and after the stimulus, and Cbg is the background count. Relative ejection fraction was calculated from

sEF(t)/sEF(0), where sEF(t) is the ejection fraction at six months after RT, and sEF(0) is the baseline value.

4.6. Evaluation of treatment-related acute and late toxicity (Studies I-II)

Treatment related toxicity was scored according to CTCAE 3.0. The toxicities were recorded retrospectively from the patient records.

4.7. Statistical analyses

In all studies, data were analysed using the SPSS software (SPSS Inc., Chicago, IL, USA). Local control and survival rates were calculated using the Kaplan-Meier product-limit estimate method (Study I). In study II-III, t-test, Mann-Whitney test and Wilcoxon Signed Ranks test were applied to compare differences between ADC values and 15D scores. Results were considered statistically significant if $p<0.05$.

4.8. Ethical considerations

All studies were designed and conducted in agreement with the Declaration of Helsinki. An institutional research permit was obtained for each study from Helsinki and Uusimaa Hospital, department of Oncology. An institutional Research Ethics Board approval was granted for the study III, and an informed consent was obtained from all patients prior to participation.

4.9. Results

4.9.1. Local control, survival and patterns of relapse (Studies I-II)

In Study I, the 2-year locoregional control, overall survival, and disease specific survival rates were 84%, 82%, and 89%, respectively. The corresponding 5-year Kaplan-Meier estimates were 79%, 69%, and 76% (Figures 2-3). Eight out of 83 patients (9.6%) had persistent locoregional disease after treatments: two in the primary tumour site, three at the nodal regional site, and three at both sites. All of these failures occurred at the high-dose CTV volumes at the site of the original macroscopic tumour. During the follow-up period (mean 51 months, range 24-99 months) additional ten locoregional failures were encountered, three of which were at the primary tumour site, six at nodal sites, and one at both sites. Nine of these recurrences were at high-dose CTV volume, and one at the margin of the high-dose nodal area. Distant metastases were observed in 11 patients during the follow-up period. At the end of the follow up, 22 (25%) patients were dead, 15 of which due to persistent cancer.

In Study II, locoregional failure was observed in five patients (7.8%) and distant failure in one patient (1.6%) during the 1-year follow-up. Three of these patients had residual disease at 3 months after the treatment, the rest of the failures were detected later during the follow-up period.

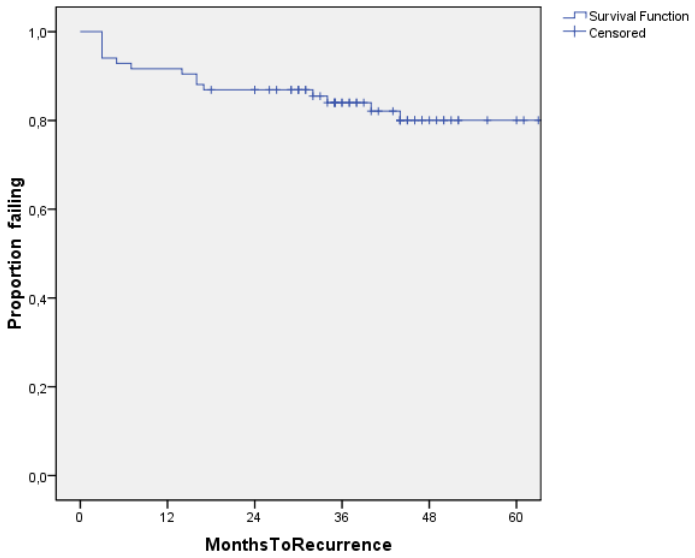

Fig. 2. Locoregional control following definitive chemoIMRT with weekly cisplatin

