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PATIENTS WITH HEAD AND NECK CANCER
– ASPECTS ON TREATMENT, COMPLICATIONS AND REHABILITATION

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ABSTRACT

Head and neck cancer is reported to be the fifth most common cancer globally and around 1,200 new patients are diagnosed in Sweden every year. Historically, survival rates have been rather constant but have started to improve over the last few decades as a result of new and more aggressive oncological treatments. For this reason, there is a need to re-evaluate surgical treatment—both its necessity and its morbidity in comparison to the oncological treatments available. There is also a risk of higher incidence of side effects from newer oncological regimens, which still needs to be evaluated.

In this thesis, different populations of head and neck cancer patients from our institution have been analysed concerning aspects of treatment, sequelae, and rehabilitation. The material is highly applicable to everyday clinical situations.

In paper I, patients diagnosed between1998 and 2002 with metastases in the neck that were treated with full-dose external beam radiotherapy (EBRT) were evaluated concerning histopathology and clinical outcome, with a view to evaluating the necessity of a planned neck dissection after EBRT. One hundred and fifty-six patients were included. Overall survival was 62% and disease-specific survival was 76%. There was a clinically complete response to radiotherapy in the neck in 63 patients (40%). Of these, 15 had viable tumor cells in the neck specimen. In patients who did not achieve a clinically complete response, 40% (37/93) had viable tumor cells in the neck specimen. Disease-specific survival in patients with viable tumor cells in the neck after EBRT was 48% (25/52), and it was 90% (93/104) in patients without viable tumor cells.

Paper II describes a retrospective case-control study of patients diagnosed and treated for stricture of the upper oesophagus after EBRT for head and neck cancer between 1992 and 2005. The aim of the study was to identify possible risk factors for stricture formation. Clinical parameters were collected from the medical files. The EBRT dose delivered to the upper oesophagus was calculated using the dose-planning system data. Seventy patients with stricture and 66 patients without were identified. The incidence of upper esophageal stricture at the institution during the study period was 3.3%. A multivariate analysis showed an increased risk of stricture in patients who received enteral feeding during EBRT or with a mean dose of > 45 Gy delivered to the upper oesophagus. Treatment of the stricture with Savary-Gilliard bougienage or through-the-scope balloon dilatation was found to be safe and successful, but often had to be repeated.

In paper III, the morbidity of supraomohyoidal neck dissection (SOND) or modified radical neck dissection (MRND) combined with EBRT was evaluated regarding cervical range of movement, lymphoedema, mouth opening, swallowing, and shoulder disability. The patient material was collected from the study population in paper IV. Ninety-eight patients who received only EBRT were identified, 25 patients were treated with both SOND and EBRT, and 83 were treated with MRND and EBRT. The overall incidence of shoulder disability after both types of neck dissection was 18%. SOND had no other significant negative effects on the parameters under evaluation at any time

point, while with MRND there was significantly reduced CROM and mouth opening two months after treatment. After 12 months, only cervical rotation was still significantly reduced.

In paper IV, the aim of the study was to evaluate the effect of an early preventive rehabilitation programme on functional losses and quality of life. The programme started at diagnosis before the start of treatment and was based on self-care after receiving instructions from a speech language pathologist and a physiotherapist. The patients were instructed to use the training programme during and after the treatment period. One hundred and ninety patients were included in the early experimental rehabilitation programme. A control group of 184 patients who did not receive early rehabilitation was constructed. It was shown that the programme could be implemented without delaying the start of oncological treatment, but no positive effects concerning survival, weight loss, functional loss, working ability, or quality of life were observed.

The need for a neck dissection after EBRT cannot be determined by clinical examination as a high percentage of patients with clinical complete response showed viable tumor cells in the neck specimen. When performing a neck dissection, a SOND should be considered in suitable patients as morbidity of SOND is low except for shoulder disability. An EBRT dose delivered to the upper 5 cm of the oesophagus should be kept below 45 Gy to lower the risk of oesophageal stricture, and patients should be instructed to continue to swallow even if they receive enteral nutrition during treatment. Finally, even though no positive effects of early rehabilitation could be shown, the results do not contradict the idea that rehabilitation based on self-care can be effective. Efforts should be made to identify rehabilitation that can reduce functional losses and improve quality of life. Future rehabilitation programmes should also concentrate on identification of proper instruments for selection of patients and for evaluation of intervention in head and neck cancer patients.

