Radiotherapy for head and neck cancer
- costs and benefits of time, dose and volume

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“I det enkla bor det vackra”

Ernst Kirchsteiger
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Abstract

Background In the treatment of head and neck cancers (HNCs), radiotherapy (RT) has the advantage of organ preservation compared to surgery. However, treatment toxicities associated with RT can affect important functions for everyday life, both in the acute and late stage. RT to macroscopic tumour in HNC is commonly combined with elective RT to cervical lymph nodes at risk of microscopic involvement. The resulting risk reduction of the elective treatment based on dose-volume parameters is sparsely evaluated. So is the relationship between the elective treatment and treatment toxicity. The present thesis addresses these aspects.

A strategy aimed at improving the outcome of RT is accelerated fractionation (AF). AF strives to shorten total treatment time to minimise proliferation of the tumour tissue during the RT period. We have investigated the impact of AF on both disease control and toxicity.

Methods In the ARTSCAN study, 750 patients with localised HNC were randomised between AF (68 Gy in 4.5 weeks) and conventional fractionation (CF) (68 Gy in 7 weeks). The elective treatment volume was prescribed 46 Gy with CF in both treatment arms. The thesis is based on four individual papers, investigating the issues above in the whole study population or in sub-populations.

Results No difference in disease control or late toxicity between CF and AF was observed at five years. However, there was an increased acute toxicity with AF. Weight loss was associated with treatment volume, independent of tumour stage. The elective treatment volume was found to be an independent risk factor for late aspiration, as well as mean dose to the pharyngeal constrictor muscles, neck dissection, and age at randomisation. There was a significant risk reduction for node relapses in volumes treated to an elective dose. Only a relapse in volumes treated to >60 Gy affected the survival.

Conclusion The present thesis questions the benefit of AF in definitive RT as well as extensive elective treatment of the cervical nodes.
Abbreviations

HNC  Head and Neck Cancer (squamous cell carcinoma)
RT   Radiation Therapy/Radiotherapy
3DCRT Three Dimensional Conformal Radiotherapy
IMRT Intensity Modulated Radiotherapy
AF   Accelerated Fractionation
CF   Conventional Fractionation
TV   Treated Volume
OS   Overall Survival
CSS  Cancer Specific Survival
LRC  Loco-Regional Control
QoL  Quality of Life
OAR  Organ at Risk
SWOAR Swallowing-Related Organ at Risk
HPV  Human Papilloma Virus
BMI  Body Mass Index
CT   Computerised Tomography
UICC The Union for International Cancer Control
EORTC The European Organization for Research and Treatment of Cancer
### Glossary

These terms have been defined in the present thesis as follows:

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Dysphagia</td>
<td>Swallowing difficulties</td>
</tr>
<tr>
<td>Target Volume</td>
<td>The prescribed treatment volume, delineated by the treating physician.</td>
</tr>
<tr>
<td>Treated Volume</td>
<td>The volume of a patient irradiated to a dose of at least X Gy (TVᵢ). The treated volume is derived from the treatment plan.</td>
</tr>
<tr>
<td>Fractionation</td>
<td>The division of the total RT-dose into fractions. Often used when describing an RT scheme, e.g. hyperfractionation.</td>
</tr>
<tr>
<td>Neck Dissection</td>
<td>Surgical procedure to clear out cervical nodes in risk of/with established dissemination.</td>
</tr>
<tr>
<td>EQD₂ₓ</td>
<td>A calculated dose (used when fractions ≠ 2 Gy) equivalent to a dose delivered in 2 Gy fractions. X is a ratio assumed to be tissue specific (α/β, used in the Linear Quadratic Equation) which must be specified.</td>
</tr>
</tbody>
</table>
Original papers

The thesis is based on the following papers, referred to in the text with their Roman numerals:


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Enkel sammanfattning på svenska

Bakgrund och syfte


I detta avhandlingsarbete som består av fyra delarbeten har resultatet av denna studie undersökt. Vi har även undersökt effekterna av förebyggande behandling vad gäller risk för återfall samt biverkningar i form av sväljningssvårigheter och viktnedgång.
Resultat

En skyddande effekt mot återfall i lymfkörtlarna av doser motsvarande den som förskrivits för förebyggande behandling i ARTSCAN har påvisats i arbetet. Däremot finns ingen överrisk för död för patienter som råkar ut för ett återfall i halslymfkörtlar utanför strålbehandlat område.

Slutsats
Resultatet av ARTSCAN ifrågasätter rollen för förkortad behandlingstid vid botande strålbehandling av patienter med huvud-, halscancer. Värdet av den förebyggande behandlingen av halsens lymfkörtlar bör noga vägas mot risker, speciellt för de riskgrupper som identifierats i denna avhandling.
Introduction

Head and neck cancer
HNC is a group of cancers with origin in the squamous cells that line the mucosal surfaces inside the head and neck region (Fig 1). More uncommonly, HNC can originate from different cell types in the salivary glands.