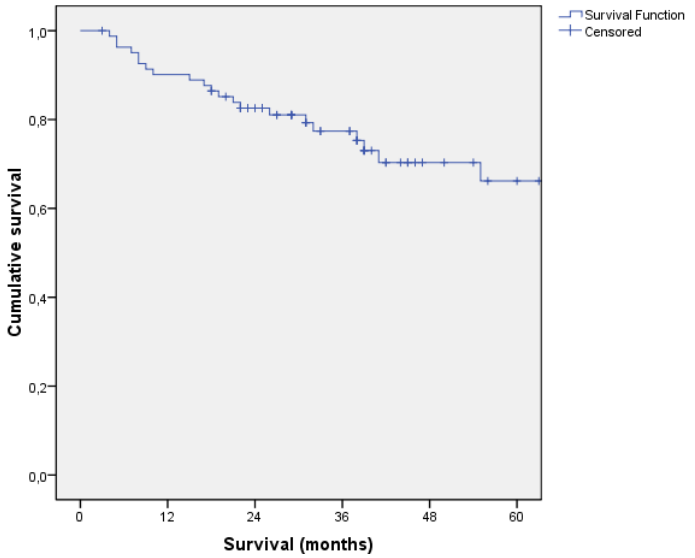

Fig. 3. Overall survival following definitive chemoIMRT with weekly cisplatin

4.9.2. Treatment-related toxicity (Studies I-II)

In Study I, the most common acute radiation-induced side effects were local skin and mucosal irritation, which occurred in 100% and 94% of the patients, respectively. Dermatological toxicity was mild to moderate (Gr 1-2) in all but one patient, whereas Grade 1-2 mucositis was observed in 70% of the patients and Grade 3 mucositis in 24% of the patients. Medication for mucosal pain was needed in 53 (64%) patients. Anemia, thrombocytopenia, and neutropenia were reported in 96%, 70%, and 51% of the patients, respectively. Nausea was reported in 70% of the patients; in five patients, nausea was of Grade 3. Mild to moderate serum creatinine elevations were seen in 37% of the patients but no irreversible renal toxicity was recorded. Eighteen (22%) patients needed hospitalisation during the treatment.

In Study II, treatment-related acute toxicity was mostly of mild to moderate grade (Gr 1-2). The most common Grade 3-4 toxicities were leukopenia (25%), mucositis (19%), infection (16%), and nausea (8%), in addition, single cases of Grade 3-4 thrombocytopenia, serum creatinine elevation, tinnitus, and hearing loss were recorded.

4.9.3. Treatment adherence (Study I)

In Study I, at least five cycles of cisplatin were given in 71 (86%) patients. Dose reductions were necessary in 25 (30%) patients. 71 patients (86%) were treated in the planned total treatment time. Unplanned treatment gaps of 2-13 days were recorded in 12 (15%) of the patients: nine due to side effects and three due to patient compliance.

4.9.4. Health-related quality of life measured with 15D (Study II)

The mean 15D scores of all patients at baseline and 3, 6, and 12 months were 0.886, 0.829, 0.860 and 0.862, respectively, showing a clinically meaningful and statistically significant decline at 3 months and gradual, statistically significant improvement towards the end of the follow-up. The mean 15D scores at baseline and 12 months timepoint did not differ in clinically meaningful or statistically significant manner from those of the general population.

At 3 months, significantly lower scores compared with the baseline were reported on the dimensions of Eating, Usual activities, Discomfort and symptoms, Vitality, and Sexual activity. All these dimensions showed significant improvement ad 6 and 12 months.

The dimension of Depression showed notable, even though not statistically significant deterioration at 3 months compared with the baseline, with notable improvement towards the end of the follow-up, exceeding the baseline scores statistically significantly at 12 months. Additionally, other domains reflecting mental well-being, such as Mental function and Distress, showed similar improvement during the follow-up. However, on none of these dimensions, the patient-reported scores reached those of the general population during the follow-up.

Patients with pharyngeal cancer reported markedly worse scores on most domains compared with patients with laryngeal carcinoma.