LIST OF PUBLICATIONS

I. **Ahlberg A***, Lagerlund M*, Lewin F, Friesland S, Lundgren J.
Clinical outcome following radiotherapy and planned neck dissection in N+ head and neck cancer patients.
Acta Otolaryngol. 2008;128(12):1354-60

II. **Ahlberg A**, al-Abany M, Alevronta E, Friesland S, Hellborg H, Mavroidis P, Lind BK, Laurell G.
Esophageal stricture after radiotherapy in patients with head and neck cancer: experience of a single institution over 2 treatment periods.
Head Neck. 2010 Apr;32(4):452-61

III. **Ahlberg A**, Nikolaidis P, Engström T, Gunnarsson K, Johansson H, Sharp L, Laurell G
Morbidity of supraomohyoidal and modified radical neck dissection combined with radiotherapy for head and neck cancer. A prospective longitudinal study.
Head & Neck 2010 [in press]

IV. **Ahlberg A**, Engström T, Nikolaidis P, Gunnarsson K, Johansson H, Sharp L, Laurell G
Early self-care rehabilitation of head and neck cancer patients.
Acta Oto-Laryngologica 2010 [in press]

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CONTENTS

LIST OF ABBREVIATIONS

BL	Baseline
CI	Confidence interval
CR	Complete response
CROM	Cervical range of motion
CT	Computer tomography
DVH	Dose-volume histogram
EBRT	External beam radiotherapy
EGFR	Epidermal growth factor receptor
EORTC	European organisation for research and treatment of cancer
Gy	Gray
HADS	Hospital anxiety and depression scale
HRQOL	Health-related quality of life
MDADI	M.D. Anderson Dysphagia Inventory
MRI	Magnetic resonance imaging
MRND	Modified radical neck dissection
ND	Neck dissection
NG tube	Nasogastric tube
NR	No response
OR	Odds ratio
PAD	Histopathological analysis
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PR	Partial response
P-S	Project-specific questionnaire
PT	Physiotherapist
RT	Radiotherapy
SD	Standard deviation
SLP	Speech-language pathologist
SOND	Supraomohyoidal neck dissection

