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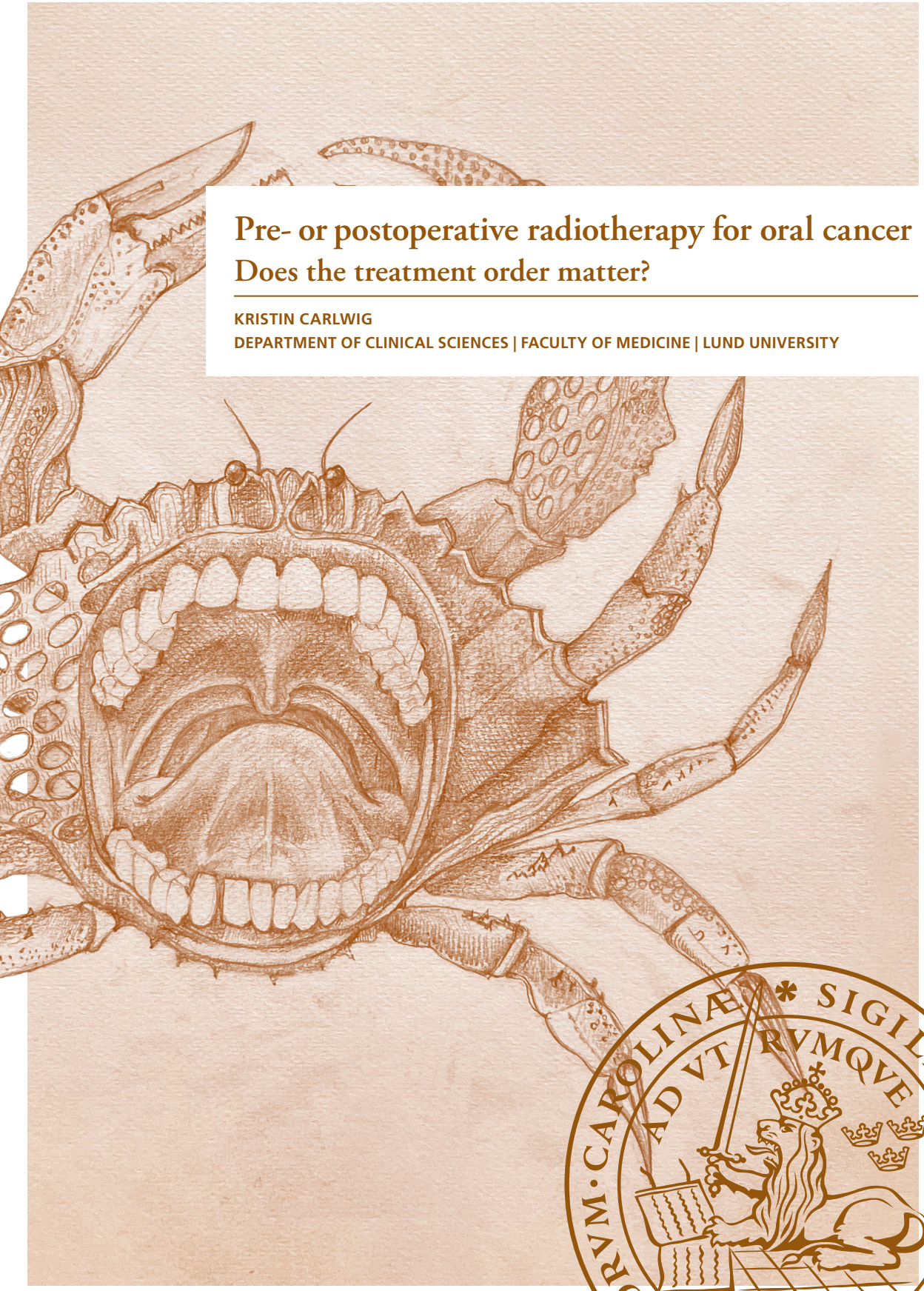

Pre- or postoperative radiotherapy for oral cancer
Does the treatment order matter?

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Kristin Carlwig

LUNDS UNIVERSITET

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be publicly defended at The Lecture Hall at the Department of Oncology and Radiation Physics on 26 September 2025, at 08:30.

Faculty opponent
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Organisation: LUND UNIVERSITY, Department of Clinical Sciences, Otorhinolaryngology and Head & Neck Surgery

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Author: Kristin Carlwig

Title: Pre- or postoperative radiotherapy for oral cancer – Does the treatment order matter?

Abstract

Background: The curatively intended treatment for resectable locally advanced stages of oral cavity cancer (OCC) generally involves a combination of surgery and radiotherapy (RT). However, whether to apply RT first and then proceed with surgery, or to resect the cancer and subsequently administer RT, has not been extensively studied.

Aims: This thesis examines various aspects of pre- versus postoperative radiotherapy in the treatment of OCC, focusing on mandibular complications after mandibulotomy, overall survival (OS), locoregional control (LRC), side effects, postoperative complications, health-related quality of life (HRQoL), and an economic evaluation. Additionally, two different RT fractionation concepts, i.e., accelerated or conventional fractionation, are explored. The overall clinical goal is to contribute knowledge for future discussions and treatment choices.

Methods: In Paper I, we retrospectively compared mandibular complication rates between patients exposed to RT before or after surgery involving a mandibulotomy to access the tumour. Papers II-IV evaluated the results from the Swedish multicentre randomised controlled ARTSCAN 2 trial, where patients with oral cancer squamous cell carcinoma (OCSCC) received either preoperative accelerated fractionation (AF) RT or postoperative conventional fractionation (CF) RT. In Paper II, which is the primary report of the ARTSCAN 2 trial, we compared the OS and LRC rates, as well as the acute and late toxicity rates. Paper III assessed the early postoperative surgical and medical complication rates in the preoperatively irradiated group (AF RT) compared to the group not yet irradiated. In Paper IV, we compared the HRQoL data and performed an economic evaluation (a cost-utility analysis).

Results: To summarise, patients exposed to RT before a surgical resection involving a mandibulotomy for tumour access experienced significantly more complications at the mandibulotomy site compared to those receiving postoperative RT. In the ARTSCAN 2 study, no statistically significant differences in OS or LRC were observed, but acute and late toxicity were significantly more pronounced in the preoperative AF RT arm. Early postoperative complications did not differ significantly between the preoperative AF RT group and the group not yet exposed to RT. Patients exposed to preoperative AF RT experienced a significantly greater negative impact on their HRQoL compared to the postoperative CF RT group. Postoperative CF RT was found to be more beneficial than preoperative AF RT in the cost-utility analysis.

Conclusions: Postoperative CF RT should continue to be the primary treatment for patients with OCC when combining surgery and RT.

Key words: Oral cancer, Oral surgery, Preoperative radiotherapy, Postoperative radiotherapy, Accelerated fractionation, Postoperative complications, Quality of life, Cost-utility analysis

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Table of Contents

List of papers

I. Carlwig K, Fransson P, Bengtsson M, Gebre-Medhin M, Sjövall J, Greiff L. Mandibulotomy access to tumour sites: fewer complications for postoperative compared with preoperative radiotherapy. Int J Oral Maxillofac Surg 2021; 50: 851-856.

II. Wennerberg J, Gebre-Medhin M, Nilsson P, Brun E, Kjellén E, **Carlwig K**, Reizenstein J, Kristiansson S, Söderkvist K, Wahlgren M, Zackrisson B, on behalf of the ARTSCAN study group, Högmo A, Hammarstedt-Nordenvall L, Sjödin H, Wickart-Johansson G, Farnebo L, Rzpecki J, Lödén B, Cederblad L, Ekberg T, Bergström S. Results from a prospective, randomised study on (accelerated) preoperative versus (conventional) postoperative radiotherapy in treatment of patients with resectable squamous cell carcinoma of the oral cavity – The ARTSCAN 2 study. Radiother Oncol 2022; 166: 26-32.

III. Carlwig K, Gebre-Medhin M, Greiff L, Hällman P, Nilsson P, Wennerberg J, Zackrisson B, Sjövall J. Preoperative radiotherapy does not increase the risk for early complications following surgery for oral cancer: a study on data from the randomized ARTSCAN 2 trial. J Otolaryngol Head Neck Surg. Epub 14 June 2025.

IV. Carlwig K, Jarl J, Nilsson P, Rasmusson E, Sjövall J, Silfverschiöld M, Zackrisson B, Gebre-Medhin M, Greiff L. Quality of life and cost-effectiveness of preoperative accelerated versus postoperative conventional radiotherapy for oral cavity cancer: results from the randomised ARTSCAN 2 trial. Manuscript.

Abbreviations

AF	Accelerated fractionation
ARTSCAN	Accelerated radiotherapy of squamous cell carcinoma of the head and neck
CF	Conventional fractionation
ChRT	Chemoradiotherapy
CI	Confidence interval
COI	Cost of illness
CT	Computed tomography
CUA	Cost-utility analysis
DFS	Disease-free survival
DOI	Depth of invasion
ENE	Extranodal extension
EORTC	European Organisation for Research and Treatment of Cancer
Gy	Gray (unit of ionising radiation absorbed dose)
HADS	Hospital anxiety and depression scale
HR	Hazard ratio
HF	Hyperfractionation
HRQoL	Health-related quality of life
HU	Health utility
LRC	Locoregional control
MRI	Magnetic resonance imaging
ND	Neck dissection
OCC	Oral cavity cancer
OCSCC	Oral cavity squamous cell cancer
OPC	Oropharyngeal cancer
ORN	Osteoradionecrosis
OS	Overall survival
PET CT	Positron-emission tomography CT

PFS	Progression-free survival
PS	Performance status
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
RT	Radiotherapy
SCC	Squamous cell cancer
SLNB	Sentinel lymph node biopsy
SN	Sentinel node
SVF	Standardiserat vårdförlopp (Standardised care pathway)
UICC	Union for International Cancer Control

Thesis at a glance

Aim	Design	Principal findings
Paper I To assess the local complication rates in OCC/OPC cancer patients subjected to surgery + pre- versus postoperative RT, where a mandibulotomy was required to gain access to the tumour.	A retrospective study (case series).	A significantly greater number of complications were observed in the preoperative RT group compared to the postoperative RT group.
Paper II To compare the OS and LRC between the two groups of patients with OCSCC exposed to either preoperative AF RT or postoperative CF RT, and to assess physician-evaluated side effects.	A multicentre RCT (ARTSCAN 2).	While no significant differences in OS or LRC were observed between the study groups, side effects were more common in the preoperative AF RT group.
Paper III To assess the early postoperative surgical and medical complication rates in the preoperatively irradiated group (AF RT) compared to the group not yet irradiated.	A multicentre RCT (ARTSCAN 2).	No significant differences were observed in surgical or medical complication rates between the two treatment groups.
Paper IV To compare HRQoL data between the two treatment groups of the ARTSCAN 2 study and perform a cost-utility analysis.	A multicentre RCT (ARTSCAN 2).	HRQoL was significantly more impaired in the preoperative AF RT group. The CUA revealed that preoperative AF RT was both more costly and less effective.

Introduction

Cancer treatment is a continuously evolving field. New therapies are being introduced, and existing ones are being modified. For patients with cancer in the oral cavity, one of the subsites of head and neck cancer, the treatment has transformed over the past few decades. In the first half of the 20th century, monotherapy with either surgery or radiotherapy (RT) was the preferred option, but by the 1950s, combining surgery with RT improved outcomes and became the standard treatment for patients with locally advanced resectable disease.

However, the best treatment sequence – whether to perform RT first and then the surgical resection (preoperative RT) or to start with the resection and subsequently administer RT (postoperative RT) – has not been thoroughly investigated for oral cavity cancer (OCC). Nonetheless, based primarily on studies concerning head and neck cancer as a whole, postoperative RT is now recognised as the gold standard for locally advanced OCC, albeit with variations in the administration of RT.

This thesis aims to examine the outcomes of RT given before or after surgery in patients with oral cancer. It focuses on locoregional control (LRC), overall survival (OS), complication rates, morbidities, health-related quality of life (HRQoL), and cost-effectiveness, while considering the treatment order and the fractionation scheme of RT. Ultimately, the purpose is to inform future clinical decision-making and healthcare prioritisations.

Background

Oral cavity cancer

Oral cavity cancer (OCC) constitutes approximately 28% of all head and neck cancers in Sweden, and comprises six different subsites: the tongue, gingiva, floor of the mouth, buccal mucosa, hard palate, and others (retromolar trigone, gingivobuccal sulcus), with the tongue being the most common site (41%), followed by gingival localisation (26%) (**Figure 1**). Oral cavity squamous cell carcinoma (OCSCC) is the dominant histological subtype, accounting for 92% of all OCC in Sweden[1].

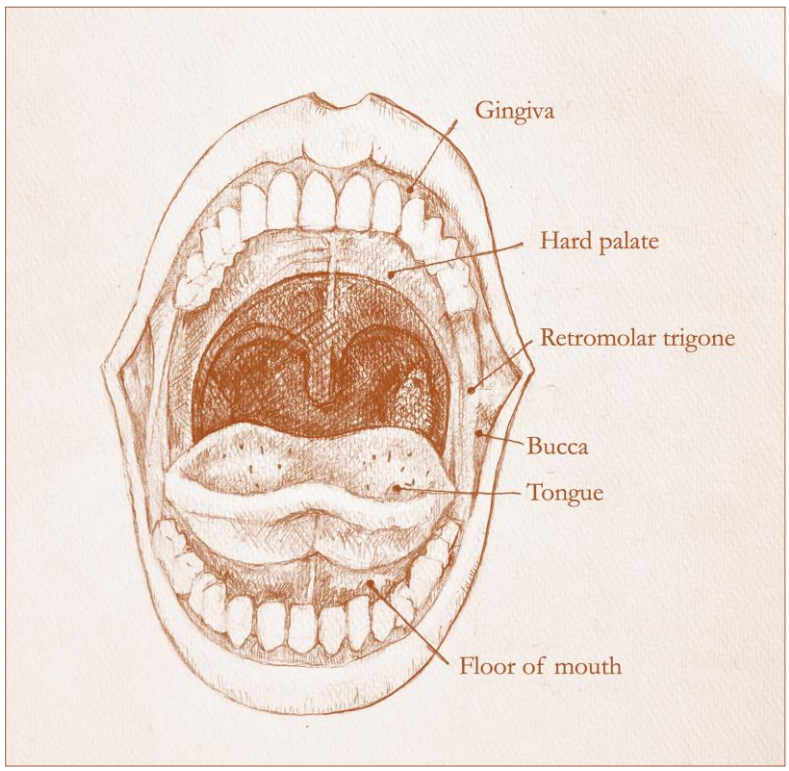

Figure 1. Subsites of the oral cavity

Incidence and epidemiology

OCC (lip cancer included) is the 16th most prevalent cancer globally, affecting approximately 400,000 patients annually[2]. In Sweden, 504 patients were diagnosed with OCC in 2023, of which 467 had OCSCC (**Figure 2**). These figures correspond to an age-standardised incidence rate of 4.9 and 4.0 per 100,000 for men and women, respectively[1]. The median age at diagnosis is around 70 years. The incidence in Sweden is rising[3], with an age-standardised cumulative annual increase from 2008 to 2022 of 1 per 100,000 inhabitants[4]. The cause of the increase is not known. Specifically, in recent decades, there has been a noted increase in tongue squamous cell cancer (SCC) among younger adults, the reason for which remains unclear[5].

Common symptoms include localised pain or discomfort, a lump or a non-healing wound in the mouth, bleeding, difficulties opening the mouth (trismus), or a lump in the neck. Tobacco smoking, excessive alcohol consumption, poor dental hygiene, and betel quid chewing – especially prevalent in Asia – are known risk factors for developing OCSCC. However, in many cases, no specific cause can be identified. Interestingly, despite a decrease in smoking rates in Sweden from 17% to 5% between 2004 and 2024, the incidence of OCSCC is on the rise[6]. Unlike oropharyngeal cancer (OPC), where human papillomavirus (HPV) significantly impacts prognosis, HPV has not been associated with OCSCC[7].