4.9.5. Diffusion-weighted MRI and scintigraphy in evaluation of salivary gland function (Study III)

The pre-RT mean ADC ($10^{-3}mm^2/s$) of unstimulated salivary glands was 1.15 for parotid glands and 1.35 in submandibular glands. The corresponding post-RT values were 1.48 and 1.72, respectively. This increase was statistically significant for both parotid and submandibular glands ($p<0.001$) and correlated linearly to the RT dose absorbed by the salivary glands.

After salivary stimulation with ascorbic acid, the ADC showed an initial increase and subsequent decrease. This pattern was seen both pre and post RT. The maximum ADC value was significantly higher in post-RT setting compared with the pre-RT state ($p<0.001$).

Relative ejection fraction, measured with the salivary gland scintigraphy, declined as a function of RT dose absorbed by the gland. A moderate statistical correlation between pre- and post-RT ADCs at rest and rEFs for all salivary glands was found ($r=-0.38$, $p<0.01$) .

Figure 4 presents the T2 and diffusion sequences and baseline ADC maps of a single patient before and at 6 months after the treatments.

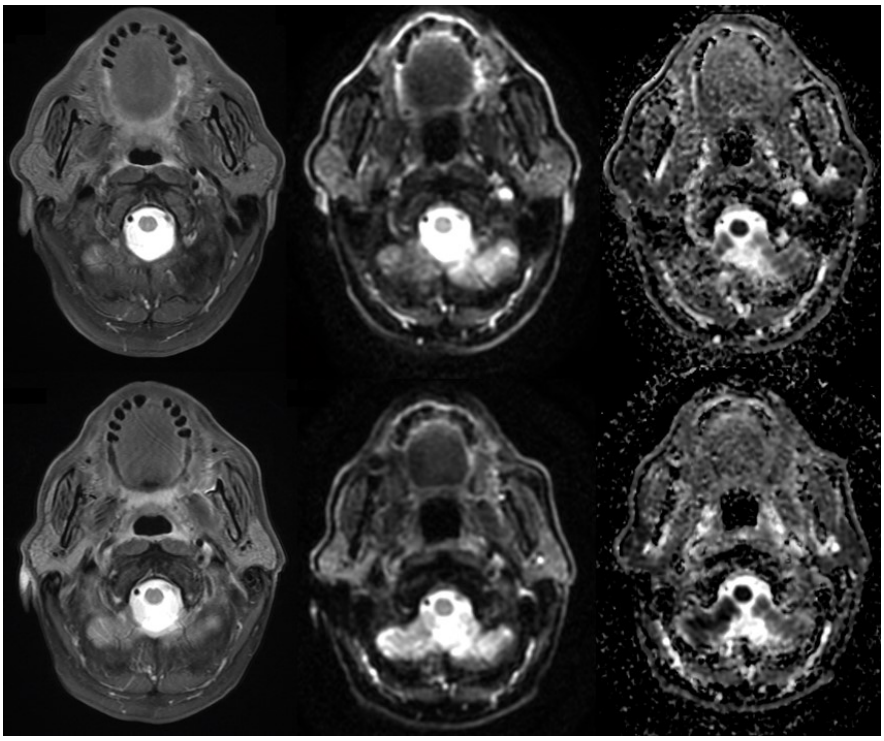

Fig. 4. T2, diffusion and baseline ADC maps of an example patient before (upper row) and at 6 months after (lower row) completing the RT

5. Discussion

Radiation treatment of head and neck carcinoma requires balancing between optimal oncological results and minimal functional impairment. While the modern chemo-IMRT has provided excellent survival outcomes, morbidity and quality of life remain concerns.

The current studies focused on evaluation the treatment outcomes of and quality of life following IMRT of the head and neck, and evaluation of the salivary gland function during and after RT.

5.1. Disease control and patterns of recurrence

In our studies, IMRT with or without concomitant chemotherapy resulted in excellent locoregional control: In Study I, 2-year locoregional control rate was 84%, and in Study II, 1-year locoregional control rate was 92,2%. All of the eight primary locoregional failures and nine out of ten subsequent locoregional failures in Study I were at the high-dose volumes. The remaining recurrence was at the margin of high-dose nodal area. These locoregional control rates and patterns of failure reported in Studies I and II compare extremely well with those reported in the literature.