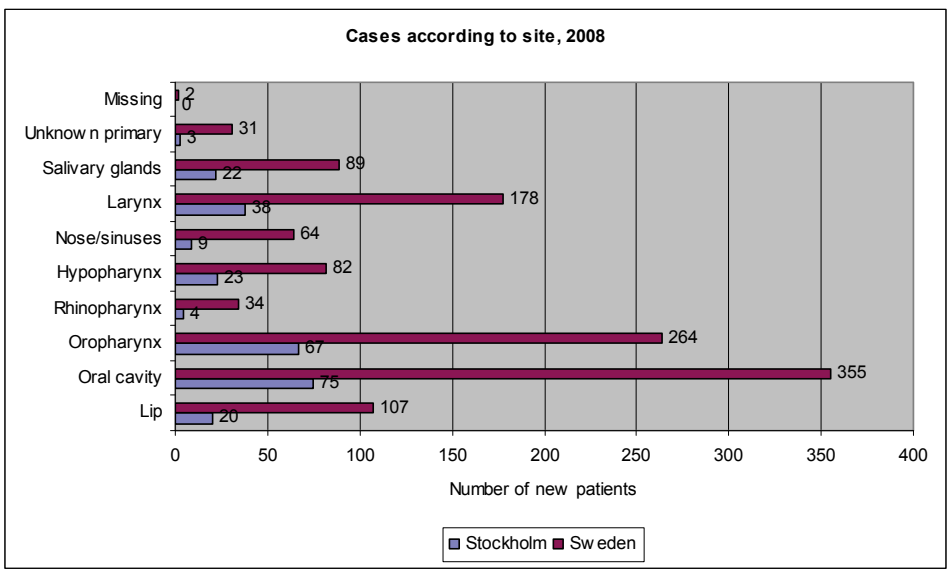
1 INTRODUCTION

1.1 HEAD AND NECK CANCER

Head and neck cancer is a heterogeneous group of tumours with different clinical patterns [1]. They are mostly grouped according to their anatomical site, i.e. the oral cavity, the rhinopharynx, the oropharynx, the hypopharynx, the larynx, the nasal cavity, the sinuses, and the salivary glands. All of these sites can be subdivided further. As in most other groups of malignant tumours, they are classified according to the TNM system (www.uicc.org). Worldwide, it is considered to be the fifth most common cancer with the seventh highest cancer mortality [2]. This estimation is highly approximate, as cancer registration is not well organised in many parts of the world, which might partly explain the large differences in the incidence of head and neck cancer between different regions [3]. Even though there are deficiencies in documentation from the developing countries, there *are* indications of an increased incidence of head and neck cancer in these parts of the world, most likely due to a change in exposure to alcohol and tobacco [4]. Other reasons for regional differences mainly involve lifestyle considerations, including exposure to different head and neck cancer-inducing agents such as bethel chewing, hot tea, smoking, alcohol consumption, and human papilloma viruses [5-7].

In 2008, there were 1,206 new cases of head and neck cancer in Sweden: 776 males and 430 females. This accounted for 2.4% of all new cancers in Sweden that year [8]. Median age at diagnosis was 66 years, 65 for men and 68 for women [9]. As shown in Figure 1, cancer in the oral cavity was most frequent, followed by oropharyngeal and laryngeal tumours. These proportions were similar for the Stockholm region alone.

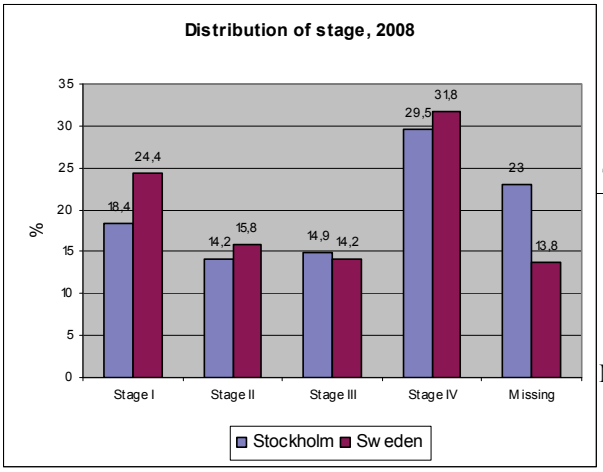
Figure 1. Number of patients diagnosed 2008 in Stockholm and Sweden.



Source: the Swedish Head and Neck Cancer Quality Register (SHNC-QR)

Around 45% of the patients in Sweden were at stages III–IV, with similar figures for the Stockholm region, as shown in Figure 2. Around 40% of the patients had cervical metastasis at diagnosis and more than 20% of the patients were at stage N2 [9].

Figure 2. Distribution of stage in patients diagnosed 2008 in Stockholm and Sweden.



Stockholm region

T-stage	%	N-stage	%
T1	31.4	N0	57.1
T2	27.2	N1	9.6
T3	16.9	N2	23.8
T4	19.9	N3	3.1
TX	2.3	NX	4.6
Missing	2.3	Missing	1.9

Source: the Swedish Head and Neck Cancer Quality Register (SHNC-QR)

1.1.1 Aspects of treatment

Treatment for head and neck cancer depends on the specific sub-site of the primary tumour and on tumour stage. It is also necessary to take into consideration the performance status of each patient, as treatment is often very intense with multiple side effects. Patients with co-morbidity have poorer survival, irrespective of the choice of treatment [10,11]. A patient might be regarded as not being operable due to co-morbidities with low performance status or if the tumour is unresectable. During most of the twentieth century, only surgery and external radiotherapy were considered effective against head and neck cancer but at the end of the century, chemotherapy in combination with radiotherapy became more common [12]. In the twenty-first century, new treatments such as monoclonal antibodies have been incorporated into the treatment arsenal [13].