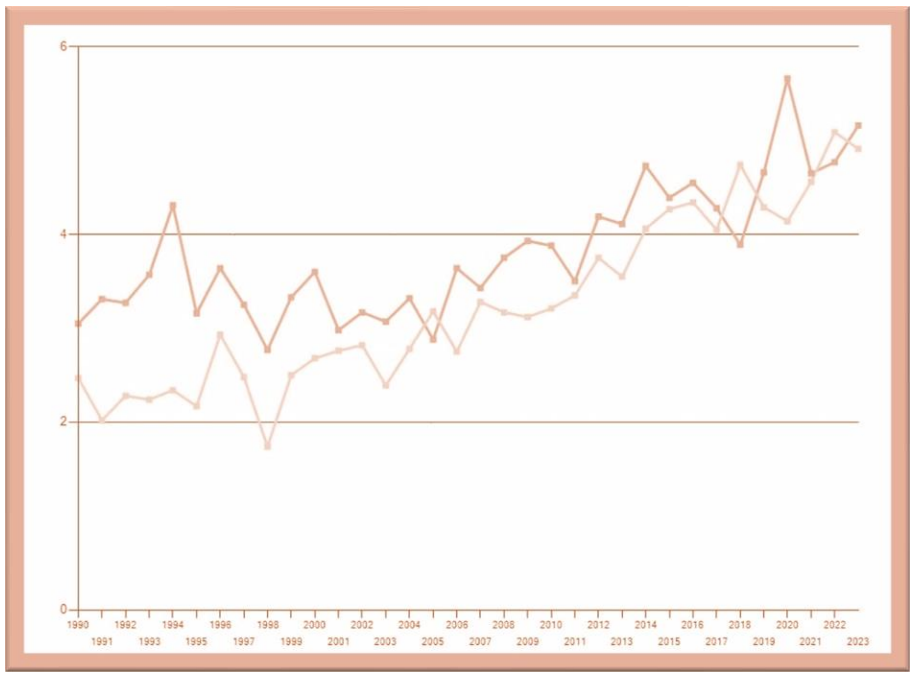

Figure 2. Annual number of reported OCSCCs in Sweden 1990-2023. Crude rate per 100,000 inhabitants. Source: the National Board of Health and Welfare (accessed 13 March 2025). Men (dark); women (light).

Clinical and diagnostic work-up

Patients with a suspected OCC should be referred to an Ear-Nose-Throat (ENT) specialist clinic for a clinical examination according to the Standardised Care Pathway (SVF), following the recommendation of the National Board of Health and Welfare in Sweden. If the suspicion persists, a tissue biopsy is performed to confirm the diagnosis and the histological subtype. A computed tomography (CT) scan of the head, neck, and chest is conducted, and magnetic resonance imaging (MRI) can provide additional information on the tumour boundaries. If suspicious metastases are found in the neck, a fine-needle aspiration, ultrasound-guided if necessary, is conducted. Should bony invasion be suspected, an orthopantomography is carried out. Positron-emission tomography CT (PET CT) provides further information regarding distant disease and the extent of regional lymph node metastases, making it particularly valuable in the initial assessment of advanced-stage disease.

Patients are discussed in a multidisciplinary meeting, and the cancer is staged according to the Union for International Cancer Control (UICC) Tumour Node Metastasis (TNM) classification where the information on T, N and M status, based on clinical and radiographical findings, forms the basis for the clinical tumour stage. Stages I-II are considered low stages, while III-IV are advanced, or high, tumour stages (**Table 1**). Fifty-three per cent of OCSCC patients in Sweden are diagnosed at stages I-II, while forty-seven per cent are in stages III-IV[4].

Treatment recommendations, adhering to national guidelines, are then made, considering tumour resectability, patients' operability, and predicted functional outcomes. The patient's overall condition is assessed using the performance status (PS) according to the World Health Organisation (WHO), along with comorbidities that may increase the risk of treatment-related complications. These factors are taken into account when discussing different treatment options. The treatment recommendation is presented to the patient for final discussion and decision.

Table 1. Clinical tumour stages for oral cavity cancer based on TNM-status according to the 8th edition of the UICC classification.

	N0	N1	N2	N3	M1
T1	I	III	IVA	IVB	IVC
T2	II	III	IVA	IVB	IVC
T3	III	III	IVA	IVB	IVC
T4a	IVA	IVA	IVA	IVB	IVC
T4b	IVB	IVB	IVB	IVB	IVC

TNM classification and staging

The TNM classification, as defined by the UICC, was updated to its 8th edition in 2017[8]. In this thesis, the patients included in the randomised ARTSCAN 2 trial, which compared preoperative RT to postoperative RT for patients with locally advanced resectable oral cancer (**II-IV**), were enrolled from 2008 to 2016 and staged accordingly based on the 7th edition. The main differences in the staging of OCC between the editions are the inclusion of the depth of invasion (DOI) of the tumour (T stage) and the presence or absence of extranodal extension (ENE) in regional lymph node metastases (N stage) in the 8th edition.

These changes were made since the addition of DOI was shown to correlate better with prognosis than tumour size alone. A deeper DOI correlates with a higher risk of nodal metastases and locoregional recurrences, negatively impacting survival[9,10]. The introduction of DOI has resulted in a higher number of advanced cancers, with an enhanced prognostic accuracy. For example, a 20 mm tumour with DOI > 10 mm is now classified as a T3 lesion, whereas in the 7th edition it was classified as a T1.

Importantly, the concept of DOI differs from tumour thickness and should be measured from the level of intact mucosa. Accordingly, by palpation and assessing scans, the clinician must distinguish between an exophytic and less invasive tumour and a flat, ulcerated tumour that invades to depth[11]. Intraoral ultrasound imaging of the tumour has been shown to significantly improve DOI assessments for tongue cancer compared to MRI, especially for T1-T2[12,13].

Histopathological assessment

After a histopathological assessment following surgery, a definitive DOI and tumour size can be measured, allowing for accurate staging of the tumour (pathological T-stage; pT).

ENE, i.e., the extension of the carcinoma from the lymph node through the capsule, is not always clinically evident or visible on scans; it is frequently diagnosed by analysing pathological specimens[14]. For this reason, the most accurate N-stage is therefore achieved after surgery (pathological N-stage; pN). ENE negatively influences prognosis, significantly affecting both locoregional and distant relapses as well as survival rates and concurrent chemotherapy during postoperative RT (ChRT) is recommended for patients where ENE is found[15–17].

The degree of ENE is a prognostic factor, with studies suggesting that there should be a cut-off limit for minor and major ENE. OCSCC patients with minor ENE (defined as an ENE <1.9 or <2.0 mm) had significantly better survival rates compared to those with major ENE [18,19]. Future treatment de-escalation for patients with minor ENE, e.g., without administering concurrent chemotherapy, may be indicated.

Treatment recommendations rely on the clinical TNM (cTNM) classification. This classification can be adjusted based on histological postoperative analysis, resulting

in a pathological TNM (pTNM) that may necessitate a shift towards a more aggressive or less aggressive treatment approach. Such a situation arises, for example, when the histopathological report indicates positive margins or ENE (**Figure 3**). As initially stated, DOI and ENE were not part of the staging system when the ARTSCAN 2 study (**II-IV**) was performed. Even if not included in the TNM classification, histological risk assessment of the tumour's invasion pattern, as well as any perineural and lymphovascular invasion, may also aid in the treatment decision. Between 2022 and 2023, a total of 65 patients with OCSCC underwent local resection and neck dissection (ND) and were found to have pN0 disease. Of these, 54 had been correctly classified as cN0 preoperatively, yielding a sensitivity for cN0 of 83% (unpublished data, Department of ORL-HNS, Skåne University Hospital)

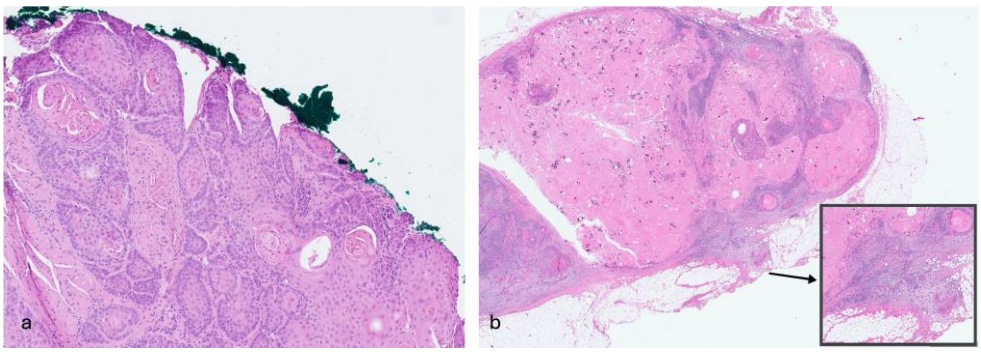

Figure 3. (a) Positive margins following a tongue cancer resection, with the cancer extending to the green-inked margin. (b) Extranodal extension with the cancer extending through the lymph node capsule (small frame). Photos: Dr. Henryk Domanski

Treatment for oral cavity cancer

Curatively intended treatment for OCC normally includes single-modality treatment with surgery for low-stage tumours and combined therapy with surgery and RT ± chemotherapy for more advanced tumours. For patients with unresectable tumours, definitive RT (i.e., primary treatment with curative intent) ± concurrent chemotherapy is offered. For patients with a poor PS or who are otherwise not fit for surgery or definitive RT, palliative oncological treatment is considered.

Surgery

Primary tumour

A primary tumour resection aims to achieve a 10 mm clinical resection margin. Historically, there has been variability in the definitions of positive, close, and clear margins. A 5 mm histological margin is currently regarded as a clear resection

margin, although some experts argue that closer histological margins may better predict the risk of local recurrence[20].

The surgical specimen shrinks during preparation due to contraction and formalin fixation. Depending on its location in the oral cavity, the specimen can shrink by up to 50 %. Therefore, to achieve a 5 mm margin, at least a 10 mm surgical margin is considered necessary[21].

Depending on the size and location of the tumour, the resection surface is either left for secondary healing or reconstructed with flaps. Local flaps include, for example, the nasolabial flap, the facial artery musculomucosal (FAMM) flap, the submental flap and the platysma flap. Larger local flaps to reconstruct defects in the neck include the pectoralis major myocutaneous flap, the suprascapular flap, or the deltopectoral flap.

For larger resections, a free flap may be necessary. A free flap refers to a surgical technique in which tissue, such as skin, muscle, or bone, with its associated blood vessels, is completely detached from its original location and transferred to the defect site in the oral cavity, where microvascular anastomosis to vessels in the neck is performed to re-establish blood flow. Depending on the location and extent of the resection, either a soft tissue (radial forearm flap, anterolateral thigh flap, medial sural artery perforator flap) or a free flap including bone (fibula flap, scapula flap) may be selected. Surgery involving free flap reconstruction is conducted in a multidisciplinary manner involving both head and neck surgeons, plastic surgeons, and, for bony resections and reconstructions, maxillofacial surgeons (**Figure 4**).

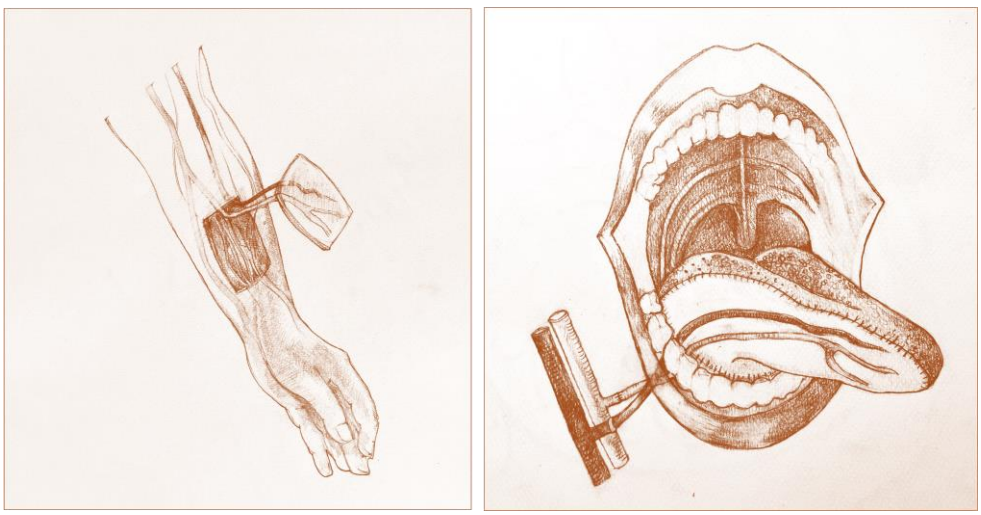

Figure 4. Radial forearm flap harvested from the forearm, sutured in place to the defect site in the tongue and floor of the mouth, and anastomosed to vessels in the neck.

Mandibulotomy

For tumours located in the posterior part of the oral cavity, access can sometimes be challenging, and a temporary mandibulotomy may be required to gain access to the tumour. After splitting the lip, the mandible is divided with a paramedian osteotomy (**Figure 5**) and, following the completion of the resection and reconstruction, the mandible is repositioned with plates and screws and the lip is sutured back in place.

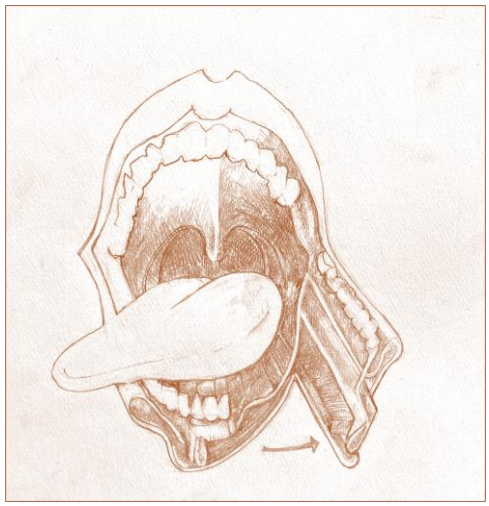

Figure 5. Mandibulotomy

Treatment of the neck

OCC spreads via the lymphatics to lymph nodes in the neck. The neck anatomy is divided into six neck node levels, and certain tumour locations are more prone to spread to specific neck levels (**Figure 6**).

Occult metastases refer to lymph node metastases that are not detectable through clinical examination or imaging (subclinical), but are only identified upon histopathological analysis following surgical removal. In a review of 45 studies involving surgically treated necks for cT1-T2N0 tongue cancer, the incidence of occult metastases (pN+) ranged from 8% to 46%, with an average of 26%[22]. In Sweden, 72% of OCSCC cases are classified as cN0, and 28% are classified as cN+[4]. Unpublished data from the Department of ORL-HNS at Skåne University Hospital, Lund, indicate an incidence of occult metastases of 17%.

The management of the neck, particularly in patients with clinically node-negative (cN0) disease, has differed between institutions and has significantly evolved over time. An ND, in which lymph nodes at different levels are removed, may be performed as an elective (as in cN0 cases where the risk of occult metastases is significant) or as a therapeutic (as in cN+ cases) procedure. Over the decades, the

ND procedure has been refined. In the past, a radical ND was routinely performed, removing levels I-V, the sternocleidomastoid muscle, the internal jugular vein and the accessory nerve. This procedure comes with substantial morbidity. It was later shown that a more limited ND could be performed in many cases without jeopardising the oncological outcome. With the modified radical ND, levels I-V are removed, but one or more of the non-lymphatic structures are preserved.