Smoking and alcohol are well established etiological factors and have been shown to potentiate each other. Together they are estimated to contribute to 75 % of the HNCs (1). The patients diagnosed with HNC in Sweden are more commonly males (2:1) and usually in the age of 65-70 years (2). HNC constitutes only 2.3 % of all cancers in Sweden, with approx. 1300 new cases per year (2). Globally, HNC comprises 6% of all cancers (3). The incidence of HNC in Sweden is increasing, mainly due to a 5 % annual increase of cancer cases originating in the lymphatic tissue of the oropharynx (2). The increase of this specific subtype has been convincingly linked to high risk/carcinogenic strains of HPV, primarily HPV-16 (4, 5). Patients with HPV-positive cancer have slightly different
patient characteristics with notably younger age, and lack of smoking, as well as a better overall prognosis than those with HPV-negative disease (6-8).

Common symptoms of HNC at diagnosis are palpable lump in the neck, sore throat, swallowing difficulties and oral ulcers (1, 9). Due to often vague symptoms and a tendency early dissemination to cervical nodes, HNC tend to be diagnosed at a late stage. Distant metastases are, however, uncommon at diagnosis, making LRC the primary focus of the treatment (9, 10). In Sweden, the relative survival rate in HNC at five years is close to 70 % (2).

HNC is categorised into separate diagnoses depending on anatomical site of origin. The diagnoses differ in many important aspects, such as ethological factors, prognosis and treatment principles. The diagnoses investigated in the present theses are;

**Oral cavity cancer**
Oral cavity cancer is the most common HNC in Sweden (approx. 380 cases annually). Male to female ratio 1:1. Relative survival at five years is 63 % (2). Includes the tumour sites; the mobile tongue, the gums, the lining inside the cheeks and lips, the floor of the mouth, the hard palate, and the area behind the lower wisdom teeth.

**Oropharyngeal cancer**
Oropharyngeal cancer is the second most common HNC in Sweden (approximately 350 cases annually). 70 % of the patients are male. Relative survival at 5 years is close to 75 % (2). Includes the tumour sites; soft palate, the tonsils, and the base of the tongue.

**Hypopharyngeal cancer**
Hypopharyngeal cancer is the least common of the investigated diagnoses (60 cases annually) and it has the lowest relative survival after 5 years (30 %) of the HNC in Sweden. 75 % are male (2). Includes pharyngeal tumours located between the oropharynx and the larynx.

**Laryngeal cancer**
Laryngeal cancer is the third most common diagnosis in Sweden (175 cases annually) with a male to female ratio of 4:1. The relative survival at 5 years is close to 70 % (2). Includes the tumour sites; larynx and epiglottis.

Hereafter, in the present thesis, HNC refers to squamous cell carcinoma originating in these specific locations.

**Clinical stage**
Other than site, HNC is classified according to the UICC TNM Classification of Malignant Tumours-system (available at
T represents size of the primary tumour and is graded from 1-4. M reflects the presence of distant metastases, and if present, the disease is classified as M1. N represents dissemination to the cervical lymph nodes, often referred to as regional disease, and is graded 1-3. The cervical nodes are divided into anatomical levels (Fig.2) depending on location (11-13). Different diagnoses have different patterns of primary dissemination, which is reflected in the elective treatment strategies for the neck (elective RT/neck dissection). T-, N- and M-classification combined gives the clinical stage for the patient.

![Lymph node levels](image)

**Figure 2.** Lymph node levels of the neck. Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 9618.

**Treatment principles**
The treatment of localised HNC (M=0) involves surgery and/or RT to the primary tumour and/or the lymph nodes of the neck. Oncological treatment in the head and neck area is a delicate matter depending on the proximity of the tumour to structures/organs crucial to key functions in everyday life, e.g. breathing, eating and speech. The cosmetic results are also important for the patient's future social interactions. Considering these factors, RT has the obvious advantage of organ preservation.
RT can be delivered to different doses with different purposes;

- **Definitive RT** given to macroscopic disease to a dose determined by acceptable level of toxicity in the surrounding normal tissue, 68-73 Gy\(^1\).
- **Pre- or post-operative RT** to address any microscopic disease outside of the surgical specimen, often to a slightly lower dose than that of definitive RT, 60-70 Gy\(^1\).
- **Elective RT** to cervical nodes at risk for microscopic dissemination to a lower prescribed total dose, 46-54 Gy\(^1\).

**Treatment modifications**

The clinical stage (based on the UICC TNM classification) is a strong predictor of outcome, and is used when deciding the treatment strategy for the HNC-patient, in combination with the patient’s performance status (9, 10). The prognosis for the more advanced stages in HNC has historically been poor, and is below 50 % at five years for some of the HNCs in Sweden (14).