Randomised trials from large-volume centres with high expertise in head and neck IMRT have reported on similar or better oncological results on patients treated with IMRT compared with conventional techniques. This benefit comes with reduced toxicity, as IMRT allows for more conformal dose distribution and thus reduced dose to surrounding healthy tissues. Thus, in capable hands, the use of IMRT will result in excellent treatment outcomes.

Despite of the excellent outcomes reported by several high-quality centres, special attention needs to be paid to precise target volume delineation and accurate dose delivery in everyday clinical practice. Several studies have reported on impaired OS among HNSCC patients treated at low-volume RT centres, with incorrect target volume delineation and radiotherapy planning being the main contributors to poor outcome [73, 223]. For example, in an analysis of 107 patients with HPV-positive oropharyngeal carcinoma referred to a tertiary centre for consideration of re-irradiation, Chen et al. found 41% of the failures to be a marginal miss and 18% a true miss [168]. The authors pointed out the

importance of adequate target delineation and concluded that given the well-known radiosensitivity of HPV-related oropharyngeal cancers and scarce loco-regional failures related to them, contouring error should be assumed to be the cause of recurrence unless proven otherwise. Moreover, in a population-based study of 6212 patients, Boero et al. [224] evaluated the influence of radiation oncologist experience on outcomes in patients treated with RT for HNC. In this analysis, patients were treated by 788 radiation oncologists, and the number of HNC patients treated by a provider per year (provider volume) ranged from 1 to 70. A multivariable analysis showed a decreased mortality among patients treated by high-volume providers. Among HNC patients treated with IMRT, risk of all-cause mortality decreased by 21% for every additional five patients treated per provider per year. Keeping this in mind, head and neck IMRT should always be planned and delivered by experienced caregivers. Strict adherence to contouring guidelines and institutional peer-review of the treatment plans are necessary to ensure the treatment quality.

Despite of the precise target volume delineation and high-quality treatment delivery achieved with IMRT, around thirty percent of patients treated with RT for HNC will eventually develop a locoregional relapse [163], a vast majority of which occur in the high-dose volumes [170, 171, 225-230]. The risk of in-field recurrence may be attributed to intrinsic radioresistance, particularly tumour hypoxia [231] [232]. The reportedly low risk of geographical miss with IMRT could yield a potential means of improving the outcomes by dose-escalation to high-risk areas [172].

5.2. Health-related quality of life

The significance of quality of life as one of the most important endpoints in the treatment of HNSCC has gained increasing interest. The anatomical location of head and neck tumours can have a detrimental effect on patients' functional and social ability, which also affects their families [204]. With generally good survival outcomes following IMRT of HNSCC, an increasing number of patients must cope with the long-term consequences of the treatments.

Assessment of QoL is complicated since the measures are not uniform. Patient-reported outcome measures (PROMs) are nowadays the golden standard of HRQoL measurements [233]. Unlike observer-reported measures, which often underestimate the symptoms, PROMs take into account patients' own perspective and thus give a more realistic picture of the well-being of the patients.

In our Study II, the mean 15D HRQoL score declined significantly at 3 months after treatment onset and then gradually recovered towards the end of the 12-month follow-up, while specific domains for hearing, eating, and usual activities remained significantly lower compared with the baseline at the end of the follow-up. Similar pattern of initial decrease and subsequent recovery in overall QoL after IMRT for HNSCC has been reported previously using other questionnaires (SF-36, EORTC QLQ-H&N35, EORTC-QLQ-C30) [173, 183]. This may be partly attributable to patients adapting to their disabilities over time [234, 235], despite some function-specific domains, such as those reflecting xerostomia, fatigue, and physical/cognitive functioning remain impaired.