With the selective ND, one or more of the lymph node levels are preserved, and the selection of levels to remove is based on the location of the primary tumour and its lymphatic drainage pattern. The supraomohyoid ND is a selective dissection often performed for clinically node-negative OCC, where levels I-III are removed[23]. For known metastatic disease, a more radical ND is performed, and for midline advanced tumours, both sides of the neck should be addressed.

According to Ganly *et al*., occult metastases in early tongue cancers increase the risk of mortality from the disease five-fold compared with patients without such metastases[10]. Given their prevalence in OCSCC, elective ND has been shown to improve LRC and survival rates compared to active observation[22,24]. In a randomised study by D'Cruz *et al*., involving patients with cT1-T2N0 OCSCC, the three-year OS rates were 80% for the elective ND group versus 67.5% for the watchful waiting with therapeutic ND when nodal relapse occurred[24].

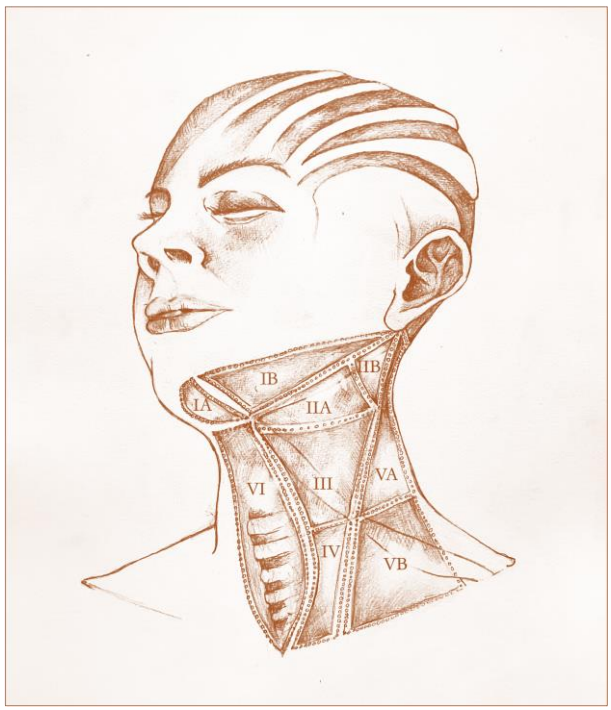

Figure 6. Lymph node levels of the neck.

Since approximately 75% of patients may have no involved lymph nodes[22] , it is essential to identify those with metastases and avoid an unnecessary elective ND. Recently, the sentinel lymph node biopsy (SLNB) has been introduced in many head and neck centres for patients with a lower risk of occult metastases, i.e., patients with cT1-T2 tumours.

The SLNB procedure identifies the first lymph node(s) draining the primary tumour, i.e., the sentinel node (SN). This approach is recommended for cT1-T2 tumours without known regional spread (cN0) to facilitate the detection of occult metastases and to guide further treatment. This more limited surgical procedure detects occult disease and spares patients from the side effects of an ND. A radiotracer is injected around the tumour, followed by a scan using single-photon emission computed tomography (SPECT) to determine the location of the SN(s). A handheld gamma probe assists the surgeon in detecting the radioactive lymph nodes for removal. To facilitate the identification of the SN, indocyanine green can be injected peritumorally and used in conjunction with the radiotracer. A near-infrared fluorescence imaging system provides the surgeon with real-time intraoperative visual information[25].

In a prospective study from 2010 on T1-T2 cN0 OCSCC, patients underwent SLNB followed immediately by an ND, yielding a negative predictive value of 0.96[26]. Hence, SLNB correctly predicted a negative neck in 96% of cases. At our institution, SLNB is currently used for early-stage OCSCC to identify patients who warrant further treatment (positive SLNB) and those suitable for watchful waiting (negative SLNB). Hasegawa *et al*. conducted a multicentre randomised controlled trial (RCT) for cT1-T2N0 OCSCC, comparing elective ND with SLNB, finding that survival results for SLNB were non-inferior to ND (3-year OS 87.9% versus 86.6%). Additionally, and not surprisingly, neck morbidity was lower in the SLNB group[27]. Notably, the SLNB procedure had not been introduced during the ARTSCAN 2 study (**II-IV**). In patients with a clinically N0 neck, and where treatment of neck nodes is indicated (generally for T2 tumours or more), RT is an alternative to surgery.

Radiotherapy

Radiobiology

Ionising radiation refers to electromagnetic (photon) radiation or charged particle radiation with sufficient energy to remove electrons from atoms, resulting in free electrons and positively charged ions. Photon RT, the most widely used form of radiation therapy, employs deep-penetrating high-energy X-rays or gamma rays that interact with tissue atoms primarily by ejecting electrons from them, which in turn produce further ionisations and excitations along their paths through the tissue. Examples of charged particle RT, which is less commonly used, include electron

therapy, typically applied to superficial tumours such as skin cancer due to its limited penetration, and proton therapy, which delivers most of its energy at a defined depth, thereby minimising dose beyond the target. A reduced integral RT dose (low dose spillage) can therefore often be achieved with this techniqe[28].

The primary target of ionising radiation at the cellular level is DNA. Damage may occur directly, through the ionisation of the DNA molecule itself, or indirectly, which is the predominant mechanism, via the ionisation of water molecules leading to the formation of reactive free radicals. These free radicals, in turn, attack cellular components, including DNA. RT can induce both single-strand and double-strand DNA breaks, with double-strand breaks being more lethal due to their lower likelihood of accurate repair. Upon DNA damage, cellular DNA repair mechanisms are activated, potentially resulting in successful repair, apoptosis, or other forms of cell death. In some cases, misrepair may lead to mutations, which can contribute to carcinogenesis later in life. Normal tissues generally have a more efficient DNA repair capacity, which contributes to the therapeutic effect of RT[28,29].

Oxygen concentration plays a critical role in the effectiveness of RT, as oxygen enhances the damage caused by ionising radiation. Specifically, the presence of oxygen increases the production and persistence of free radicals, amplifying indirect DNA damage. However, tumour tissue is often hypoxic, and hypoxic cells are more resistant to radiation, requiring higher doses for effective cell kill. As treatment progresses and tumour volume decreases, oxygen levels may rise in previously hypoxic regions, particularly at the tumour margins, a process known as reoxygenation, which increases radiosensitivity in these cells.

Smoking cessation is strongly recommended during RT, as continued smoking has been shown to significantly impair treatment outcomes. One reason for this is thought to be a reduced oxygen supply to the tumour[30,31]. Additionally, low haemoglobin (Hb) levels prior to irradiation have been associated with poorer response to RT, which may be linked to oxygenation levels in the tumour. Interestingly, blood transfusions do not appear to improve outcomes in this context, suggesting that the relationship between oxygen delivery and radiosensitivity is complex and not easily corrected by transfusion[32].

The rationale for fractionation, which involves dividing the total radiation dose into multiple smaller doses over time, is underpinned by five key biological principles known as the five Rs of radiobiology. These factors help explain how fractionation enhances tumour control while limiting normal tissue toxicity:

- Redistribution: Cells exhibit varying radiosensitivity depending on their phase in the cell cycle. Fractionation increases the chance of tumour cells progressing into more radiosensitive phases between fractions, thereby improving treatment efficacy.

- Reoxygenation: Oxygen enhances radiosensitivity. As treatment kills tumour cells and reduces tumour mass, oxygen can more readily reach previously hypoxic regions, making subsequent doses more effective.
- Repopulation: Both normal and tumour cells can proliferate during RT. However, irradiated cells can also start to divide rapidly during the treatment ("accelerated repopulation"). This is a well-known phenomenon in squamous cell carcinomas of the head and neck, typically starting 3–4 weeks into treatment. This can compromise tumour control if the overall treatment time is prolonged.
- Radiosensitivity: Different tissues and cell types vary in their sensitivity to RT. For example, mucosal epithelium is more radiosensitive than muscle, and hypoxic tumour cells are more resistant than well-oxygenated ones.
- Repair: Normal cells generally have better repair mechanisms than tumour cells. Fractionation provides time between doses for normal cells to repair sublethal damage, thereby improving normal tissue tolerance[28,29,33].

Cell kill, and consequently tissue effect, after a single radiation dose D can be approximated as proportional to $\alpha D+\beta D^2$, where α and β are constants specific to a given cell type or tissue. The αD component reflects non-repairable (lethal) damage, while the βD^2 component represents repairable sublethal damage. The quotient between the constants, the α/β ratio, is a fundamental concept in radiobiology, describing how a tissue or tumour responds to changes in fraction size, e.g., the dose delivered per radiotherapy session.

Tissues or tumours with a "high" α/β ratio (typically around 10 Gy), such as skin, mucosa, and many rapidly proliferating tumours like squamous cell carcinomas, are less sensitive to changes in fraction size and respond primarily to the total dose. These tissues tend to exhibit early radiation effects, such as acute side effects in the skin and mucosa during head and neck RT.

In contrast, tissues with a "low" α/β ratio (typically around 3 Gy), including the spinal cord, brain, and muscle, are more sensitive to fraction size and are more likely to exhibit late radiation effects, which may not become apparent until months or years after treatment.

Absorbed dose and fractionation

The absorbed radiation dose is defined as the amount of energy deposited per unit mass of tissue, measured in joules per kilogram (J/kg). The SI unit for absorbed dose is the gray (Gy), where 1 Gy equals 1 joule per kilogram.

To optimise cancer cell kill while minimising harm to surrounding healthy tissue, RT is typically delivered in multiple fractions, i.e., small, individual doses administered over a period of time. This approach allows normal tissue time to

repair sublethal DNA damage between sessions, a process that generally requires at least six hours to be considered complete, which is why daily fractions are spaced accordingly[28]. Tumour cells, in contrast, are generally less efficient at DNA repair, making them more susceptible to cumulative damage through fractionation.

Curatively intended or definitive RT involves doses of 66-70 Gy targeting the visible or palpable tumour (GTV, see below), and around 50 Gy for elective volumes. In the postoperative setting, after a radically performed surgery, doses are generally 60 Gy to tumour-bearing sites and higher, typically 66 Gy if margins are positive or in the presence of ENE, with the addition of concurrent chemotherapy[34] .

Concurrent chemotherapy

Chemotherapy can enhance the effectiveness of RT when used concurrently, i.e., ChRT[35]. ChRT for OCSCC is mainly applied postoperatively in cases with positive histopathological margins or ENE, and for advanced inoperable tumours. Medical oncological treatment, such as chemotherapy in the neoadjuvant (also called induction chemotherapy) or adjuvant setting – that is, chemotherapy given before or after primary tumour treatment – can be used in selected cases but is not standard care.

Cisplatin is a platinum-based agent that is the most commonly used chemotherapy in head and neck cancer treatment, administered concurrently with RT. In the ARTSCAN 2 study (**II-IV**), patients in the postoperative CF RT group with histopathological ENE and/or positive margins received cisplatin concurrently with RT, administered weekly. In many studies, cisplatin has been given in high-dose 3-weekly regimens. However, high-dose regimens can lead to significant toxicity, which may result in patients having to discontinue the treatment. A randomised study has demonstrated that postoperative concurrent cisplatin given weekly (40 mg/m^2) for high-risk head and neck cancer was non-inferior to 3-weekly cisplatin (100 mg/m^2) and had a favourable toxicity profile[36].

Cisplatin enters the cell and binds to the DNA, causing cross-links that disrupt the DNA function. It is a radiosensitiser, meaning that it works synergistically with RT, attacking DNA in a complementary way, causing more DNA damage and cell death. Nephro- and ototoxicity are common side effects. Although chemotherapy impacts both normal and cancer cells, tumour cells are more likely to die because they divide more rapidly, repair poorly, and are less resilient overall compared to healthy tissue[35].

Two RCTs on concurrent postoperative ChRT for stage III-IV head and neck cancers, both published in 2004, have gained much attention. Both demonstrated the advantage in terms of LRC when administering cisplatin concurrently with RT compared to RT alone. There was no difference between the groups regarding distant metastases, suggesting that cisplatin primarily acted as a locoregional

radiosensitiser[37,38]. A combined analysis of the two trials concluded that the benefit was observed for patients with ENE and/or positive margins[17].

A Cochrane review from 2021 on chemotherapy for the treatment of oral and oropharyngeal cancers concluded that there is a survival benefit for postoperative ChRT as compared to postoperative RT alone, with moderate-certainty evidence (HR 0.84, 95% CI 0.72-0.98, p=0.03). For unresectable cancers, primary treatment with ChRT as compared to RT alone, similarly reduced the risk of death. Moreover, there was insufficient evidence to demonstrate a survival benefit for induction chemotherapy prior to surgery/RT/ChRT[39]. The updated 2021 meta-analysis of chemotherapy in squamous cell head and neck cancer (MACH-NC) confirmed the survival benefit of concurrent ChRT but highlighted the diminishing effect for older patients (>70 years)[40].

In conclusion, concurrent postoperative ChRT may benefit patients with high-risk tumours, but it carries a risk of increased adverse events. Therefore, clinical judgement regarding the patient's fitness and life expectancy must be considered when deciding whether to add chemotherapy to RT in the postoperative setting for patients with ENE and/or positive margins.

Radiotherapy fractionation schedules

Fractionated RT is a fundamental approach in RT with curative intent, allowing normal tissues to recover between treatment sessions while maximising tumour control. The standard schedule typically delivers 2.0 Gy per fraction, once daily, five days per week, resulting in a total dose of 10 Gy per week. This is referred to as conventional fractionation (CF) and remains the most widely used schedule in curative head and neck RT.

With an improved understanding of the five Rs of radiobiology, alternative fractionation schemes have been tested. These differ in dose per fraction, number of fractions, and overall treatment duration, and are tailored to tumour type, location, and clinical goals.

Any deviation from the standard CF is considered altered fractionation, which includes the following strategies:

- Hyperfractionation (HF): The dose per fraction is reduced (typically <2.0 Gy), and fractions are given more frequently, often twice daily, without extending the overall treatment duration compared to CF. This approach allows for escalation of the total dose, aiming to improve tumour control without increasing long-term side effects[41].
- Accelerated fractionation (AF): The total dose is similar to that of CF, but it is delivered over a shorter overall treatment time, either by administering two fractions per day or increasing the number of treatment days per week. The goal is to reduce the window for tumour repopulation during therapy[42].

- Hypofractionation: In this approach, the dose per fraction is increased (typically >2.0 Gy), and the number of fractions is reduced. This method is mainly used in the palliative setting for head and neck cancer, where shorter treatment courses are desirable.

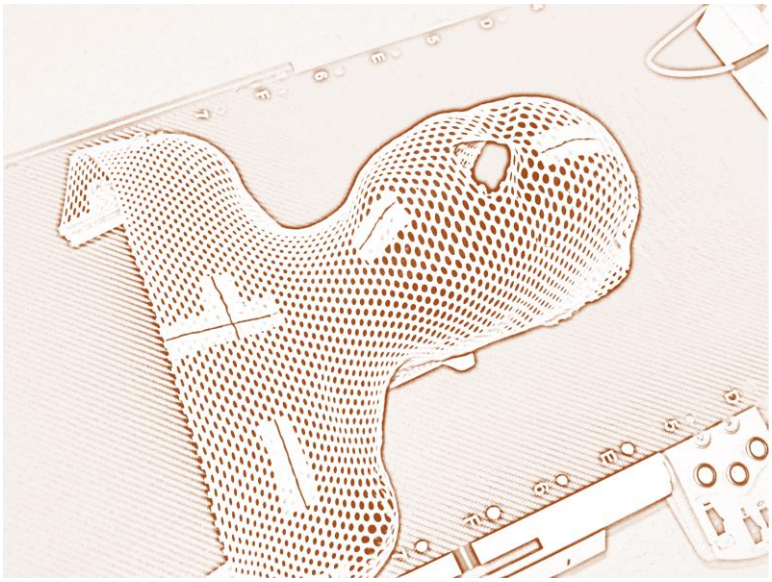

Figure 7. A thermoplastic immobilisation mask used during RT for head and neck cancer. The mask is custom-moulded to the patient's anatomy to ensure precise and reproducible positioning during each treatment session, minimising movement and thereby improving the accuracy of radiation delivery.