Different medical treatments such as chemotherapy, targeted drugs or hypoxic cell sensitisers have been combined with RT in efforts to improve the LRC and survival. A meta-analysis presented in 2000 based on 70 individual studies could not unequivocally support the use of chemo-RT in HNC (15). An updated meta-analysis in 2009 by the same group (MACH-NC) demonstrated a survival benefit of 6.5 % with concomitant chemo-RT (16). The present recommendation in Sweden is concomitant use of the chemotherapeutic drug cisplatinum with RT for more advanced disease (clinical stage III-IV).

The ability to predict the prognosis by the clinical stage derived from the TNM classification-system (UICC/AJCC) in use until present date in a particular subpopulation of HNC, namely the HPV-positive oropharyngeal cancers, is however under debate (17). In December 2016, a revised 8\(^{th}\) edition was published with new classifications for this entity (13). The current trend is rather to de-escalate the treatment in HPV positive oropharyngeal cancer due to equal or superior survival in this subpopulation with RT alone, without the adverse events of chemo-RT (18, 19).

Another strategy to improve RT outcome is the concept of altered fractionation. Based on empirics, RT has been delivered with a dose of 2 Gy per day, 5 days of the week to the prescribed dose. This is

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\(^{1}\) Examples of dose prescriptions in practise in Sweden today
referred to as CF. The background to fractionation of the RT dose is that there is an assumption of difference in the ability to repair sub-lethal radiation damage between normal cells and tumour cells. In the interval between two fractions, there is enough time for the slowly proliferating normal tissue to repair sub-lethal damages. Tumour cells, are hypothesised to have incomplete cell repair as part of the transformation from a normal cell into a tumour cell, and will therefore succumb to the radiation induced cell damage. Squamous cells and tumour cells derived from such cell types are relatively rapidly proliferating. This proliferation continues during the RT and protects the tissue from the effects of the RT, a phenomenon called repopulation, or accelerated repopulation. A theoretical strategy to overcome repopulation is to shorten the overall treatment time with or without significant dose reduction. This is referred to as AF. The shorter treatment time can be achieved by multiple RT fractions per day or alternatively treatment also during weekends, i.e. 6-7 treatment days per week. It is important to allow sufficient time for normal tissue repair between the fractions to avoid severe late side effects. Another altered fractionation strategy often used in HNC is hyperfractionation. An increased total dose is then delivered without shortened total treatment time, but with lower doses per fraction (<1.8 Gy) and with multiple fractions per day. The fractions are separated by a time interval sufficient for normal tissue damage repair. In short, hyperfractionation is used to increase the dose without increasing side effects. These two types of alternative fractionations in HNC have been the focus of several randomised controlled trials, as well as a meta-analysis (20). The results differ somewhat between individual studies and altered fractionation schemes, but the meta-analysis showed improvement in LRC for altered fractionation.

**Treatment related morbidity**

Even though RT spares the anatomical integrity of the organs in the treated area, RT can be detrimental for the patients, with side effects both in the acute stage and with a later onset. The severity of these side effects is determined by a number of factors, such as dose, concomitant medical treatment with chemotherapy or targeted drugs, altered fractionation and patient susceptibility. Over time, specific side effects have been linked to specific organs, so called OARs. With modern IMRT, it is often possible to spare at least one of the parotid glands, the most important OAR for the most infamous RT induced side effect, dry mouth. The side effect with the
most pronounced impact on patient reported quality of QoL, dysphagia, is however more complex (21). There are multiple identified OARs for dysphagia as well as multiple clinical factors (treatment- and patient related) connected to different aspects of swallowing difficulties (22-27). The SWOARs are notoriously difficult to spare, even with the use of novel RT-techniques. In some cases due to their close vicinity to the macroscopic tumour. In others the sparing of SWOARs come at the expense of increased dose in other OARs (28, 29). The possibility to adjust the size of the treatment volume for macroscopic disease to avoid OARs is limited without jeopardising tumour control probability. Elective RT of the cervical nodes has been part of standard treatment in HNC for many decades (30-32). When defining the elective volume, the benefits of the treatment (reduced risk of regional recurrences) must be weighed against possible toxicity of the treatment. The impact of dose-volume parameters of the elective treatment volume on treatment toxicity is seldom reported, other than impact of unilateral vs. bilateral treatment of the neck (33).

One of the most severe effects of dysphagia is aspiration which can cause aspiration pneumonia and ultimately respiratory insufficiency, both with possible fatal outcome for the patient (34). This, and the fact that aspiration assessed with video-flouroscopy is reproducible and facilitates comparisons, lead us to investigate aspiration further in a cohort of the ARTSCAN-study (IV).