The high rate of depression and suicide among HNSCC patients [222] stresses the significance of mental well-being as an important endpoint after treatments. In our Study II, the domains reflecting mental well-being, such as Depression and Mental function, declined at 3 months but gradually recovered during the follow-up. At 12 months, depression score was statistically significantly improved compared with the baseline score. However, on most domains reflecting mental well-being, such as Distress, Depression, Vitality, and Sexual activity, the patient-reported scores remained significantly lower compared with the general population throughout the 12-month follow-up.

Quality of life has been shown to be a strong prognostic factor on overall survival among patients with HNSCC [217-220]. Poor QoL may surrogate for recurrent or advanced disease and may relate to systemic physiologic responses associated with cancer burden [236]. Patients with poor QoL may tolerate treatments poorly and require less intensive treatment strategies.

More efforts are needed to take this into account in future studies, and more uniform measures would be useful to facilitate comparison between studies.

5.3. Evaluation of salivary gland function

Salivary gland dysfunction and consequential xerostomia remain one of the most distressing long-term adverse events following head and neck IMRT. Permanent xerostomia has adverse impacts on oral functions such as eating and speaking and predisposes to mucosal and dental infections [237-239], thus reducing the quality of life.

The mechanisms of salivary gland damage related to RT still remain incompletely understood [240]. Due to the anatomical location of tumours of the head and neck, sparing of salivary glands is not always possible even with highly conformal RT delivery techniques. Measuring of physiological changes during RT may point out the patients most at risk of severe toxicity and allow for biologically adaptive RT strategies in the future [241].

Our main finding in Study III was the increase of post-RT ADC in both parotid and submandibular glands. This ADC increase correlated linearly to the RT dose absorbed by the glands. Further, we found a moderate correlation between pre- and post-RT ADC in unstimulated glands and ejection fraction measured with scintigraphy.

In subsequent prospective studies on diffusion-weighted MRI for evaluation of salivary gland function during and after RT of the head and neck, a similar pattern of post-RT ADC increase has been reported [191-194]. Fan et al. found a linear correlation between the absorbed dose and ADC increase [192]. Moreover, Fan [192] and Shi [193] found a correlation between post-RT ADC increase and patient-reported post-RT xerostomia scores. Of note, Zhang [194] reported on a significant ADC increase already at 2 weeks after initiation of the treatment. This early ADC increase showed a correlation with the degree of patient-reported xerostomia 6 months post-RT. This early ADC rise was postulated to be due to the increased molecular flow of the functional cells undergoing apoptosis, eventually leading to clinical xerostomia.

5.4. Future perspectives in the radiation therapy of HNSCC

5.4.1. Treatment de-intensification in HPV positive oropharyngeal carcinoma

As nowadays widely acknowledged, HPV-associated oropharyngeal cancers exhibit significant radiosensitivity and superior prognosis compared with their HPV-negative counterparts, and several deintensification studies have been conducted with the aim of reducing treatment-related toxicities while still maintaining the oncological efficacy. Phase II trials have shown comparable survival outcomes and less toxicity following de-intensified definitive RT but randomised data directly comparing standard-dose RT and de-intensified RT are needed to confirm these findings. In two randomised phase III trials, cetuximab failed to show noninferiority compared with cisplatin as a concurrent chemotherapeutic agent. In the MC1273 and MC1675 trials evaluating aggressive de-intensification of postoperative RT, patients with ENE showed inferior survival outcomes. Prospective trials investigating RT deintensification in response to induction chemotherapy reported on favourable survival outcomes in patients with good response to induction therapy.

The heterogeneity among deintensification protocols and HPV-diagnostics as well as lack of long-term follow-up data from randomised Phase III trials make the interpretation of these studies difficult. Further, the considerable rate of toxicity associated with induction chemotherapy raises questions whether a moderate RT dose reduction followed by a favourable response to ICT actually leads to a reduction in total toxicity. Importantly, in non-responders to ICT, delay of definitive CRT could compromise the treatment outcome.

In conclusion, optimal de-intensification approach for HPV-related oropharyngeal carcinoma remains still under investigation. Long-term follow-up data as well as phase III randomised data are needed to determine the optimal way of deintensification. Until then, no specific recommendations on treatment deintensification can be given.