Radiotherapy planning

RT planning begins with a planning CT scan performed while the patient is immobilised using a thermoplastic mask (**Figure 7**) to ensure reproducible positioning throughout the treatment course. To improve the accuracy of target delineation, MRI or PET-CT images may be fused with the planning CT. Based on this information, the radiation oncologist delineates the treatment volumes in a stepwise process:

- GTV (Gross Tumour Volume): The visible or palpable macroscopic tumour, as defined by imaging and clinical findings.
- CTV (Clinical Target Volume): The GTV plus volumes considered at risk for microscopic disease spread, such as adjacent tissues or elective lymph node regions.
- PTV (Planning Target Volume): The CTV plus a margin to account for daily setup variations and internal motion, ensuring adequate dose coverage during treatment.

Following contouring, dose planning is performed by a medical physicist or an oncology nurse trained in treatment planning, using specialised software. The objective is to optimise the dose distribution based on the tumour's location, histology, and treatment intent (curative versus palliative), while accounting for the proximity and tolerance of organs at risk (OARs). Different dose levels are prescribed for the various target volumes, and planning is guided by pre-specified dose–volume constraints for both tumour targets and surrounding normal tissues to ensure effective treatment delivery with acceptable toxicity (**Figure 8**).

External beam radiation therapy

The most common form of RT for cancer treatment is external beam radiotherapy, where high-energy X-rays are delivered from a linear accelerator. Intensity-modulated radiation therapy (IMRT) and the more recent volumetric modulated arc therapy (VMAT), along with image guidance, are central techniques in modern RT for head and neck cancer. Compared to earlier methods such as three-dimensional conformal radiotherapy (3D-CRT), these advanced techniques offer improved dose conformity and superior sparing of surrounding healthy tissue. In the anatomically complex head and neck region, where critical structures such as the brain, spinal cord, optic apparatus, and parotid glands are often close to the tumour, such precision is crucial. IMRT delivers radiation from multiple static beam angles, while VMAT utilises a continuously rotating gantry, allowing dynamic modulation of the beam shape and intensity. Both techniques enable highly conformal dose distributions, thereby enhancing tumour targeting while reducing normal tissue exposure. VMAT also shortens treatment time, with a single fraction typically administered in just a few minutes[29].

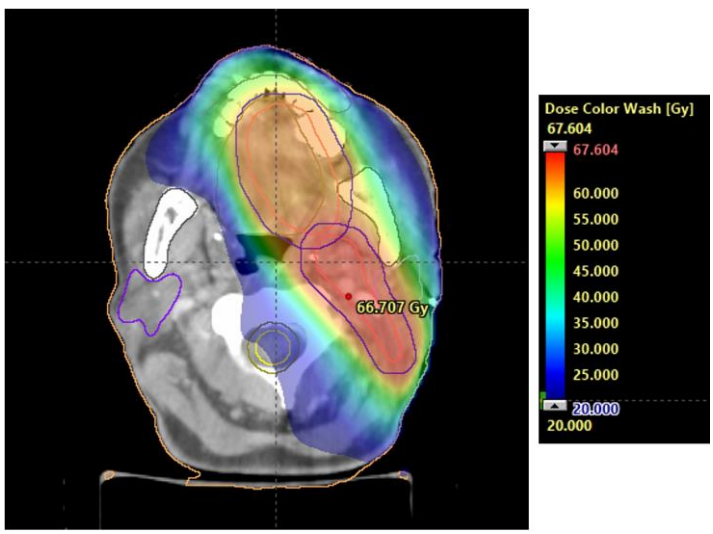

Figure 8. Example of a treatment dose plan for a patient with tongue cancer staged T3N3b.

Altered fractionation outcomes in head and neck cancer

The Radiation Therapy Oncology Group (RTOG) 9003 phase III trial, which included patients with unresectable locally advanced head and neck SCC (10% OCSCC), was designed to compare definitive CF RT against three experimental arms: HF RT, AF RT (a concomitant boost dose during the final 12 days of treatment), and AF RT with a split (allowing for a two-week break in the middle of the treatment). The five-year report revealed that only HF RT significantly improved LRC and OS compared to CF RT, without increasing late phase toxicity[43].

A phase III trial conducted by the Groupe Oncologie Radiothérapie Tête et Cou (GORTEC) involved patients with advanced head and neck SCC (14% of whom had OCSCC) who were not candidates for surgery. Patients were randomised to receive either CF RT or very accelerated RT. The results showed that LRC was significantly improved in the accelerated arm, although OS did not show a similar benefit. Additionally, the accelerated arm experienced significantly higher acute toxicity, while late toxicity levels were comparable to those in the CF RT group[44].

The Danish Head and Neck Cancer Group (DAHANCA) has shown that accelerated fractionation is advantageous for head and neck SCC in the definitive setting. The typical schedule delivers RT in six fractions per week, which shortens the overall treatment duration by one week compared to CF RT. This approach significantly improved local control, which was particularly beneficial for patients with low tumour burdens in the neck, although it did not notably enhance regional control[45,46].

In 2010, Cochrane published a review on RT regimens for OCC and OPC. The review mainly included altered fractionation regimens in the definitive RT setting, but also included a number of studies of combined therapy with RT and surgery. The findings revealed a significant difference in OS and LRC when comparing HF RT to CF RT, favouring the former (hazard ratio (HR) 0.78, 95% CI 0.68-0.90 for OS; HR 0.74, 95% CI 0.62-0.89 for LRC). Additionally, hyperfractionated/ accelerated RT showed a significant advantage for LRC, although no significant difference in OS was noted. Pooling all altered fractionation schedules against CF RT indicated a significant improvement in OS for the altered fractionation group[47]. In 2010, Cochrane published an additional review comparing AF and HF schedules with CF RT for head and neck cancers, primarily focusing on OPC and laryngeal cancers. It found that altered fractionations were superior to CF RT regarding OS and LRC, with hyperfractionation being the most effective, a benefit particularly evident for young patients and those with a high-performance status[48].

In 2017, Lacas *et al*. updated the meta-analysis of radiotherapy in carcinomas of the head and neck (MARCH) on fractionation schedules for head and neck cancer, incorporating 34 trials and 11,969 patients. The analysis compared CF RT with altered fractionation and CF RT plus chemotherapy against altered fractionation. Notably, 75% of patients had OPC or laryngeal cancers. OS was significantly better for altered fractionation, but this was restricted to the hyperfractionated group (HR

0.83, 95% CI 0.74-0.92). Additionally, CF RT plus chemotherapy also showed improved OS compared to altered fractionation, although this latter finding was based on only five trials[41,42]. Subsequently, a meta-analysis of treatments for locally advanced head and neck cancer compared various altered fractionation designs, with or without chemotherapy. Hyperfractionated RT with concurrent chemotherapy was the most effective treatment for OS (HR 0.63, 95% CI 0.51-0.77) compared to locoregional treatment alone[49].

To conclude, HF RT, particularly when combined with chemotherapy, enhances OS and LRC for locally advanced head and neck cancers, raising the question of its effectiveness when combined with surgery.

Pre- versus postoperative RT for OCSCC

As previously stated, the combination of RT and surgery is the preferred treatment for advanced OCSCC. This is based on historical findings where surgery alone often left microscopic disease behind, which RT could eradicate. Currently, postoperative RT is considered the gold standard, but there is a lack of randomised trial data supporting this (or any) treatment order. Theoretical advantages of preoperative RT include delivering RT to a well-oxygenated peritumoral area to treat microscopic disease and to prevent delays from potential postoperative complications. Conversely, postoperative RT benefits from information from the histopathological report, guiding treatment adjustments, and operating in a non-irradiated field may reduce the risk of postoperative complications (evaluated in **III**)[50].

An early randomised study indicated that LRC improved with postoperative RT compared to preoperative RT in patients with locally advanced head and neck SCC. However, there were no significant differences in OS or morbidity, and the rate of distant metastases remained similar across the groups. Among the 277 randomised patients, only 40 had OCSCC. Notably, the postoperative dose was higher (60 Gy) than the preoperative dose (50 Gy), which may have influenced the outcomes[51]. Overall, there is a clear lack of randomised studies comparing pre- versus postoperative RT, and no RCTs have specifically addressed OCSCC. Furthermore, the role of altered fractionation in the preoperative setting has previously not been explored, emphasising the need for the ARTSCAN 2 trial.

A review of studies on preoperative RT, either alone or combined with chemotherapy, in patients primarily with advanced oral cancer, found notably high OS rates[52]. However, significant heterogeneity was observed, with only 3 out of 32 studies being randomised, underscoring the necessity for further RCTs to better define the role of preoperative RT. Conversely, numerous studies have examined postoperative RT for head and neck cancer.

In an RCT comparing postoperative AF RT to CF RT for high-risk head and neck cancers, no significant differences in LRC or OS were found[53]. A small RCT showed no OS difference between postoperative accelerated hyperfractionation (46.2 Gy)

and CF RT (60 Gy), although LRC was significantly better in the accelerated group[54]. Sanguineti *et al*. found no significant differences in LRC or OS in 226 patients receiving postoperative CF RT versus an accelerated regimen[55]. However, an accelerated regimen given seven days a week postoperatively compared to CF RT significantly improved LRC (+20%) for OCC and OPC, a difference which was not identified for laryngeal cancers[56]. This highlights the importance of studying head and neck cancer subsites separately.

The abovementioned study[56] showed that the LRC benefit was comparable to adding chemotherapy to RT. However, no studies have compared postoperative accelerated RT with postoperative ChRT for high-risk patients. Given the evidence for adjuvant ChRT, it remains the preferred option for these patients[37,38,57]. Eventually, a 2018 meta-analysis of six RCTs found no advantage of postoperative AF RT over CF RT in high-risk head and neck SCC patients, and acute toxicity, but not the late side effects, was more pronounced in the AF RT group[58].

In conclusion, no survival benefit of AF RT in the postoperative setting compared to CF RT has been identified. The strong tradition of postoperative CF RT in OCSCC is supported by evidence that postoperative concurrent ChRT significantly improves survival in high-risk patients. As a result, postoperative CF RT has become the standard treatment.

Prognosis

In Sweden, the prognosis for OCSCC has slowly improved from a five-year relative survival rate of 59% (years 2008-2016) to 63% (years 2017-2025)[4]. In the United States, the prognosis has similarly improved over the past few decades[59]. Among subsites, patients with cancer in the hard palate demonstrate the highest survival rates, whereas the floor of the mouth exhibits the lowest[4]. The prognosis heavily depends on the presence of regional metastases in the neck, which is the most significant prognostic factor for both survival and LRC in early-stage OCSCC[10,22].

The tumour stage affects prognosis, with five-year survival rates for OCSCC in Sweden (years 2017-2025) being 85%, 71%, 55% and 37% for stages I, II, III, and IV, respectively[4].

Factors contributing to a positive trend in the survival rates include a more proactive surgical approach to neck treatment[24], improvements in imaging, which enable more accurate target volume delineation, advances in RT planning and delivery, particularly the implementation of IMRT/VMAT, leading to improved dose conformity. Radiographically, the introduction of PET-CT has improved the detection of regional and distant metastases. In 2015, Sweden published its first national guidelines for head and neck cancer treatment, undoubtedly leading to a more standardised care for OCC. That same year, the Standardised Care Pathway

(SVF) for head and neck cancer was implemented as part of a national initiative to enhance cancer care, aiming to minimise unnecessary waiting times and ensure a well-organised and professional healthcare process for patients across the country.

Treatment-related complications and morbidity

Following treatment with surgery and RT for OCSCC, various side effects may arise (**Figure 9**). Immediate complications of oral resections and neck surgery include perioperative bleeding, infection, flap failure, orocutaneous fistulas, and chyle leakage. Nerve injuries, whether accidental or intentional, may cause sensory loss in the tongue (lingual nerve), the palate (greater palatine nerve), the lip and chin (mental nerve), the ear (great auricular nerve), or the neck (cervical plexus). Motor nerve injuries may lead to weakness in the lower lip (marginal branch of the facial nerve), shoulder impairment (accessory nerve), or restricted tongue movement (hypoglossal nerve).

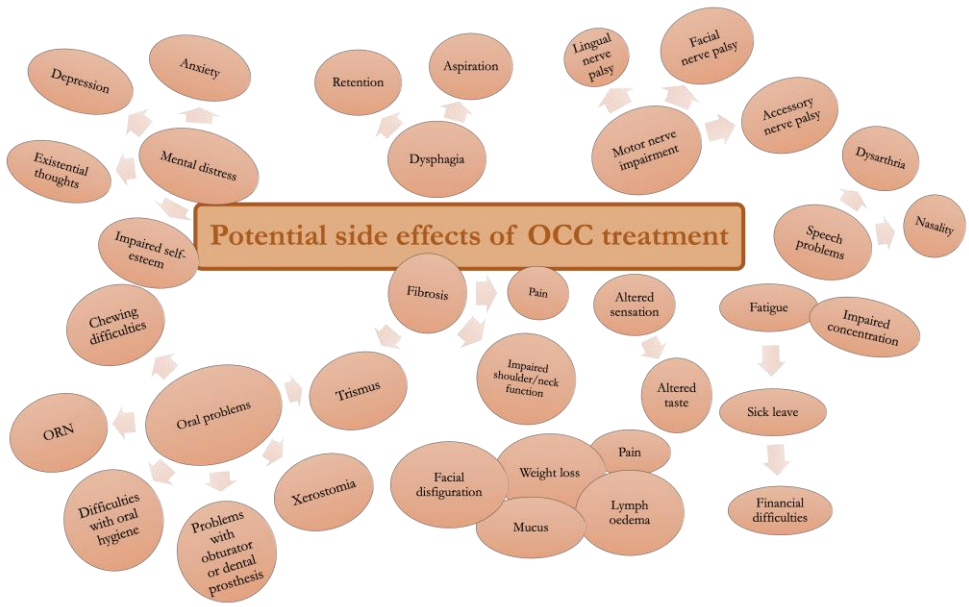

Figure 9. Examples of potential side effects following treatment for oral cavity cancer.

Extensive surgery, especially when the resection site is reconstructed with a flap, can significantly alter the anatomy, leading to aesthetic and functional impairments. Patients may face difficulties with chewing and swallowing, often exacerbated by RT. By convention, acute RT toxicity is defined as occurring within 90 days from the treatment onset, whereas late toxicity appears or persists beyond this period.

Skin reactions and oral mucositis typically develop about two weeks into RT. Mucositis can be very painful and often hinders eating and drinking, sometimes necessitating a feeding tube. In cases of persistent dysphagia, gastrostomy may be necessary. The addition of chemotherapy generally exacerbates these symptoms.

Mucositis usually subsides a few weeks after the end of treatment. Like the skin and mucosa, the salivary glands also react early, resulting in a reduced salivary flow and a subjective sensation of dry mouth, xerostomia. However, unlike the skin or oral mucosa, salivary glands exhibit limited regenerative capacity following radiation, often resulting in long-term or permanent side effects such as xerostomia[60]. Xerostomia is the most common long-term side effect of radiotherapy and is strongly associated with the radiation dose delivered to the salivary glands and the volume of glandular tissue exposed. Xerostomia has been shown to significantly affect health-related quality of life (HRQoL)[61]. It may lead to difficulties with chewing, swallowing, articulation, and altered taste perception. Additionally, it increases the risk of caries and oral infections. Moreover, social eating can often be challenging.