Weight loss in patients with HNC is a multifactorial symptom that can be caused both by dysphagia, nausea, loss of taste and appetite as well as other problems caused by both treatment and the disease itself (35). If corrected for different tumour factors such as stage of the disease and site specific diagnosis, weight loss can reveal the joint effect of many different toxicities caused by the treatment.
Aims
The purpose of the present thesis was to explore cost/benefit of RT for HNC patients, with emphasis on the dose-volume parameters of the elective RT. This was carried out in four separate papers with specific objectives as follows:
I. To compare the outcome of AF versus CF in a large prospective randomised trial - the ARTSCAN study.
II. To analyse the relation between treated volume and weight loss, and between weight-parameters and survival.
III. To investigate the dose-dependent risk reduction of regional recurrences and the dose dependent impact of regional recurrences on survival.
IV. To evaluate potential dose-response relationships for swallowing organs at risk and late aspiration and to establish multifactorial models to predict late aspiration.
Materials and methods

Patients

The patients investigated in the present thesis were included in the prospective Swedish phase III multicentre randomised controlled study, ARTSCAN, between 1998 and 2006. Figure 3 depicts the profile of I-IV.

Figure 3. Flow chart of in/exclusions. Bold letters=study populations I-IV, CR=complete response, TF=treatment failure, RR=regional recurrence.

The demographics of the patients in I are published previously together with the preliminary results (36). In short, 750 patients
>18 years with previously untreated localised squamous cell carcinoma were included in the study, distributed as follows; oral cancer (13 %), oropharyngeal cancer (49 %), hypopharyngeal cancer (17 %) and laryngeal cancer (21 %). No chemotherapy prior to or during RT and no surgery prior to RT was allowed. The patients were randomised 1:1 between AF with a treatment time of 4.5 weeks or to CF with a treatment time of 7 weeks. The total dose was 68 Gy in both treatment arms. The study was well balanced with regard to patient and disease characteristics. Median age was 62 years, 75 % were male and 51 % had a Karnofsky Performance Status of 100 (37). 82 % of the CF patients and 83 % of AF patients had clinical stage III-IV (UICC) disease. After RT, 5 % of the patients had a resection of the primary tumour. In 28 % of the patients a neck dissection was performed. Surgery of the primary tumour together with neck dissection was performed in 5 and 2 % of the patients treated with CF or AF, respectively. In II and III, the cohort of patients with oropharyngeal cancer included in ARTSCAN was investigated (Fig 3). The diagnoses constituting HNC differ in many aspects including side effects, patterns of failure, and RT dose distribution. II and III both present retrospective studies and, as such, it is particularly important to minimise possible biases in the results by homogenising the study population. Oropharyngeal cancer constitutes half of the patients in ARTSCAN. They have a good prognosis allowing long follow up, and is the most common entity of HNC treated with definitive RT in Sweden. This made oropharyngeal cancer the best suited sub-group for the objectives in II and III. In III, an additional case-control study with cases consisting of all patients form cohort III (Fig 3) with regional recurrences and four controls per case derived from the remaining patients. The cases and controls were well balanced in respect to known prognostic factors such as T- and N-classification, Karnofsky performance status and HPV-status.

Twelve treatment centres participated in the ARTSCAN study. Two of these, Umeå and Lund, contributed with more than half of all patients. At a minimum of fifteen months after the last inclusion, all patients alive and free from recurrence from Umeå and Lund were invited to a videofluoroscopy examination of the swallowing function. The patients who signed informed consent for this additional examination comprises cohort IV (Fig 3).
During the follow-up period of ARTSCAN, the relation between HPV and oropharyngeal cancers as well as the prognostic impact of HPV association has been recognised (6). To investigate the proportion of HPV-positive oropharyngeal cancer and its possible impact on the result of the ARTSCAN-study, an additional analysis of the oropharyngeal cancer population in the study was performed and presented in I. Potential impact on survival of HPV-status after regional recurrences was also investigated in II. P16-staining in the tumour cells with immunohistochemistry was chosen as a surrogate marker for HPV-positivity (38, 39). From the four largest centres, the paraffin embedded tumour material from 206 patients was possible to retrieve (58 % of all oropharyngeal cancer patients) and re-process for p16 staining. A strong p16-staining in >70 % of the cells were interpreted as p16-positivity (6). In seventy-eight of the patients, an additional analysis of HPV-DNA in the tumour tissue by Polymerase Chain Reaction (PCR) was performed, including sub-typing of HPV-strain.