5.4.2. Proton therapy

As opposed to IMRT, proton therapy (PT) is associated with little or no beam exit dose, which allows for more conformal dose distribution and potentially less toxicity compared with photon therapy [242]. This benefit associated with PT is due to the physical property of protons to deposit their energy at a narrow range of tissue depth by the Bragg peak [243]. However, the use of proton beam therapy globally is relatively low due to the limited availability and high installation and operating costs [244]. Hence, current data on proton beam therapy in the treatment of HNSCC are largely confined to comparative dosimetric analyses and retrospective single-institution series. Evidence from randomised trials comparing PT and IMRT are still missing. In definitive treatment, PT has mostly been examined in patients with nasopharyngeal [245-247] and oropharyngeal carcinoma [248-251]. Its feasibility has also been examined for re-irradiation of HNSCC [252-254]. Several randomised trials are ongoing to investigate the cost-effectiveness and feasibility of PT in terms of oncological outcomes and reduction of toxicities. More data is needed to establish the role of proton therapy in the treatment of HNSCC.

5.4.3. Boron neutron capture therapy

Boron neutron capture therapy (BNCT) is a radiation treatment modality based on nuclear capture and fission following the irradiation of non-radioactive boron (^{10}B) with low-energy thermal neutrons. This leads to the production of high linear energy transfer alpha particles and a recoiling lithium (^{7}Li) nuclei. Since alpha particles and ^{7}Li only have a range of 5 to 9 μm in tissue, they produce dense ionisation along their tracks, yielding localised radiation effect in the boron-containing cells [255]. In patients with head and neck cancer, BNCT has shown to yield responses in primary setting [256, 257] and for re-irradiation of locally recurrent tumours [258, 259]. However, despite the encouraging results, current data on BNCT is very limited and the interpretation of findings is difficult due to heterogeneity between different study designs. Future research with our novel accelerator-based BNCT facility is being eagerly anticipated.

5.4.4. Adaptive radiotherapy and MRI-guided radiotherapy

With complex RT techniques, great care should be taken in target volume delineation and treatment delivery. Changes in tumour volume or patient anatomy might lead to dosimetrical changes and eventually to treatment failure or increased toxicity. Adaptive radiotherapy (ART), based on sequential imaging during the treatment and adapting the RT plans to adjust to anatomical changes, might be helpful in certain situations [260]. A dosimetric study showed that the use of ART reduced the volume of parotid glands receiving significant RT dose [261], and in a randomised trial an improvement in locoregional control was seen in the ART arm [262]. Magnetic resonance guided radiotherapy allows for superior soft-tissue contrast, repetitive imaging without additional radiation exposure, target volume gating, and online plan adaptation [263]. With the anatomical and functional information provided by MR-imaging, MR-guided RT could allow for anatomical and functional treatment adaptation in the future, thus allowing for better sparing of the organs at risk (OARs), adjusting the target volumes, and dose escalation or de-escalation according to the response [264, 265]. Currently, the usefulness of MRI-guided RT is limited by lack of availability, heterogeneity in imaging acquisition, incompatibility with VMAT and longer treatment duration compared with image-guided IMRT. Several trials are ongoing to investigate the feasibility of MRI-guided RT for the treatment of HNSCC.

6. Conclusions

1. IMRT with concomitant weekly cisplatin provides excellent locoregional disease control with no unexpected toxicity in the treatment of patients with locoregionally advanced HNSCC.
2. The 15D HRQoL scores of the patients receiving definitive IMRT for HNSCC declined during the first 3 months after the treatment and improved gradually towards the end of the 12-month follow-up. The instrument was feasible in detecting differences between different primary tumour sites.
3. Post-RT ADC changes correlate with RT dose absorbed by salivary glands and rEF measured with SGS. DW-MRI seems to be a useful tool for detection of radiation-induced physiological changes in the major salivary glands in patients treated with IMRT for head and neck cancer.

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9. Original publications