Symptom-relieving local treatments for xerostomia include salivary stimulating tablets and moisturising mouth sprays/oils. Preventive acupuncture is an additional method that may be offered. A meta-analysis assessed various local and systemic treatments to alleviate RT-induced xerostomia, revealing limited evidence for methods beyond minimising the salivary gland RT dose, such as with IMRT/VMAT[62]. In Paper **IV**, we assessed HRQoL within the ARTSCAN 2 study. The symptom of "dry mouth" significantly impaired both study groups six months post-treatment, with similar levels of impairment persisting over a five-year follow-up period. Difficulty opening the mouth (trismus) is a known complication of RT and/or surgery in the oral cavity, prompting patients to engage in lifelong jaw exercises to prevent its onset or deterioration.

The most feared complication in the mandible following RT is osteoradionecrosis (ORN). In this condition, bone within the radiation field becomes devitalised and is exposed through the mucosa. Clinical diagnostic criteria additionally stipulate that the bone exposure must persist for a minimum of three months[63]. Pain, trismus, dysaesthesia, food impaction, pathological fractures, sequestration of the bone and the development of fistulas are other common clinical symptoms and signs of ORN. Identified risk factors include dental extractions prior to or following RT, poor dental health, use of tobacco, total radiation dose given, tumour site and stage and mandibular surgery such as a marginal mandibulectomy or a mandibulotomy[64–67]. The prevalence of ORN has decreased since the 1990s[68] , which may be related to new radiation techniques that deliver lower doses to the bone, as well as improved dental preventive care[63]. Treatment for ORN includes removing the devitalised bone and covering the area with healthy tissue. If a segmental mandibulectomy has been performed, a bone-encasing free flap is often required[63,69].

Health-related quality of life

Early cancer trials focused almost exclusively on outcomes such as survival, tumour recurrence or standardised toxicity grading by health professionals. However, since the 1970s, the importance of subjective outcomes has gained increased recognition, and regulatory agencies, such as the U.S. Food and Drug Administration and the National Institute for Health and Care Excellence, now encourage the inclusion of patient-reported outcome measures in clinical trials. HRQoL is a multidimensional concept reflecting a patient's perceived physical (e.g., pain, fatigue, insomnia), psychological (e.g., anxiety, depression), and social (e.g., social interactions, financial difficulties) well-being, alongside disease-specific symptoms (e.g., trismus, xerostomia, dysphagia) related to their health condition and its treatment.

The importance of measuring HRQoL

Measuring HRQoL in clinical trials is crucial for several reasons. Treatment-related impairments from OCSCC can significantly affect speech, swallowing, taste, and appearance, which in turn affect social interactions, mental health, and employment. Given that many OCSCC patients survive long-term, understanding HRQoL outcomes is essential alongside standard oncological metrics such as OS and LRC. Additionally, HRQoL data empower patients and clinicians to engage in informed discussions about trade-offs between survival and side effects. Furthermore, when differences between treatments in OS or LRC are small, such as in the ARTSCAN 2 study, HRQoL results may sway a decision towards the option with fewer patient-reported burdens. Assessments of HRQoL can be equally important for pinpointing areas where prehabilitation and rehabilitation should be initiated[70].

Validity, reliability and responsiveness

When developing HRQoL questionnaires, it is critical to ensure that the designated tool accurately and reliably measures what it claims. Four fundamental concepts are essential in this context:

- Validity: Ensures the questionnaire measures its intended constructs, including validation in a sociocultural context.
- Reliability: Confirms that the results are reproducible in stable settings.
- Sensitivity: Assesses the tool's capacity to identify differences *between patient groups*.
- Responsiveness: Measures the tool's capability to record changes (improvements or deteriorations) *within patients*[70,71].

Statistical versus clinical significance

In HRQoL studies, it is important to report both statistically significant differences and whether these changes are clinically meaningful for the patients. For example, if the study groups are large enough, clinically trivial differences can yield statistically significant results. However, this does not mean that the difference meaningfully improves patients' well-being. Statistical significance should not overshadow clinical significance.

In the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires (used in the ARTSCAN 2 study), a change of more than 10 points on a 0-100 scale is considered a clinically meaningful difference. Presenting results on clinical significance in HRQoL studies is strongly recommended. Nevertheless, randomised studies using EORTC questionnaires have historically addressed clinical significance in only 38% of the papers[72–75].

Response shift

Self-reported health is known to be influenced by response shift, which refers to a patient's ability to adapt over time to a disease and its treatment-related symptoms. This adaptation can change how patients perceive their HRQoL, independent of their actual health status. Consequently, individuals may provide varying responses on questionnaires over time, not solely due to changes in their HRQoL, but also because their perception of health or quality of life evolves[76–78] .

Response shift can be quantified using advanced statistical methods, but a more straightforward approach is the "then-test". In this method, patients retrospectively assess their HRQoL at baseline, which is then compared to their original responses[79]. General quality-of-life questions are particularly susceptible to response shift. Therefore, the more specific the concept being measured, the less likely a response shift will occur. This phenomenon poses a greater challenge in non-randomised studies, as it undermines the assumption that response shift occurs uniformly across randomised groups.

Health economics

In healthcare, data on health-economic evaluations are crucial due to limited resources. A cost of illness (COI) analysis quantifies all costs related to a disease. Direct costs include inpatient and outpatient care, while indirect costs cover sick leave and early retirement. The costs associated with the two treatment groups of the ARTSCAN 2 study were calculated using a bottom-up approach[80]. By assessing all costs, detailed information on costs related to a treatment is retrieved and cleared of unrelated comorbidities. Although COI studies identify cost drivers, they do not facilitate treatment comparisons. Decision-makers need information on the costs

associated with different treatments relative to their efficacy. Hence, health-economic evaluations are essential for this purpose.

In health-economic evaluations, the aim is to assess the value for money of healthcare interventions by comparing their costs and health outcomes. Costs for different treatments are linked to various outcome measures, including survival rates and quality-adjusted life years (QALYs). QALY is a measure that combines the quality (HRQoL) and the duration spent in a particular health state: 1 QALY = one year of life in perfect health.

When calculating QALYs, a health utility (HU) score is required. This score represents a quality-of-life value that ranges from 0 to 1, where 1 signifies perfect health and 0 denotes death. HU scores are obtained using validated instruments such as the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L). The HU score is combined with the duration spent in that health state to generate QALYs[81].

When performing a cost-utility analysis (CUA), assessing costs in relation to QALYs, an Incremental Cost-Effectiveness Ratio (ICER) is obtained. The ICER represents the cost per additional QALY gained[82]: ICER = (Cost of Treatment A – Cost of Treatment B) ÷ (QALYs of Treatment A – QALYs of Treatment B).

The cost-effectiveness of a treatment is determined by the willingness-to-pay threshold, which reflects how much a decision-maker is prepared to spend for each additional QALY gained. This threshold varies and is influenced by the severity of the disease. In Sweden, an intervention is deemed cost-effective if it costs up to 500,000 SEK per QALY gained.

Background of the ARTSCAN 2 study

In 2011, the Swedish ARTSCAN (Accelerated RadioTherapy of Squamous cell CArcinoma of the head and Neck) study group published their first study. The aim was to evaluate whether AF RT improved the outcomes for patients with head and neck cancers compared to CF RT in a definitive RT setting. A total of 750 patients with SCC in the head and neck region diagnosed from 1998 to 2006, were randomised to receive either AF RT (1.1 Gy + 2.0 Gy, 5 days/week for 4.5 weeks, total dose 68 Gy) or CF RT (2.0 Gy/day, 5 fractions/week for 7 weeks, total dose 68 Gy). In the AF RT group, the RT was given with a concomitant boost technique where the tumour volumes received a morning boost dose of 1.1 Gy. The interfraction interval was at least 6 hours, with the afternoon dose (2 Gy) given to the tumour volumes and elective volumes. OPC constituted 48% of the patients and OCSCC 14%.

In the 2-year follow-up, no significant differences in terms of LRC (primary endpoint) or OS were observed. However, acute toxicity, but not late toxicity, was

significantly increased in the AF RT group. Furthermore, when the different subsites were analysed separately, there was a non-significant trend towards better LRC for OCSCC given AF RT compared to CF RT (p=0.07). The mature 5-year results confirmed these findings, with a trend towards improved LRC for AF RT (p=0.10)[83,84]. The combination of surgery following the preoperative RT (either AF RT or CF RT) was permitted and could be applied to resectable OCSCC.

The ARTSCAN patients with OCSCC who underwent subsequent surgery were later compared to the OCSCC patients in Lund treated with postoperative CF RT during the same period (unpublished data). OS was similar between the preoperative CF RT and the postoperative CF RT groups. However, in comparison, preoperative AF RT appeared to be associated with a better OS compared to postoperative CF RT. Even if no definitive scientific conclusions could be drawn from this comparison, it was hypothesis-generating for the formation of the ARTSCAN 2 study.

Purpose and aims

Purpose

The purpose of this thesis is to improve the treatment of patients with OCC undergoing surgery and RT by gaining a deeper understanding of the optimal sequencing of these treatments.

Aims

Paper I

To compare complication rates at the mandibulotomy site between patients receiving preoperative versus postoperative RT for OCC/OPC who require mandibulotomy for access to the tumour site.

Paper II

To compare LRC and OS between patients with OCSCC receiving either preoperative AF RT or postoperative CF RT in the ARTSCAN 2 trial. Additionally, to evaluate physician-assessed side effects.

Paper III

To evaluate early postoperative surgical and medical complication rates in patients with OCSCC receiving preoperative AF RT in the ARTSCAN 2 trial, compared to those scheduled for postoperative CF RT but not yet irradiated.

Paper IV

To compare HRQoL data between the two study groups in the ARTSCAN 2 trial. Furthermore, to perform an economic evaluation with QALY as an outcome measure.

Materials and methods

Paper I

In a retrospective study, we reviewed the medical records of 64 consecutive patients between the years 2000 and 2015. The focus was on identifying patients treated for cancer that involved or extended into the oral/oropharyngeal cavity who underwent a temporary mandibular split to gain access to the tumour site. We collected data on patient characteristics, dates and doses of RT, and postoperative complications at the mandibulotomy site. All patients had at least one year of regular follow-up and were examined clinically and with an X-ray of the mandible before surgery and one year thereafter. Three patient groups were identified: (**i**) patients who received RT within six months before surgery (n=15), (**ii**) patients who received RT within six months after surgery (n=31), and (**iii**) patients who received RT at various times or for recurrent disease (n=18). Statistical comparisons focused on the first two groups.

Paper II

Paper **II** is the primary report of the multicentre ARTSCAN 2 RCT, comparing preoperative AF RT with postoperative CF RT for OCSCC. A total of 250 adult patients with OCSCC, scheduled for combination treatment with surgery and RT, were randomly assigned (1:1) to the two treatment groups. Ten patients were excluded before the start of treatment, leaving 240 patients (120 in each arm) for the intention-to-treat analysis. Patients in the preoperative AF RT group received two fractions daily (1.1 + 2.0 Gy), five days per week, to a total dose of 68 Gy in 43 fractions. Elective lymph nodes received a dose of 46 Gy. Patients in the postoperative CF RT group received one fraction of 2.0 Gy daily, five days per week, to a total dose of 60 or 66 Gy in 30 or 33 fractions. Patients in the postoperative CF RT group with high-risk features in the pathological report (i.e., ENE or non-radical surgery) received the higher RT dose and were administered concurrent doses of 50 mg cisplatin weekly (**Figure 10**). Elective lymph nodes received a dose of 50 Gy. The interval between RT and surgery and vice versa was four weeks (up to a maximum of six weeks). Patients were stratified according to the study centre, clinical stage (stage I-II versus III-IV) and subsite (tongue and floor of mouth versus gingiva and other oral subsites).

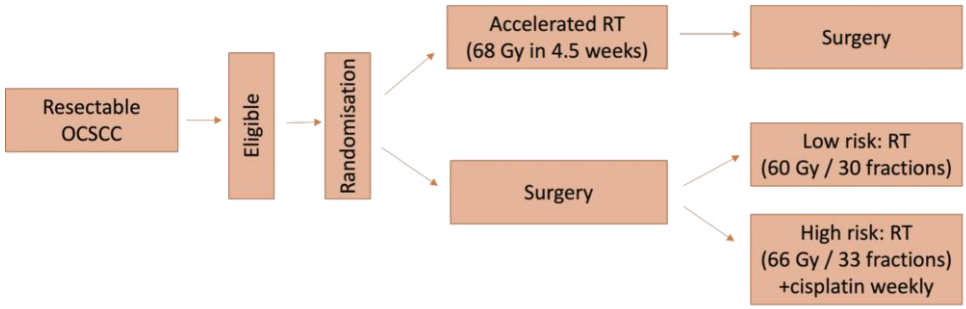

Figure 10. Study design of ARTSCAN 2.

Paper III

This study was based on data from the ARTSCAN 2 RCT (**II**). Early postoperative medical and surgical complications (during hospitalisation) were assessed and compared between the preoperative AF RT group (n=103) and the group that had not yet received RT (i.e., unirradiated at the time of analysis) (n=118).

Paper IV

This study was based on data from the ARTSCAN 2 RCT (**II**) and evaluated HRQoL. Three questionnaires (EORTC QLQ-C30, EORTC QLQ-H&N35, and HADS) were distributed to the patients on five separate occasions during the follow-up period (five years). Additionally, a CUA was performed, using QALY as the outcome measure. Costs were assessed from a societal perspective using a bottom-up approach.

Oncological outcome measures

- Locoregional control (**LRC**): In general, this refers to the time from the date of diagnosis until recurrence in T or N-site. In RCTs, it denotes the time from randomisation until recurrence at the primary site or regional lymph nodes.
- Overall survival (**OS**): This generally indicates the time from the date of diagnosis until death from any cause. In RCTs, it refers to the time from randomisation until death from any cause.

- Disease-free survival (**DFS**): This is the time after treatment during which the patient shows no evidence of cancer recurrence (locally, regionally, or at distant sites) and has not developed a second primary tumour or died. The term is commonly used in studies of adjuvant therapy and differs from, e.g., locoregional control (LRC), which only reflects tumour control within the primary and regional sites. For example, if a patient remains free of local and regional recurrence but develops distant metastases, LRC is maintained while DFS has failed.
- Progression-free survival (**PFS**): This denotes the time from the start of treatment until cancer progresses or death from any cause. This measure is often used in trials evaluating the treatment of metastatic disease. Trials with DFS or PFS as the primary endpoint can be evaluated earlier and require a smaller sample size than OS. Disadvantages include that an improved DFS or PFS does not necessarily correlate with improved OS, and uncertainties may arise regarding the timing of relapse or progression[85].
- Health-related quality of life (**HRQoL**): This assesses patients' self-reported experiences of their physical, emotional and social well-being. For instance, if a new treatment improves OS but significantly compromises quality of life, its clinical value may be questioned.
- Adverse events: These are unfavourable symptoms or diseases that occur during treatment and are not necessarily caused by the treatment itself.
- Toxicity: This refers to unfavourable effects that are directly caused by the treatment, such as neutropenia caused by chemotherapy or mucositis caused by RT.

Patient-reported outcome measures

EORTC QLQ-C30 and QLQ-H&N35

In Paper **IV**, health-related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) QLQ-C30 and the site-specific QLQ-H&N35 questionnaires. These are validated, reliable, and widely used in oncological research to evaluate both general and head and neck cancer–specific aspects of HRQoL[86–89]. The EORTC QLQ-C30 comprises 30 questions that assess five functional scales (physical, role, emotional, cognitive, and social functioning), a global health status/quality of life scale, three symptom scales (fatigue, nausea/vomiting, and pain), and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) (Appendix). The QLQ-H&N35 comprises 35 questions, which include seven symptom scales (pain, swallowing, senses, speech,

social eating, social contact, and sexuality), six single-item symptom measures (problems with teeth, mouth opening, dry mouth, sticky saliva, coughing, and feeling ill), and five dichotomous items assessing the use of painkillers, nutritional supplements, feeding tube, and weight gain or loss (Appendix). All scale and single-item scores were linearly transformed to a 0–100 scale in accordance with the EORTC scoring manual[90].