**Radiotherapy in ARTSCAN**

Dose prescriptions and target volumes were defined according to the recommendations of the International Commission on Radiation Units & Measurements (ICRU) (40, 41). A comprehensive RT quality assurance program was established to ensure that all patients were treated in accordance with the study protocol (42). The elective treatment was delivered with CF in both treatment arms; 2.0 Gy, 5 days a week to a total dose of 46 Gy. The treatment volume including macroscopic tumour was treated with an integrated boost technique in the AF arm consisting of 1.1 Gy given during twenty of the treatment days. All efforts were made to ensure a minimum seven-hour interval between the two daily fractions given during the first twenty treatment days in the AF arm. In conclusion, 68 Gy to the treatment volume including macroscopic disease was delivered in seven weeks for the CF arm and in 4.5 weeks in the AF arm. The elective treatment volume was prescribed 2.0 Gy, per day, five days a week delivered in 4.5 weeks in both treatment arms. The extent of the elective target volume was not defined in the study protocol, but left to the treating physician to decide. At the time of the study, there was no national or international consensus on which of the lymph node levels to treat prophylactic for the different clinical stages or diagnoses. Some of
the centres practiced limited elective treatment with unilateral or selective (not all the lymph node levels of the neck) treatment and some used bilateral treatment for all N-positive cases. This resulted in a substantial variation of the size of the elective target volume in ARTSCAN that did not solely depend on clinical stage. In N-positive oropharyngeal cancer the difference was two-fold and statistically significant (42). The study protocol stipulated the use of CT-based 3DCRT or IMRT. The latter treatment technique was used in approximately 10% of the patients.

Data collection and processing

**Follow up in ARTSCAN**

During the RT, the patients were assessed weekly by the attending physician. The patients were examined clinically 4-8 weeks after RT and then every three months until two years after the end of therapy. During years three to year five after treatment, the patients were scheduled for follow-up every six months. After five years only survival and cause of death from the Swedish Health and Welfare Statistical Database on Cause of Death were obtained.

Morbidity six months after the end of RT was classified as late toxicity in the ARTSCAN-study. Acute and late morbidity was assessed with selected items from the LENT-SOMA scale (43). Acute morbidity was scored at every visit during the first six months and late morbidity every six months thereafter during the follow-up of five years.

Health related QoL and patient reported function and symptoms were assessed with EORTC-C30 and the disease specific EORTC H&N35 questionnaire before, during and every year thereafter during follow-up (44, 45).

**Additional data collection and processing**

Radiotherapy data, i.e. treatment planning CT images, delineated structures, treatment plans and dose distributions for all segmented volumes were collected and stored in the ARTSCAN DICOM database after the completion of the patient’s treatment. The original CT images for all patients analysed in III and IV were restored in the treatment planning system (Oncentra®, Electa, Sweden) and a systematic-delineation of the lymph node levels according to Gregoire et al. (46, 47) applied in III and for selected SWOARs according to Christianen et al. (48) for IV was performed by the undersigned. Dose-volume data for these new structures
used in III and IV (lymph node levels and SWOARs) were derived from the updated DICOM-RT structure files and the original DICOM-RT dose files using the software package RT Bench® (Cureos AB, Uppsala, Sweden).

Patient weight was registered in the clinical report form at each follow up. For calculation of BMI used in II, height was obtained from the medical records. BMI was used to classify the patients into three groups: overweight (BMI > 25 kg/m²), normal weight (BMI 20-25 kg/m²) and underweight (BMI < 20 kg/m²) (49). These cut-offs were used for patients with age < 70 years. For patients ≥ 70 years, the cut off in BMI used for classification were 2 kg/m² higher (49).

The weight change used in II was calculated with the weight registered at start of RT as the reference and the weight registered at five months post RT as endpoint, as the patient weights registered in ARTSCAN reach their lowest registered value at that time (50). When investigating the potential correlation between weight loss and survival, the cut-off of ≥ 10 % in weight loss was used as it has been linked to clinical deterioration (51).

In order to address the objectives in III, the medical records of all patients in cohort III with regional recurrences were revised including any radiological imaging to identify the lymph node level and laterality of the regional recurrence in relation to primary tumour.

To investigate the dose-volume parameters related to elective treatment, all cases and controls in III were categorised into groups depending on the dose delivered to the lymph node level of interest. The dose intervals used for grouping cases and controls were chosen to reflect the location of the lymph node level in relation to; out of field (0-40 Gy), in low risk elective TV (40-50 Gy), high risk (close to the tumour volume) elective TV (50-60 Gy), and in the TV of macroscopic tumour (60-60 Gy). This allowed comparisons of number of regional relapses in different TVs between cases and controls.