1.1.1.1 Clinical work-up

At our institution, head and neck cancer patients are examined with a CT-scan or an MRI from the base of the skull over the neck and including the thorax, to determine the extent of the tumour and to look for distant metastases. Patients are also examined under full anaesthesia to allow a thorough clinical examination with biopsies and to exclude a second primary in the upper aerodigestive tract. In most cases, an ultrasound-guided fine needle aspiration is performed to look for regional metastasis. All patients are then discussed at a multidisciplinary meeting. The patients are staged according to the TNM staging system and a treatment plan is established [14]. At our institution, those participating at the meeting are the head-neck surgeons, the oncologists, a reconstructive plastic surgeon, a pathologist, a maxillofacial surgeon, a dentist, and a

coordinator oncology nurse. This multidisciplinary approach provides a forum for discussion and allows the coordinator nurse to quickly establish a treatment programme and a time schedule for the patient.

The TNM staging system:

- T (1–4): size or direct extent of the primary tumour; Tis: carcinoma in situ; T0: no evidence of primary tumour.
- N (0–3): degree of spread to regional lymph nodes.
- N0: tumour cells absent from regional lymph nodes.
- N1: metastasis in a single ipsilateral (same-side) lymph node, 3 cm or less in size.
- N2a: metastasis in a single ipsilateral (same side) lymph node, more than 3 cm but not more than 6 cm in greatest dimension.
- N2b: metastasis in multiple ipsilateral (same-side) lymph nodes, none more than 6 cm in greatest dimension.
- N2c: metastasis in bilateral (both) or contralateral (opposite-side) lymph nodes, none more than 6 cm in greatest dimension.
- N3: metastasis in a lymph node more than 6 cm in greatest dimension.
- M (0/1): presence of metastasis.
- M0: no distant metastasis.
- M1: metastasis to distant organs (beyond regional lymph nodes).

Use of an "X" instead of a number or other suffix means that the parameter was not assessed.

	NO	N1	N2a	N2b	N2c	N3
T1	Stage 1	Stage 3	Stage 4a	Stage 4a	Stage 4a	Stage 4b
T2	Stage 2	Stage 3	Stage 4a	Stage 4a	Stage 4a	Stage 4b
T3	Stage 3	Stage 3	Stage 4a	Stage 4a	Stage 4a	Stage 4b
T4	Stage 4a	Stage 4a	Stage 4a	Stage 4a	Stage 4a	Stage 4b

1.1.1.2 Surgery – neck dissection

1.1.1.2.1 Primary surgery

Surgery was the only treatment available for these patients until radiotherapy was introduced, and radiotherapy was initially intended to replace surgery as treatment [15]. This has not been the case, however; instead, the two modalities are used together [16]. Over time, surgeons have strived to produce as little morbidity and disfigurement as possible, resulting in a continuous evolution of new techniques [17]. Surgery on the primary tumour has changed, and today surgery is rarely performed primarily on pharyngeal tumours as these mostly respond well to oncological treatments. However, in cases where there is no response or where there is recurrence, these patients are treated with salvage surgery [18] if possible, often requiring reconstructions with free flaps [19]. Tumours in the oral cavity are still often subjects for primary surgery, and in many cases they require free-flap reconstructions with soft tissue and, in the case of mandibular resections, bone also [20]. Lower-stage tumours of the oral cavity are often treated with surgery alone while those of higher stages are treated with combined modalities [21]. Concerning laryngeal tumours, small T1a tumours are often treated with

surgery while T1b and T2-3 are treated with EBRT alone and T4 are treated with a laryngectomy followed by EBRT [22-24], however local traditions are strong and guidelines for treatment vary both nationally and internationally. The Department of Veterans Affairs Laryngeal Cancer Study Group [25] is a landmark in the development towards organ preservation in this field. There are, however, new forms of surgery with better organ-preserving capability that might broaden the field for surgery at the primary site [26].