HADS

Anxiety and depression (**IV**) were evaluated using the Hospital Anxiety and Depression Scale (HADS), a validated instrument for assessing psychological distress in somatic care populations (Appendix). Each subscale (anxiety and depression) ranges from 0 to 21, with scores of 8–10 indicating possible cases of anxiety or depressive disorders, and scores above 10 indicating probable cases[91].

EQ-5D-5L

The EQ-5D-5L is a widely used generic (i.e., not disease-specific) questionnaire for assessing quality of life and generating an HU score. The HU score ranges from 0 to 1, with 1 indicating perfect health and 0 signifying death. The questionnaire comprises five dimensions (5D): mobility, self-care, usual activities, pain/discomfort, and depression/anxiety, each containing five different levels (5L) of severity. Additionally, there is a visual analogue scale for assessing the overall health status. This instrument is widely used in cost-utility evaluations[92]. In Paper **IV**, to enable QALY calculations, HRQoL data from the EORTC questionnaires were mapped to the EQ-5D-5L questionnaire[93].

Physician-reported side effects

In the ARTSCAN 2 study, treatment-related side effects were scored by the physician at the planned follow-up appointments during the five-year follow-up using the following tools. The Common Terminology Criteria for Adverse Events (CTCAE) is a standardised tool used for the classification of adverse events in clinical trials and covers a wide range of side effects[94]. The Radiation Therapy Oncology Group Criteria (RTOG) is designed specifically to grade radiation-related toxicity, including both the acute and late effects. Both scales are graded from 0 to 5, with 0 signifying no adverse effect and 5 indicating death related to an adverse effect[95]. The Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENT-SOMA) is a questionnaire designed to assess late radiation toxicity in more depth than the RTOG. It includes both a subjective (patient-reported symptoms) and an objective (physician-reported side effects) component, each scored from 0 to 4, with 0 signifying no symptoms and 4 indicating life-threatening toxicity[96].

Statistical methods

Descriptive statistics were used to summarise baseline characteristics and outcome variables. Continuous variables with a normal distribution were reported as means with standard deviations (SD), whereas non-normally distributed variables were summarised using medians and either minimum–maximum values or interquartile ranges (Q1–Q3). Categorical variables were presented as proportions and percentages.

Group comparisons for continuous variables were conducted using the independent samples t-test (for normally distributed data) or the Wilcoxon rank-sum test (for non-normally distributed data). Categorical data were analysed using Pearson's chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant unless otherwise stated.

Differences in complication rates and adverse events between treatment arms were assessed using Fisher's exact test. Associations between complications and potential predictors were analysed using univariate and multivariate logistic regression models, with results presented as odds ratios (OR) and 95% confidence intervals (CIs).

Survival outcomes, including LRC, OS, and DFS, were estimated using the Kaplan–Meier method, and treatment group comparisons were performed using the log-rank test. Additional survival analyses were conducted using the Cox proportional hazards model with model assumptions evaluated using Schoenfeld residuals. Gray's test was applied in the presence of competing risks.

In the HRQoL analysis, mean scores and 95% CIs were calculated for the EORTC QLQ-C30 and QLQ-H&N35 scales. Group comparisons at each follow-up were made using the Wilcoxon rank-sum test with adjustment for ties. All p-values were based on two-sided hypotheses, and to address the issue of multiple comparisons, the Benjamini–Hochberg procedure was applied with a false discovery rate of 5%.

For longitudinal HRQoL analyses, a linear mixed-effects model was used, incorporating treatment group, time point, and their interaction as fixed effects, with a random intercept specified for patient ID. The significance of the model was evaluated through F-tests focusing on three fixed effects: the treatment group, time, and the interaction between group and time.

In the economic evaluation, EORTC QLQ-C30 and QLQ-H&N35 scores were mapped to EQ-5D-5L health utilities using a published algorithm. To facilitate QALY calculations, multiple imputation was employed. Uncertainties in the CUA were assessed using non-parametric bootstrapping.

All analyses were conducted based on either the intention-to-treat or per-protocol population, as specified in each study. The statistical analyses were performed using IBM SPSS version 24 (**I**), 26 (**III**) and using R version 4.4.3 (**II** and **IV**).

Methodological considerations

Paper I: The retrospective study design has inherent limitations. The fact that dental extractions are known to impact complications occurring in the mandible, such as ORN, and our inability to assess them, represents a possible confounder. Additionally, excluding the "mixed group" from our analyses introduces a risk of selection bias. This was necessary, however, to ensure comparability regarding the timing of RT.

We selected a follow-up period of 12 months post-surgery to capture most mandibulotomy-related complications, as these typically arise in the first months post-surgery[97]. Additionally, this period was deemed sufficient to record cases of ORN at the mandibulotomy site, which occur earlier than spontaneous ORN[98,99]. Consequently, we may have missed complications arising after the 12-month mark.

Paper II: The ARTSCAN 2 study included a number of T1N0 tumours (9%), as the protocol allowed for the inclusion of T1-T2N0 tumours if they were "invading" upon clinical or radiological examination. We infer that these tumours had a DOI qualifying them for combination therapy and study inclusion. At the time of the trial, reporting of DOI in the histopathological report was not standardised. Including low-stage tumours raises concerns about overtreatment and potentially diluting the results. Nevertheless, these patients suitable for combined treatment were stratified by stage (I-II vs III-IV), with a similar number of stage I patients across the study groups. Moreover, we conducted *post-hoc* analyses of LRC and OS, excluding the T1N0 tumours, which did not impact our overall findings.

Paper III: A 30-day morbidity period is a common timeframe for reporting postoperative complications. However, data on the recorded postoperative complication variables were not available for the period following discharge from the hospital. Regarding morbidity after discharge, we depend on the outcomes of the physician-assessed toxicity (**II**) and the patient-reported HRQoL (**IV**). As an additional *post-hoc* test, we combined all complications and compared the study groups, with results remaining non-significant. Given the heterogeneity by which postoperative complications are reported in the literature, standardised classification systems like the Clavien-Dindo have been introduced[100]. Later studies from our institution have applied such standardised systems for postoperative complications.

Paper IV: Interpreting HRQoL is challenging due to the subjective nature of the data, which is influenced by individual expectations and cultural factors. The

phenomenon of response shift, where patients' perceptions of their symptoms evolve over time irrespective of actual health changes, adds further complexity. Additionally, comparability with other studies is hindered by diverse analytical and presentation methods. In this context, our adherence to the EORTC guidelines in our analyses is crucial, and we welcome the EORTC initiative, in collaboration with the SISAQOL (Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data) expert group, aimed at establishing international standards for analysing and reporting HRQoL data (www.sisaqol-imi.org). This project, which will be presented in 2025, will standardise data presentation, thereby enhancing comparability across trials.

In HRQoL studies, the results that emerge as both statistically significant (the difference is unlikely to be due to chance) and clinically significant (the difference is meaningful from a patient's perspective) are the most robust and reliable. Inferentially, statistical significance should not prevail over clinical importance when interpreting the relevance of trial results[72]. In Paper **IV**, we therefore considered the domains that emerged as *both* clinically relevant and statistically significant to be the most important.

Baseline HRQoL response rates were comparatively low when compared with later time points, the reason for which is unclear. However, no association between missing baseline data and treatment arm, hospital, age, sex, tumour subsite or clinical stage could be identified. We therefore considered the data to be missing at random and conducted a sensitivity analysis using multiple imputation for the missing baseline values, and our findings remained consistent. In a review of HRQoL response rates from patients in surgical surveys, the average rate was 70%[101]. A response rate below 50% is considered inadequate[102]. Considering these numbers, our response rates at baseline (78% versus 76%) are comparatively good.

The multidimensional attributes of HRQoL and the use of repeated measurements over time pose the risk of Type I errors, which means finding statistically significant results by chance (false positive results). Adjusting for multiple testing, making the threshold for significance stricter, is a viable approach[103]. We employed the Benjamini-Hochberg method, which is moderately conservative, to adjust for multiple testing.

It is worth noting that patients answered the questionnaires at certain time points after *the start of treatment*, meaning that, for example, patients in the postoperative CF RT arm answered the 6-month follow-up at around *3 months* after the end of RT. In contrast, patients in the preoperative AF RT arm answered the same questionnaire at around *five months* after the end of RT. Even though it is hard to know the timely causalities regarding HRQoL levels in relation to when surgery or RT was performed, it is worth noting that even if more time (2 months) passed since the end of RT in the preoperative group (when answering the first post-treatment assessment), HRQoL was still inferior compared to the postoperative group. From

an RT fractionation perspective, this indicates that HRQoL improves earlier in the postoperative CF RT group. An alternative explanation is that the added surgical trauma, which occurred 3.5 months before the first post-treatment HRQoL evaluation in the preoperative AF RT group, explains the difference.

A mapping algorithm was used to convert scores from the EORTC QLQ-C30 and QLQ-H&N35 to EQ-5D-5L utility values, enabling a CUA. In economic evaluations, EQ-5D is the most widely used tool for QALY calculations[82]. While mapping is beneficial when HU values are unavailable, it has limitations. Firstly, since the EORTC questionnaires capture cancer-specific aspects of quality of life and the EQ-5D-5L focuses on broader, general health dimensions, the two tools do not fully overlap. Consequently, some symptoms or functional impairments are overlooked in the estimated HU scores. Secondly, mapping introduces a statistical uncertainty. The predicted EQ-5D-5L values are model-based estimates rather than actual patient responses, which may be imprecise, especially for patients whose characteristics differ from those in the original mapping dataset. Lastly, the algorithm's performance may vary across subgroups or countries due to cultural and healthcare differences, affecting patients' interpretation and response to HRQoL instruments. With respect to the loss of information, mapping procedures are acknowledged as a means to receive HU values[82,104,105]. Ideally, questionnaires enabling QALY calculations should have been included from the onset in the ARTSCAN 2 trial; however, even then, head and neck-specific symptoms would not have been entirely captured. Future studies should aim to develop a disease-specific HU questionnaire that addresses the unique symptoms of head and neck cancer[106].

Ethics

Paper **I** was approved by the regional ethics committee in Lund, Sweden (2016/968). The ARTSCAN 2 study (**II-IV**) was approved by the regional ethics committee in Umeå, Sweden (07-178M), and written informed consent was obtained from all patients. The studies in this thesis were conducted following the ethical principles outlined in the Declaration of Helsinki, ensuring that the rights, safety, and well-being of all participants were protected.

Results

Paper I

Patients who received RT preoperatively had a higher complication rate (9/15; 60%) than those who received RT postoperatively (2/31; 6.5%) ($p < 0.001$) (**Table 2**). Among the specific complications, oro-cutaneous fistula, bone exposure, and non-union at the mandibulotomy site were significantly more common in patients in the preoperative RT group (**Table 3**).

Table 2. Complication rates at the mandibulotomy site, n (%).

	Complication		
	No	**Yes**	**Total**
Preoperative RT	6 (40)	9 (60)	15
Postoperative RT	29 (94)	2 (6)	31
Mixed RT	12 (67)	6 (33)	18
Total	47 (73)	17 (27)	64

Table 3. Number of specific local complications (%) per treatment group. P-values concern the comparisons between the pre- and postoperative RT groups.

	Preoperative RT (n=15)	**Postoperative RT** (n=31)	**Mixed RT** (n=18)	**p-value**
Oro-cutaneous fistula	8 (53)	1 (3)	5 (28)	<0.001
Bone exposure	6 (40)	1 (3)	2 (11)	0.003
Non-union	4 (27)	0 (0)	1 (6)	0.008
Plate exposure	1(7)	0 (0)	0 (0)	0.326

Paper II

There was no statistically significant difference in LRC (**Figure 11**) or OS (**Figure 12**) between the preoperative AF RT and the postoperative CF RT groups. LRC at two years was 81% (95% CI, 74-88) and 76% (95% CI, 69-84) for the preoperative AF RT and the postoperative CF RT groups, respectively. At five years, the corresponding numbers were 73% (95% CI, 65-82) for both groups (log-rank p=0.91). OS at two years was 73% (95% CI, 66-82) and 78% (95% CI, 70-85) and at five years 57% (95% CI, 48-66) and 69% (95% CI, 61-78) for the AF and CF RT groups, respectively. Acute and late toxicity were significantly more pronounced in the preoperative AF RT group.

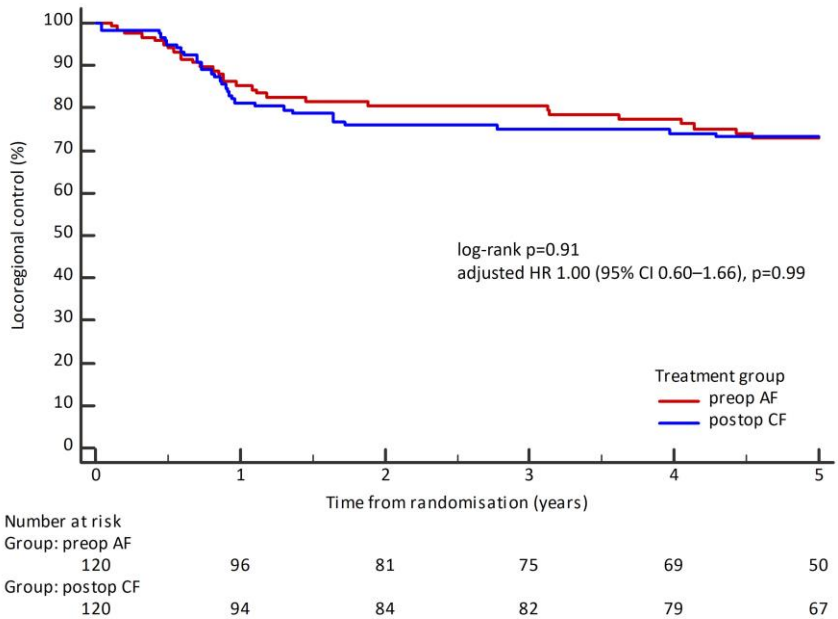

Figure 11. Locoregional control rates in the ARTSCAN 2 trial.

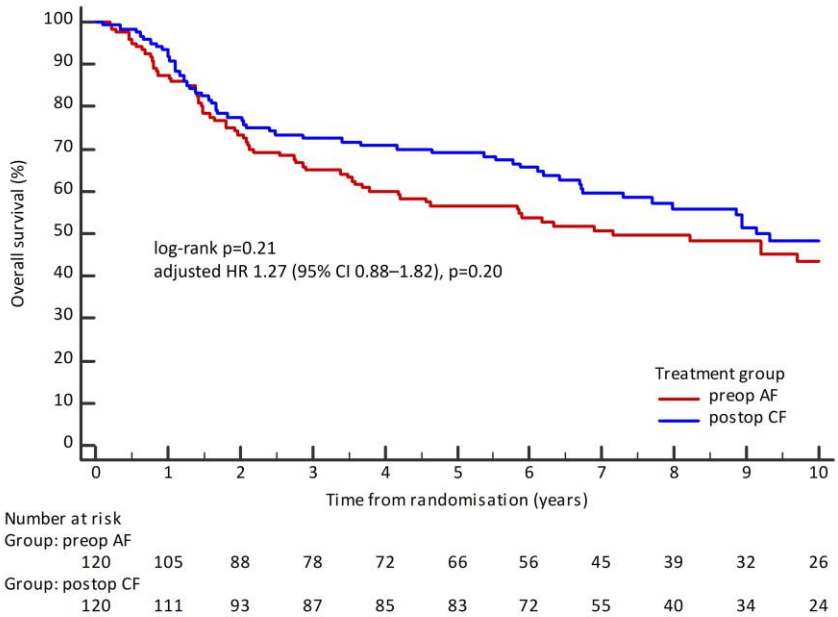

Figure 12. Overall survival rates in the ARTSCAN 2 trial.