For the objective in IV, the patients swallowing function was examined with videofluoroscopy. The patients were positioned upright and examined in frontal and lateral projections while swallowing a liquid bolus consisting of 7 ml barium sulphate, or in case of symptoms or risk of excessive aspiration, iodine contrast media. If no extensive aspiration was found during the first swallow, the patients swallowed additional boluses. Aspiration was registered if any bolus passed below the vocal cords entering the subglottal region, before, during or after swallowing (52).
Statistical considerations

It was estimated that 750 patients were needed to detect an absolute improvement of 10 percentage units at a level of 50 % in LRC at two years for AF compared to CF with a power of 80 %. To obtain a balance between the treatment arms in respect to treating centres, tumour site and nodal status, the method of minimization was used. The analyses were performed using the intention-to-treat principle. However, patients that were wrongly included, never started radiotherapy, or withdrew their consent were not included in the analysis (Fig 3). The follow up times for OS, CSS and LRC, was calculated from date of randomisation. In II, however, survival was calculated from start of RT. If a patient was never deemed free from tumour, the loco-regional failure was registered at time zero (I, III). LRC at time = 6 months was defined as complete response to primary treatment in III. Exploration of the dose-response relationship for regional recurrences in III were made in the form of a case-control study. This methodology was chosen because of the substantial variation in target volumes, irrespectively of tumour-classification, found in the N-positive patients in cohort III. This variation allowed comparisons of the dose distribution between cases and controls, balanced in regard to prognostic factors. The controls were generated with frequency matching based on T- and N-classification. To optimise the statistical power, four controls were chosen for each case.

Existing applicable statistical descriptive and inferential methods were used in the present thesis. All tests were two-sided and a p-value less than 0.05 was considered statistically significant. All statistical tests were performed with the statistical software packages IBM SPSS statistics 21.0 and the statistical software package R (version 2.15.2 and 3.1.1).

Multivariable analyses

In the multivariable analyses used in I-III, the explanatory variables were selected by statistical significance in the preceding univariable analyses. In IV, a selection based on internal correlations (calculated with Pearson product-moment correlation) between candidate explanatory variables was made between clinical parameters and dose-volume parameters, in addition to a cut off at p<0.1 from univariate analysis. Thereafter an automated variable selection based on the Bayesian information criterion (BIC) was used. The model was evaluated by calculating a cross validated area under the curve (AUC) based on the receiver operating
characteristics. In II, a regression model based on cubic splines (a piecewise third degree polynomial interpolation) was used to illustrate the nonlinear association between weight loss and TV. In III, the survival estimates from the Kaplan-Meier method for cases (patients with regional recurrences) and controls, as well as cases categorised according to delivered dose was complimented with Cox proportional hazards regression model analyses to adjust for the possible explanatory variables; fractionation type and neck dissection. The models throughout the thesis were constructed in a manner so that OR/HR > 1 indicates increased risk of event/outcome.

**Ethical considerations**

All patients gave informed written consent before inclusion in the ARTSCAN study or the additional videofluoroscopic evaluation of swallowing function. ARTSCAN was approved by the Regional Ethics Board for each of the participating centres (Fek dnr 98-139). The post hoc study of swallowing function was approved by the Regional Ethics Board in Umeå (dnr 07-023M).
Results

Possible benefits investigated in the present thesis

Accelerated fractionation (I)

No beneficial effect of statistical significance was demonstrated for LRC, OS, CSS or in the patterns of failure (T, N or M) with AF compared to CF. Median OS (95% CI) at five years was 5.1 years (3.3–6.9) and 5.4 years (3.7–7.1) in the AF and CF group, respectively.

Elective treatment (III)

The regional recurrence rate was 7.2 % in cohort III. No significant difference could be demonstrated in the demographics (including HPV-positivity) between the cases and controls. There were significantly fewer regional recurrences (OR = 0.18, p < 0.05) in the lymph node levels treated to a median dose corresponding to the TVelective (40-50 Gy) compared to lymph node levels “out of field” (III). There was a similar trend for mean dose in the same dose-interval (OR = 0.19, p = 0.07). For the lymph node levels treated to higher doses there was no protective effect against regional recurrences. The survival of patients with a regional recurrence in a lymph node level corresponding to TVelective did not differ from that of patients with a regional recurrence “out of field”. Patients with a recurrence in the TVtumour did significantly worse, HR 7.94 (p=0.006). The survival of patients with nodal recurrence in the neck was not affected by type of fractionation or neck dissection as part of primary treatment.

HPV-analysis (I, III)

Out of the 206 specimens retrieved for p16 analysis (58 %), 153 (74%) were p16-positive. For those that were analysed for HPV-DNA as well as p16-staining (n=78), the results differed between the methods in 6.4 % (n=5) of the specimens. 94 % (56/60) of the specimens positive for HPV-DNA were of type 16. Patients with p16-positivity had a significant better overall prognosis compared to patient with p16-negative tumours (I). P16 status did not discriminate for response to AF vs. CF (I), or response elective treatment (III).