1.1.1.2.2 Neck dissection

Neck dissection was introduced as palliative surgery for head and neck cancer patients, but at the beginning of the twentieth century G.W. Crile [27] established the procedure as a treatment for head and neck cancer, reducing the risk of regional recurrence [28]. The more modern form of neck dissection was later established by H. Martin [29]. From the 1960s, neck dissection was part of surgical treatment [30] in combination with radiotherapy for patients with regional metastasis (N-positive). Over time, organ preservation became more of an issue with a definitive change towards chemoradiotherapy without neck dissection in N-positive patients in the 1980s. The debate about how to handle these patients and the possible pros and cons of a planned neck dissection—regardless of the therapeutic response after radiotherapy—continued all through the 1990s [31,32]. This issue is further investigated in Paper I in this thesis. During the last decade, however, most authors have concluded that there is no need to perform a planned neck dissection in N-positive patients who achieve a complete response after radiotherapy or chemoradiotherapy [33,34], and if a neck dissection is performed, a modified procedure is recommended [35]. Parallel to this, a new role for neck dissection has evolved as a diagnostic tool in discovering micrometastasis in the N0 neck, thereby serving as a prophylactic treatment against regional recurrence. This is commonly called a staging, selective, or elective neck dissection and is mostly used for tumours of the oral cavity [36,37] due to the risk of micrometastasis [38]. There are some controversies concerning the classification of different neck dissections [39] but in Sweden we commonly use that of the Committee for Head and Neck Surgery and Oncology of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), even though other classification systems might be more distinct [40].

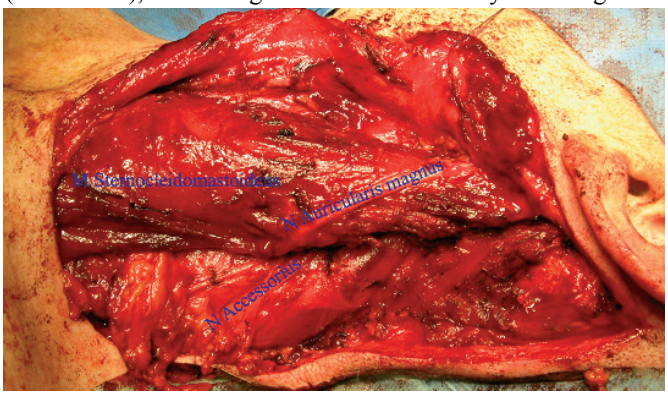


Figure 3. Modified radical neck dissection with preservation of the sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve, classified according to the AAO-HNS.

According to the AAO-HNS, there are three major types of neck surgery: radical, modified radical, and selective [41]. However, this classification is under contentious development [42].

There is a trend towards less extensive surgery, only removing the regions of the neck that are most likely to harbour metastasis. One development, the sentinel node technique, can be regarded as an extremely selective neck dissection only removing the gateway nodes [43]. This technique is certainly promising and might replace the elective neck dissection in the future [44].

1.1.1.3 Non-surgical treatment

The non-surgical treatment mainly consists of radiotherapy, external and internal (brachytherapy), chemotherapy given as induction and/or concurrently, and pharmacological treatment.