Paper III

Patients who were exposed to preoperative AF RT experienced early postoperative complication rates comparable to those of the group not yet exposed to RT (**Table 4**). Six flap necroses occurred among the 99 flap-operated patients: two in the preoperative AF RT group and four in the unirradiated group (p=0.69).

Table 4. Early postoperative complications

	Preop. RT n=103	**No RT n=118**	**p-value**
Acute reoperation needed, n (%)	8 (8)	12 (10)	0.53
Post op. blood transfusion, n (%)	9 (9)	15 (13)	0.34
Wound infection, n (%)	12 (12)	9 (8)	0.31
Oro/pharyngocutaneous fistula, n (%)	3 (3)	3 (3)	1.00
Myocardial ischemia, n (%)	1 (1)	0 (0)	0.47
Deep vein thrombosis, n (%)	0 (0)	0 (0)	-
Pulmonary embolism, n (%)	0 (0)	1 (1)	1.00
Airway infection, n (%)	1 (1)	2 (2)	1.00

Paper IV

Patients exposed to preoperative AF RT experienced a significantly greater negative impact on their HRQoL compared to the postoperative CF RT group (**Figure 13**). This was particularly evident in areas such as swallowing, trismus, and the need for feeding tubes at six months post-treatment, as well as in trismus at twelve months and coughing at 24 months post-treatment. However, at the five-year follow-up, no significant differences were observed between the study groups, nor were there any differences noted in the Hospital Anxiety and Depression Scale (HADS). In the health-economic evaluation, postoperative CF RT was found to be more advantageous than preoperative AF RT (**Table 5**).

a)

b)

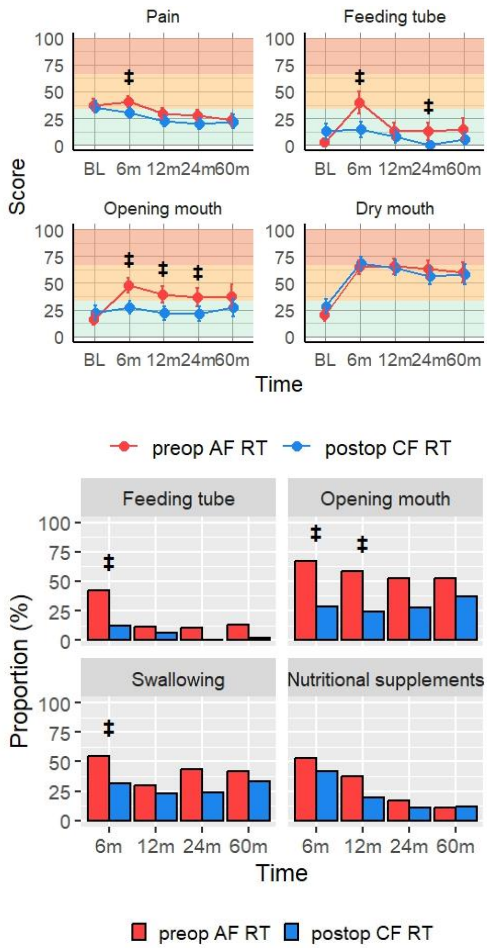

Figure 13. (a) Selected scales from EORTC QLQ-H&N35 (b) Selected scales showing clinically relevant deteriorations from baseline. ‡ Statistically significant differences after correction for multiple comparisons.

Table 5. Cost-utility analysis

	Preop AF RT n=95	**Postop CF RT n=109**	**Difference**
Total cost (€) (SD)	67,863 (41,619)	60,778 (42,830)	7,085 (-4,614 to 18,784*)
QALY (95% CI)	3.2 (2.9-3.5)	3.4 (3.1-3.6)	-0.175 (-0.582 to 0.233)
ICER			Dominated[a]

* 95% CI

[a]Preoperative AF RT is dominated by postoperative CF RT, i.e., preoperative AF RT was more costly and less effective.

Discussion

Study populations

In this series of studies (**I-IV**), the study population consisted of patients from a case series and an RCT (i.e., ARTSCAN 2). The case series (**I**) includes consecutive cases of patients referred for treatment, representing a well-defined cohort from the Southern Swedish Health Care Region. Specifically, it comprised all patients with OCC or OPC, requiring a mandibulotomy for tumour resection over a 16-year study period, minimising traditional concerns associated with patient selection. In ARTSCAN 2 (**II-IV**), the study population was determined based on statistical power calculations, with well-balanced patient characteristics across the groups. Notably, 91% of patients completed the planned treatment. RCTs offer significant advantages, as randomisation minimises bias by evenly distributing confounding factors, enhancing comparability and reliability. Furthermore, a multicentre design boosts external validity, making the results more applicable to a wider population. We believe that our study cohorts are sufficient to meet the objectives outlined for each study. For details on methodological considerations, please see the previous chapter.

Mandibular complications and treatment order

A study was conducted to investigate the complications associated with dividing the mandible, specifically examining whether the timing of RT influences these risks (**I**). Our overall complication rate of 27% compares well with previous reports[97]. We found that patients receiving RT within six months prior to surgery, including a mandibulotomy for tumour access, experienced significantly more complications at the surgical site compared to those irradiated postoperatively. Previous studies have suggested that preoperative RT is linked to increased complications related to mandibulotomies, although none reported statistically significant differences[107,108]. Additionally, no association was observed between the RT dose applied to the site of the mandibulotomy and the rate of complications. In fact, the preoperative RT group, which experienced the highest complication rates, received the lowest doses. Previous reports in the field have not demonstrated an association between radiation dose and complications at the mandibulotomy site[109,110]. In Paper **II**, we reported a

higher frequency of ORN during the five-year follow-up of the ARTSCAN 2 study population, with significantly more cases in the preoperative AF RT group compared to the postoperative CF RT group. A study on the ORN cases in the first and second ARTSCAN studies and their relationship with tooth extractions is ongoing. Overall, our results suggest that the site of mandibulotomy is more susceptible to complications from preoperative RT than from postoperative RT, and ORN is more prevalent following preoperative AF RT (33%) than postoperative CF RT (18%).

LRC and OS in relation to treatment order

In 2022, we reported the main outcomes of the ARTSCAN 2 study, which showed no significant differences in LRC or OS between preoperative AF RT and postoperative CF RT in the treatment of OCSCC (**II)**. Notably, no previous RCT has compared these treatment modalities. When treating head and neck cancers solely with RT, hyperfractionated regimens have proven beneficial[41].

Previous studies on RT for head and neck cancers have shown that altered fractionation regimens lead to more pronounced acute toxicity compared to conventional fractionation[41,42,58]. This was also observed in the first ARTSCAN study[83,84]. In Paper **II**, we reported increased acute toxicity with preoperative AF RT, including dysphagia, pain and the need for percutaneous endoscopic gastrostomy or nasogastric tube feeding. Additionally, we observed greater late toxicity, characterised by weight loss, affected laryngeal mucosa, and ORN.

The benefit of AF RT for local control in the definitive setting, as noted in other studies[41,45,46], was not reflected in our results. When analysing first failures in the two treatment arms of the ARTSCAN 2 study (Supplementary data, **II**), local failure rates were similar across the study groups.

An interesting finding from the subgroup analyses in Paper **II** was that females appeared to benefit from preoperative AF RT in terms of LRC and OS, whereas no such benefit was observed in males. Other subgroup analyses did not reveal any significant differences between the study groups. A non-significant trend suggested that large tumours (T3-T4) might achieve better LRC with postoperative CF RT. Although no firm conclusion can be drawn from this observation, it contrasts previous findings regarding OPC, where larger tumours in the definitive RT setting appeared to benefit from AF RT[111]. In conclusion, our results indicate that preoperative AF RT offers no advantage in terms of LRC or OS, while both acute and late toxicities are more pronounced.

Perioperative complications and treatment order

In Paper **III**, we assessed the perioperative surgical and medical complications in the preoperative AF RT group of the ARTSCAN 2 study, compared to those not yet irradiated. The complication rates were low, with no significant differences between the groups during the early observation period of hospitalisation. Most free flap losses, which are a serious concern, occur due to vascular compromise within the first 24-48 hours postoperatively; failures after seven days are uncommon[112,113]. Since the normal postoperative hospital stay for free flap patients is approximately 2 weeks, our study likely encompasses most cases. No differences in free flap failures were observed between the study groups.

Previous studies on postoperative complications following RT have yielded conflicting results[113–126]. Most of these are retrospective and include patients with significant variation in the time interval between RT and surgery, without specifically focusing on OCSCC. When considering RT as a potential predictor for postoperative complications across various head and neck cancers, some patients may have previously been treated for another head and neck cancer followed by a recurrence and surgical intervention. In comparison, a study group concerning planned combination treatment for oral cancer indicates a short interval between RT and surgery.

Following RT, tissue reactions develop in phases. Initially, mucositis and dermatitis occur, followed by tissue fibrosis and impaired vascularisation[127–129]. Radiation-induced fibrosis typically emerges 4-12 months post-RT and may progress for several years[130]. Studies indicate that surgery within six weeks after RT optimises free flap survival[121,122], while performing NDs within three months following RT similarly appears to reduce the risk of neck complications[131].

In conclusion, our results, characterised by low and comparable early complication rates, may stem from the surgery being part of a combined treatment and performed before the onset of RT-induced fibrosis and reduced vascular perfusion. For our study cohort, by the time fibrosis and vascular changes typically manifest (around four months post-RT), the surgical bed has already healed, thereby reducing the likelihood of complications, particularly concerning the soft tissue.

HRQoL, mental health and CUA in relation to treatment order

Evaluating health-related quality of life (HRQoL) in a randomised trial comparing pre- and postoperative RT for oral cancer is important, as it captures the patient-centred impact of treatment beyond traditional clinical endpoints. Incorporating

HRQoL outcomes allows for a more comprehensive assessment of treatment benefits and facilitates shared decision-making by balancing survival outcomes with quality of survivorship.

Our findings of more impaired HRQoL in the AF RT arm are consistent with the results from the first ARTSCAN study. However, the impairment in the AF arm diminished earlier in that study. At the end of RT and at three months after the start of RT, multiple symptoms were more impaired in the AF RT group. By six months after the treatment began, none of the symptoms were worse in the AF RT group, whereas a few were more impaired in the CF RT group. It is important to note that multiple testing was not accounted for[132].

In our study, we found that only a few patient-reported HRQoL variables could be compared with physician-assessed toxicity. Dysphagia and pain during RT were significantly more pronounced in the preoperative AF RT group, a trend also observed for dysphagia at six months in patient-reported HRQoL. No significant differences in xerostomia or taste alteration were noted by either physicians or patients. However, trismus appeared more pronounced in the patient assessments. This aligns with the literature, indicating that physicians often underestimate patient-reported complaints, highlighting the necessity of self-reported measures[133,134].

Previous studies have indicated that HRQoL in patients treated for head and neck cancer declines initially but typically returns to baseline about a year after treatment[135–138]. However, for oral cancer patients, problems with senses (smell and taste), dry mouth[138] and teeth[136] seem to persist beyond 12 months of follow-up. Our results confirm these longitudinal findings and, in addition, that trismus was a persisting long-term problem in the accelerated arm.

Anxiety levels in our study peaked at baseline and then remained comparatively stable throughout the follow-up period. This finding confirms results from a previous study on head and neck cancers conducted in Sweden and Norway[139]. The finding that levels of depression and anxiety did not reveal any statistically significant differences between the two treatment arms (**IV**) aligns with the results of the first ARTSCAN study[132]. Furthermore, a previous U.S. database study indicated that head and neck cancer patients are twice as likely to die from suicide compared to other cancer patients[140]. This underscores the importance of screening for mental illness to be able to initiate tailored interventions in time.

In the economic evaluation, the CUA indicated that postoperative CF RT dominated preoperative AF RT; that is, preoperative AF RT was more costly and yielded lower QALY than postoperative CF RT. These results, along with the other outcomes from the ARTSCAN 2 study, may inform decision-makers of the cost-utility benefits of applying CF RT postoperatively compared to preoperative AF RT.

Taken together, our results from Paper **IV** indicate that HRQoL is more impaired when preoperative AF RT is given, that mental illness is similar across the study groups, and that postoperative CF RT is more cost-effective.

ARTSCAN 2

Unlike the majority of previous reports on RT in the head and neck field, the ARTSCAN 2 study exclusively concerned patients with OCSCC. As such, the cohort was uniform, which facilitates the interpretation of the outcomes and increases the validity of the conclusions. The ARTSCAN 2 RCT has now been analysed in several studies. No significant differences were found in OS and LRC (**II**), early surgical and medical complications (**III**), or quality-adjusted life years per cost unit among the study groups (**IV**). However, preoperative AF RT showed worse outcomes concerning physician-evaluated side effects and HRQoL (**II, IV**) as well as increased societal costs[80]. In cost-effectiveness analyses, postoperative CF RT emerged as the preferred treatment option, utilising both OS and QALY as outcome measures ([80], **IV**). Taken together, we conclude that postoperative CF RT should remain the standard of care in the combined treatment of patients with OCC, and we hope our results will support future clinical decision-making.

Conclusions

Paper I

Patients with OCC/OPC who were exposed to preoperative RT prior to a surgical procedure involving a mandibulotomy to access the tumour site experienced significantly more mandibular complications compared to the postoperatively irradiated group.

Paper II

Patients with OCSCC exposed to preoperative AF RT compared to postoperative CF RT had similar OS and LRC at a median follow-up of five years, while toxicity was more pronounced in the preoperative AF RT group.

Paper III

Exposure to preoperative AF RT before surgery for OCSCC did not increase the risk of early postoperative surgical or medical complications compared to the group not yet exposed to RT.

Paper IV

Patients who received preoperative AF RT for OCSCC reported significantly worse HRQoL compared to patients exposed to postoperative CF RT. Preoperative AF RT was more expensive and less effective.

Future perspectives

Surgery followed by postoperative CF RT remains the most common treatment for advanced stages of OCSCC. The results from our studies support this strategy. The advantage of receiving a histopathological report to guide the adjuvant treatment must be underscored.

From a surgical perspective, to mitigate the need for mandibulotomies and the complications that may arise from the procedure, *transoral robotic surgery* (TORS) may be applied to selected OCSCC patients. Combining open surgery for the anterior part with TORS-assisted resection for the posterior aspect may be an option for appropriate posterior lesions.

New methods to improve sufficient tumour margins are appealing. These include the utilisation of ultrasound intraoperatively. If new techniques involving real-time imaging and optical guidance prove beneficial, it would be exciting.

Individualised therapy may become a possibility for the future treatment of head and neck cancer. Prognostic clinical variables and predictive biopsy data, e.g., selected immune markers or more complex immune profiles, may become feasible and be used to stratify patients for treatment.

Immunotherapy is becoming a promising treatment option for enhancing the immune response against cancer[141,142], particularly evident in the treatment of patients with malignant melanoma. PD-1 inhibitors, such as nivolumab and pembrolizumab, work by blocking the immune checkpoints that cancer cells use to avoid detection. In Sweden, these therapies are approved for recurrent or metastatic head and neck cancers. Current studies are exploring the integration of immunotherapy with RT, including optimal timing and combinations of immunotherapy with chemotherapy or ChRT, along with the selection of patients and consideration of tumour characteristics. Recent results from the GORTEC NIVOPOSTOP trial indicated that patients with locally advanced head and neck SCC (58% with OCSCC) with adverse features, who received postoperative ChRT plus nivolumab, had a three-year DFS of 63.1%, compared to 52.5% for standard ChRT (HR 0.76, 95% CI 0.60-0.98)[143]. The Keynote-689 trial also reported positive outcomes for pembrolizumab as neoadjuvant and adjuvant therapy for resectable head and neck SCC[144]. OS rates for both studies are pending, and full data have yet to undergo peer review and publication.