Cases with HPV-positive disease displayed the same inverse relationship between dose to the lymph node level of relaps and survival (p<0.05) (III).
Possible costs investigated in the present thesis

**Accelerated fractionation (I, II, IV)**

The high grade acute side effects investigated in ARTSCAN were significantly more frequent in the AF arm, but no statistically significant difference in late side effects has been detected between the two treatment arms.

**Weight (II)**

In cohort II, the size of both TV\textsubscript{elective} and TV\textsubscript{tumour} were shown to have a detrimental effect on the patient weight up to 5 months after the end of RT, regardless of tumour stage. Weight loss >10 % was not associated to survival. BMI>25kg/m\textsuperscript{2} at treatment start was a positive prognostic marker for survival after RT in patients with oropharyngeal cancer.

**Swallowing (IV)**

The frequency of radiologically verified aspiration in cohort IV was 48 %. In univariate analysis, there was a dose-response relationship between most of the established SWOARs as well as TV\textsubscript{elective} and late aspiration assessed by videoflouroscopy. A multivariable prediction model for late aspiration assessed with videoflouroscopy derived three risk groups based on the risk factors; neck dissection, age >55 years at randomisation and mean dose to the middle pharyngeal constrictor muscle. For high risk patients, the risk of late aspiration was close to 70 % at a mean dose to the middle pharyngeal constrictor muscle of 50 Gy (the recommended dose constraint to the pharyngeal constrictors). A similar analysis but using the TV\textsubscript{elective} as a surrogate for SWOARs produced a model with equal performance (cross validated Area Under Curve=0.74) based on the same clinical risk factors. In the same group of patients, a TV\textsubscript{elective} of 1000 cm\textsuperscript{3} (median value in ARTSCAN for bilateral treatment=969 cm\textsuperscript{3}) gave a risk of late aspiration of 80 %. A multivariable model for patient reported choking (assessed with QoL-questionnaire) at one and five years identified two significant risk factors; mean dose to the superior pharyngeal constrictor and swallowing complaints at baseline. However, only the model based on the five-year questionnaire had an acceptable performance (cross validated Area Under Curve =0.78). Patients with baseline swallowing complaints have a risk of moderate/severe problems with choking of 30 % at a mean dose of 50 Gy to the superior pharyngeal constrictor.
Discussion

No benefit from AF could be detected in the five-year results of ARTSCAN (I). The fraction size of the concomitant boost is relatively small in the ARTSCAN study (1.1 Gy). This is discussed in detail in (36). There was however a significant increase in the acute side effects in the ARTSCAN-study for AF, suggesting that the biologically effective dose for the rapidly proliferating normal tissue was at least similar in the AF arm compared to CF (36). No corresponding increase in late side-effects could be detected in the present work (I, II, IV). Beitler et al. have published the updated long term results from a similar study by the Radiation Therapy Oncology Group, RTOG 9003 (53). No difference in survival was demonstrated, but they found a trend towards increased late toxicity. In the meta-analysis of altered fractionation by Bourhis et al. (20), an improvement in LRC with AF compared to CF was demonstrated. For survival at five years, a non-significant estimated benefit of two per cent was presented. Only one of the individual studies showed significant survival benefit of AF (54). In another study by Groupe Oncologie Radiotherapie Tete Et Cou, GORTEC 98-03, Bourhis et al. demonstrated worsened survival and increased toxicity with AF alone compared to CF with concomitant carboplatin-fluorouracil (55). The analysis of HPV-status in oropharyngeal cancer for the mature results of ARTSCAN did not explain this lack of effect. Thus, the value of AF in definitive RT is questioned.

In II, BMI at treatment start, but not weight loss during treatment, was a predictive factor for survival. It is however difficult to draw any firm conclusions on the usefulness of BMI as a predictor, as a number of well-established predictive factors for survival in oropharyngeal cancer such as smoking, HPV and performance status were not corrected for in the analysis.

The size of the TVelec and TVtumour, regardless of clinical stage, was associated with an increased weight loss in oropharyngeal cancer undergoing RT (II). It is obvious that the risk of exceeding dose constraints in OARs increases with increasing size of the TV. Even though the bulk of knowledge about dose-response for individual OARs is expanding, the dose-response of the TV is not commonly investigated (22-27). The TV reflects the total radiation exposure, and as such, is an attractive approach to evaluate the risks of the treatment for the patient. With modern, highly conformal
treatment techniques, it is feasible to transfer knowledge about the TV to the delineated target volume (56). Even though the treatment technique used in the present thesis is predominantly 3DCRT, the conformity index (41) for TV\textsubscript{tumour}/target volume encompassing gross tumour was 1.89 (±0.59) and for TV\textsubscript{elective}/elective target volume was 2.03 (±0.45). This indicates that both the target volume and the TV in the ARTSCAN study are able to predict weight loss. Figure 4 depicts treatment plans used in ARTSCAN generated with 3DCRT and IMRT. It illustrates that the differences in TV and dose distribution to OARs between treatment techniques can be subtle. It also demonstrates the importance of concise target delineation and treatment planning for the resulting TV, rather than the used treatment technique.