Populärvetenskaplig sammanfattning

Munhålecancer uppstår i tungan, tandköttet, munbotten och insidan av kinderna. Den visar sig ofta som ett sår som inte läker, en knöl (tumör), eller yttrar sig som smärta eller svårigheter att öppna munnen. Den absolut vanligaste typen av munhålecancer är den som utvecklas från cellerna i munslemhinnan, s.k. skivepitelcancer. Varje år får cirka 400 000 människor i världen diagnosen och i Sverige handlar det om ungefär 500 fall per år. Antalet nya fall per år ökar stadigt, också hos yngre, men orsaken till det är okänd. Sjukdomen drabbar kvinnor och män i ungefär lika stor utsträckning. De viktigaste riskfaktorerna för att utveckla en munhålecancer är rökning, överkonsumtion av alkohol och, i vissa delar av världen, tuggning av betelnöt.

Diagnosen ställs genom att man tar ett vävnadsprov (s.k. biopsi). Bilddiagnostik i form av datortomografi (CT), magnetkamera (MR) och s.k. PET-undersökningar används för att se hur utbredd cancern är och om den spridit sig till lymfkörtlar på halsen, vilket är den vanligaste platsen för spridning, eller till lungorna. Man använder därefter TNM-systemet för att stadieindela cancern där ”T” står för tumörens storlek och djup, ”N” för information om cancern har spridit sig till halsens lymfkörtlar eller inte och ”M” för en eventuell spridning till andra organ. Spridning utanför en lymfkörtels kapsel är en särskild riskfaktor för en sämre prognos.

Kirurgi är den vanligaste behandlingen vid munhålecancer och den används ensamt i tidiga stadier. Mer avancerade fall kräver dock att kirurgin kombineras med strålbehandling och ibland även cellgifter. I Sverige lever i genomsnitt 62% av de som drabbas av munhålecancer i minst fem år efter diagnos. Chansen att överleva varierar dock beroende på var i munnen cancern sitter och på sjukdomsstadium vid diagnos. Cancer i hårda gommen har t.ex. bäst prognos, medan cancer i munbotten har sämst prognos. En sjukdom som är spridd till närliggande lymfkörtlar har sämre prognos än när så inte är fallet. All behandling är associerad med biverkningar (som ofta är uttalade), påverkad livskvalitet och dessutom stora samhällskostnader.

Strålning ges i doser (s.k. fraktioner) som är fördelade över tid för att tillåta frisk vävnad att återhämta sig mellan behandlingarna samtidigt som tumörceller fortsätter att gå under. Med konventionell fraktionering ges en standarddos dagligen. Med hyperfraktionering ges mindre doser oftare men behandlingstiden är densamma som vid konventionell fraktionering. På så vis kan man uppnå en högre stråldos utan för

mycket biverkningar på den friska vävnaden. Vid accelererad fraktionering ges samma totala dos strålning under en kortare tidsperiod, med den bakomliggande teorin att man ska överkomma tumörens benägenhet att dela sig allt snabbare (s.k. repopulation), vilket sker ett par veckor efter strålbehandlingens start.

En dåligt utforskad fråga rör huruvida strålning bör ges före (preoperativt) eller efter (postoperativt) kirurgi vid munhålecancer. I denna avhandling undersöks specifika frågeställningar relaterat till om strålbehandlingen givits före eller efter kirurgi av munhålecancer, samt olika fraktioneringsmönster av strålningen.

I **delarbete I** studerades frekvensen av biverkningar i underkäken hos patienter som genomgått ”mandibulotomi” (delning av underkäken), som man ibland tillfälligt behöver göra för att kirurgiskt kunna nå tumörområdet. Vi ville se om biverkningsfrekvensen skiljer sig åt mellan patienter som får strålbehandling före respektive efter det kirurgiska ingreppet. Vi visade att gruppen som strålats före operationen hade en statistiskt säkerställd högre frekvens av biverkningar.

I **delarbete II-IV** studerades om två olika koncept vad gäller strålbehandling för munhålecancer, accelererad strålbehandling före kirurgi eller konventionellt fraktionerad strålbehandling efter kirurgi, skiljer sig vad gäller överlevnad, tumörkontroll, biverkningar och sjuklighet, livskvalitet och kostnadseffektivitet. Dessa aspekter studerades i en randomiserad klinisk studie: ARTSCAN 2. Vi visade att överlevnad och tumörkontroll inte skiljer sig signifikant mellan grupperna men att strålningsrelaterade biverkningar var mer uttalade i gruppen som strålats före kirurgi (**II**). Vi visade också att de tidiga kirurgiska och medicinska biverkningarna inte var mer uttalade om man strålats preoperativt (**III**) samt att patientrapporterad livskvalitet var mer negativt påverkad för den preoperativt strålade gruppen (**IV**). I en hälsoekonomisk utvärdering var preoperativ accelererad strålbehandling dyrare och gav sämre nytta mätt i kvalitetsjusterade levnadsår (**IV**).

Sammantaget visar resultaten av denna avhandling (och av ARTSCAN 2) att kirurgi följt av strålning med konventionell fraktionering är att föredra framför strålning innan kirurgin då det medför färre operationsrelaterade biverkningar (vid mandibulotomin), färre strålningsrelaterade biverkningar, mindre sjuklighet, bättre livskvalitet och högre kostnadseffektivitet. Avseende överlevnad, tumörkontroll liksom tidiga kirurgiska och medicinska biverkningar är resultaten mellan grupperna likvärdiga. Genom val av behandlingsstrategi kan dessa resultat nu användas för att optimera vården och ökade rehabiliteringsinsatser för patienterna skulle kunna medföra bättre patientupplevd livskvalitet och hälsoekonomiska vinster.

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AI declaration

Grammarly, an AI-powered language tool, has been used when writing the thesis. All the text has been written by the author, and Grammarly has solely been used to improve the spelling and grammar.

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Appendix

ARTSCAN II	**LIVSKVALITÉFORMULÄR**
	Patientnummer:

EORTC QLQ-C30 (version 3.0.) **Livskvaliteformulär nr:** **Utskick:**

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig. Det finns inga svar som är ”rätt” eller ”fel”. Den information Du lämnar kommer att hållas strikt konfidentionell.

Var vänlig fyll i Dina initialer: .....

När är Du född (Dag, månad, år): .....

Dagens datum (Dag, månad, år): .....

	Inte alls	**Lite**	**En hel del**	**Mycket**
1. Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
2. Har Du svårt att ta en lång promenad?	1	2	3	4
3. Har Du svårt att ta en kort promenad utomhus?	1	2	3	4
4. Måste Du sitta eller ligga på dagarna?	1	2	3	4
5. Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
6. Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
7. Har Du varit begränsad i Dina möjligheter att utöva Dina hobbies eller andra fritids-sysselsättningar?	1	2	3	4
8. Har Du blivit andfådd?	1	2	3	4
9. Har Du haft ont?	1	2	3	4
10. Har Du behövt vila?	1	2	3	4
11. Har Du haft svårt att sova?	1	2	3	4
12. Har Du känt Dig svag?	1	2	3	4
13. Har Du haft dålig aptit?	1	2	3	4
14. Har Du känt Dig illamående?	1	2	3	4
15. Har Du kräkts?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
16. Har Du varit förstoppad?	1	2	3	4
17. Har Du haft diarré?	1	2	3	4
18. Har Du varit trött?	1	2	3	4
19. Har Dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
20. Har Du haft svårt att koncentrera Dig, till exempel läsa tidningen eller se på TV?	1	2	3	4
21. Har Du känt Dig spänd?	1	2	3	4
22. Har Du oroat Dig?	1	2	3	4
23. Har Du känt Dig irriterad?	1	2	3	4
24. Har Du känt Dig nedstämd?	1	2	3	4
25. Har Du haft svårt att komma ihåg saker?	1	2	3	4
26. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Ditt familjeliv?	1	2	3	4
27. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina sociala aktiviteter?	1	2	3	4
28. Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

EORTC QLQ-H&N 35

Patienter uppger ibland att de har följande symtom eller problem. Var vänlig att ange i vilken grad Du har haft dessa besvär under veckan som gått. Sätt en ring runt den siffra som stämmer för Dig.

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
31. Har Du haft smärtor i munnen?	1	2	3	4
32. Har Du haft smärtor i käken?	1	2	3	4
33. Har Du haft sveda i munnen?	1	2	3	4
34. Har Du haft smärtor i svalget?	1	2	3	4
35. Har Du haft problem med att svälja flytande?	1	2	3	4
36. Har Du haft problem med att svälja mosad mat?	1	2	3	4
37. Har Du haft problem med att svälja fast föda?	1	2	3	4
38. Har Du ”satt i halsen” när Du svalt?	1	2	3	4
39. Har Du haft problem med tänderna?	1	2	3	4
40. Har Du haft problem med att gapa?	1	2	3	4
41. Har Du varit torr i munnen?	1	2	3	4
42. Har saliven varit seg?	1	2	3	4
43. Har Du haft problem med luktsinnet?	1	2	3	4
44. Har Du haft problem med smaksinnet?	1	2	3	4
45. Har Du hostat?	1	2	3	4
46. Har Du varit hes?	1	2	3	4
47. Har Du känt Dig sjuk?	1	2	3	4
48. Har Ditt utseende besvärat Dig?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
49. Har Du haft problem med att äta?	1	2	3	4
50. Har Du haft svårt att äta inför familjen?	1	2	3	4
51. Har Du haft svårt att äta inför andra människor?	1	2	3	4
52. Har Du haft svårt att njuta av måltiderna?	1	2	3	4
53. Har Du haft svårt att prata med andra människor?	1	2	3	4
54. Har Du haft problem med att prata i telefon?	1	2	3	4
55. Har Du haft svårt att umgås med Din familj?	1	2	3	4
56. Har Du haft svårt att umgås med Dina vänner?	1	2	3	4
57. Har Du haft svårt för att gå ut offentligt bland andra människor?	1	2	3	4
58. Har Du haft svårt för fysisk kontakt med Din familj eller Dina vänner?	1	2	3	4
59. Har Du känt Dig mindre intresserad av sex?	1	2	3	4
60. Har Du känt mindre sexuell njutning?	1	2	3	4

Under veckan som gått:	**Nej**	**Ja**
61. Har Du använt smärtstillande mediciner?	1	2
62. Har Du tagit något näringstillskott? (förutom vitaminer)	1	2
63. Har Du haft matsond?	1	2
64. Har Du gått ner i vikt?	1	2
65. Har Du gått upp i vikt?	1	2

HUR HAR DU KÄNT DIG UNDER VECKAN SOM GÅTT? SÄTT ETT TYDLIGT KRYSS I RUTAN TILL VÄNSTER OM DET SVAR SOM PASSAR BÄST IN PÅ DIG.

1. Jag känner mig spänd eller ”uppskruvad”:
- ☐ För det mesta
- ☐ Ofta
- ☐ Då och då
- ☐ Inte alls

2. Jag uppskattar samma saker som förut:
- ☐ Precis lika mycket
- ☐ Inte lika mycket
- ☐ Bara lite
- ☐ Knappast alls

3. Jag får en slags känsla av rädsla, som om någonting förfärligt håller på att hända:
- ☐ Alldeles bestämt och rätt illa
- ☐ Ja, men inte så illa
- ☐ Lite, men det oroar mig inte
- ☐ Inte alls

4. Jag kan skratta och se saker från den humoristiska sidan:
- ☐ Lika mycket som jag alltid kunnat
- ☐ Inte riktigt lika mycket nu
- ☐ Absolut inte så mycket nu
- ☐ Inte alls

5. Oroande tankar kommer för mig:
- ☐ Mycket ofta
- ☐ Ofta
- ☐ Då och då men inte så ofta
- ☐ Bara någon enstaka gång

6. Jag känner mig glad:
- ☐ Inte alls
- ☐ Inte ofta
- ☐ Ibland
- ☐ För det mesta

7. Jag kan sitta i lugn och ro och känna mig avspänd:
- ☐ Absolut
- ☐ Oftast
- ☐ Inte ofta
- ☐ Inte alls

8. Jag känner mig som om jag gick på ”lågt varv”:
- ☐ Nästan jämt
- ☐ Mycket ofta
- ☐ Ibland
- ☐ Inte alls

9. Jag får en slags känsla av rädsla ”fjärilar” i magen:
- ☐ Inte alls
- ☐ Någon gång
- ☐ Rätt ofta
- ☐ Mycket ofta

10. Jag har tappat intresset för mitt utseende:
- ☐ Absolut
- ☐ Jag bryr mig inte så mycket om det som jag borde
- ☐ Jag kanske inte bryr mig om det riktigt så mycket
- ☐ Jag bryr mig precis lika mycket om det som förut

11. Jag känner mig rastlös som om jag måste vara på språng:
- ☐ Verkligen mycket
- ☐ En hel del
- ☐ Inte så mycket
- ☐ Inte alls

12. Jag ser fram emot saker och ting med glädje:
- ☐ Lika mycket som förut
- ☐ Något mindre än jag brukade
- ☐ Klart mindre än jag brukade
- ☐ Nästan inte alls

13. Jag får plötsliga panikkänslor:
- ☐ Verkligen ofta
- ☐ Rätt ofta
- ☐ Inte så ofta
- ☐ Inte alls

14. Jag kan njuta av en bra bok, ett bra radio eller TV-program:
- ☐ Ofta
- ☐ Ibland
- ☐ Inte så ofta
- ☐ Mycket sällan

Hur lång tid tog det Dig att fylla i frågeformuläret?

☐ Under 10 minuter ☐ 11 - 15 minuter ☐ 16 - 20 minuter

☐ 21 - 30 minuter ☐ mer än 30 minuter

Var det någon som hjälpte Dig att fylla i frågeformuläret?

☐ Nej ☐ Ja

Om JA, vem hjälpte Dig:

☐ Familjen ☐ Sjukvårdspersonal ☐ Andra

Vad behövde Du hjälp med? .....

.....

.....

Fann Du någon av frågorna oklara eller svåra att besvara?

☐ Nej ☐ Ja

Om JA, vilken eller vilka frågor gällde det?

Fråga nr: .....

Gjorde någon av frågorna dig orolig?

☐ Nej ☐ Ja

Om JA, vilken eller vilka frågor gällde det?

Fråga nr: .....

Har andra sjukdomar än tumörsjukdomen påverkat Dina svar i frågeformuläret?

☐ Nej ☐ Ja

Om JA, vilken eller vilka sjukdomar rör det sig om? .....

.....

Om Du har fler kommentarer vänligen skriv ner dem på baksidan.
Har Du kontrollerat att Du svarat på alla frågorna?
TACK FÖR ATT DU SVARADE PÅ FRÅGORNA!

Pre- or postoperative radiotherapy for oral cancer

The primary treatment for resectable, locally advanced stages of oral cavity cancer generally involves a combination of surgery and radiotherapy. However, whether to apply radiotherapy first and then proceed with surgery, or to resect the tumour and subsequently administer radiotherapy, has not been extensively studied. This thesis examines various aspects of administering radiotherapy pre- or postoperatively in the treatment of oral cavity cancer. Additionally, two different radiotherapy fractionation concepts, accelerated or conventional fractionation, are explored. The overall conclusion is that postoperative conventional fractionation radiotherapy should continue to be the primary treatment for patients with oral cavity cancer when combining surgery and radiotherapy.

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