![Figure 4](image.png)

**Figure 4.** CT images with structure sets (OARs in blue, tumour target volume in pink, elective target volume in red) and isodose curves (encompassing TV\textsubscript{tumour} in dark green, encompassing TV\textsubscript{elective} in light green) modified from the ARSCAN databases.

Weight loss is highly multifactorial, and can be influenced both by dysphagia, xerostomia, mucositis as well as other factors such as systemic effects of the treatment (57, 58). Thus, we propose that
patients in need of nutritional surveillance are best identified by the treatment volume in total rather than with dose-volume parameters for individual OARs (II).

Due to the variation in elective treatment described earlier in cohort III, a case-control study corrected for obvious biases investigating the dose-response of regional recurrences was feasible. The regional recurrence rate at five years in the cohort was 7.2 %. A risk-reduction (OR<0.2) was indicated for the lymph node levels treated to 40-50 Gy with statistical significance for the dose-volume parameter median dose and a trend for mean dose. There was no difference between cases and controls in the dose intervals > 50 Gy. Doses >50 Gy indicate that the investigated lymph node level is in close proximity to previous macroscopic tumour which gives an inherent increase in risk of recurrences. Moreover, an equivalent dose in 2 Gy fractions (assuming an \( \alpha/\beta \text{=10} \) >50 Gy have not improved regional control, whereas, an EQD\(_{2_{10}}\) < 30 Gy resulted in higher regional relapse rate (59-61). A prospective study comparing elective treatment to an EQD\(_{2_{10}}\) of 50 Gy with an EQD\(_{2_{10}}\) of 40 Gy (n=193) did not show any statistical difference in regional relapses (62). However, a trend toward worsened regional relapse rate for the experimental arm was presented (p=0.08, 6 % vs 13 %) as well as no significant improvement for the primary outcome of the study, dysphagia.

Instead of a reduction of the elective dose, we believe it is reasonable to suggest a limitation of the extent of the elective treatment volume. The reason being its implication on a number of side effects. The size of the TV can be regarded as a surrogate for exposure to multiple OARs, where the resulting effects are not yet fully evaluated. An additional argument for minimising the elective volume could be found in III, where no significant effect of a regional relapse “out of field” on survival could be found. A regional recurrence in a lymph node level treated to a dose corresponding to the TV\(_{\text{tumour}}\) resulted in significantly reduced survival, part of which could be explained by more limited treatment options. It can also be speculated that recurrent or remaining tumour in a previously treated area is selected to be more treatment resistant. HPV-status did not seem to affect this inverse dose-response pattern (III).

The impact of TV\(_{\text{elective}}\), as well as the dose-volume parameters of the SWOARs on late dysphagia was investigated in IV. Aspiration was found in half of the patients in cohort IV. We demonstrated that a multivariable predictive model based on TV\(_{\text{elective}}\) instead of dose-
volume parameters for SWOARs separate or merged together was feasible and had at least an equal model performance. The additional patient (age >55 at randomisation) and treatment (neck dissection as part of primary treatment) related parameters derived by the normal tissue complication probability-model have previously been linked to dysphagia (23, 63). The risk for radiologically assessed aspiration in the high risk group using present dose constrictions is alarmingly high in the model based on mean dose to the middle pharyngeal constrictor. The same could be said for the predictive model based on TV_{elective} where the median value of TV_{elective} for patients reciving bilateral neck irradiation in the ARTSCAN study resulted in an 80 % risk of late aspiration. These models can assist in identifying patients at risk already at the planning stage, and if possible, allow for treatment modifications. 25.5 % and 28.6 % of the patients reported moderate/severe problems with choking at one and five years respectively. The patient reported choking measured with the QLQ H&N 35-questionnaire had no significant association with aspiration assessed by videoflouroscopy. In addition, a majority of the patients with demonstrated aspiration were unaware of the aspiration, which could be reflected in the much lower incidence of patient reported problems with choking compared to radiologically evaluated aspiration (IV). IV thus highlights the need to evaluate toxicity with both validated objective and patient reported methods.
Conclusions

In a large Swedish multicentre randomised controlled trial (I), no benefit was detected with accelerated fractionation compared to conventional fractionation. Although there were significantly fewer regional recurrences in the lymph node levels treated to elective doses, the survival for patients with recurrences out of field was not affected (III). The size of the treatment volume corrected for tumour classification/clinical stage was significantly correlated to the investigated side-effects, weight loss and aspiration (II, IV). The present thesis therefore questions the benefit of accelerated fractionation in definitive RT as well as extensive elective treatment of the cervical lymph nodes.
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