1.1.1.3.1 External radiotherapy

External-beam radiotherapy (EBRT) is the basis of oncological treatment for head and neck cancer, and in this thesis all patients received EBRT [45]. EBRT is commonly given using photon beams from a linear accelerator. The goal is to deliver a high dose to the tumour without damaging the surrounding tissues, especially certain organs that are known to be at risk such as the spinal cord, the inner ear, and the salivary glands [46]. To achieve this goal, dose planning is crucial and is performed using 3-dimensional CT-based imaging for identification and delineation of the tumour and organs at risk [47,48]. Treatment is given over a period of up to 7 weeks with one dose of 2.0 Gray (Gy) per day, five days a week. Other fractioning for a shorter period with two doses per day, e.g. 1.1 + 2.0 or 1.6 + 1.6 Gy, called hyperfractioned radiotherapy, is also used [49,50]. The reasoning behind this is the possibility of delivering a higher total dose or—in accelerated treatment—to deliver the same dose in a shorter time, not giving the tumour cells time to recover [49,51]. Since treatment goes on for several weeks, there is a risk of small changes in patient positioning due to weight loss, changes in the volume of the tumour, and changes in the organs at risk. This, and the fact that the patient is not fully immobilised during treatment might lead to high radiation doses to surrounding tissues. This risk might be reduced by adaptive radiation treatment with new target definition during treatment [52]. Another feasible way of limiting radiation to normal tissues while treating the tumour is the use of proton beam radiation [53,54]. There is also increased use of intensity-modulated radiotherapy (IMRT), which reduces the irradiation of normal tissues [46].

The question of whether there should be pre- or postoperative EBRT has been under debate for decades. Some argue against preoperative EBRT since this might be negative for surgery, and above all free-flap reconstructions, especially if there is a long time delay between the end of EBRT and surgery [55]. Other workers have found evidence that postoperative EBRT is associated with a higher risk of local recurrence [56]. Different protocols are used for different primary sites and stages. Even though some authors advocated preoperative EBRT for the oral cavity [57], most institutions use primary surgery for tumours smaller than T4 with postoperative EBRT depending on stage, radicality, and histopathology [21]. The relative impact on outcome of pre- and postoperative EBRT in oral cancer is presently being investigated in a Swedish national study (ARTSCAN II). For pharyngeal cancers, non-surgical treatment tends to cure more patients—making surgery superfluous in many cases—so these tumours are mainly treated with preoperative EBRT [58] As in the oral cavity, the laryngeal tumours

are treated with different modalities depending on stage as described above in section 1.1.1.2.1.

1.1.1.3.2 Brachytherapy

Internal radiation, also called brachytherapy, is less frequently used and its use depends on local traditions. Brachytherapy means that photon radiation is delivered through plastic tube catheters that are implanted around the tumour, making it possible to deliver a high dose of radiation directly to the tumour without any beams passing through normal tissue. One limitation of brachytherapy is that the tumour has to be accessible for implantation of catheters. Some authors argue that smaller tumours can be treated with brachytherapy alone while larger tumours—for example, at the base of tongue, should be treated with a combination of external and internal radiotherapy [59,60]. Brachytherapy is used at Karolinska University Hospital, but only about 15% of the patients in Paper IV were treated with brachytherapy.

1.1.1.3.3 Chemotherapy and pharmacological treatment

As mentioned earlier chemotherapy in combination with radiotherapy has been used more frequently after the Veterans Affairs Laryngeal Cancer Study [25]. In many parts of the world, the combination of EBRT and chemotherapy is very common [61] but in Sweden it is still less frequently used; however, there are regional differences [45]. In this thesis, 23% of the patients in Paper IV and 15% of the patients in paper III received chemotherapy in combination with EBRT; none of the patients in the other study populations received any chemotherapy. Chemotherapy can be given alone in palliative treatment. In curative treatment, it is always given in combination with radiotherapy either before radiotherapy (as induction or neoadjuvant), at the same time as radiotherapy (as concomitant or concurrent), or after surgery (as adjuvant) [62]. The combination of radiotherapy and chemotherapy is reported to improve loco-regional control and survival rates, at least in patients with advanced disease [63-65]. To further reduce the risk of distant relapse, there is an increasing use of the combination induction and concurrent chemoradiotherapy since induction chemotherapy has been reported to reduce distant relapse [66]. The limitations of chemotherapy are its side effects, in particular the acute side effects, but there is growing evidence of higher rates of late toxicity side effects as well [67]. There is a lack of research into patient satisfaction and quality of life associated with chemoradiotherapy [68].

Since the study by Bonner *et al*. in 2006, where they found an improved loco-regional control for patients with advanced head and neck cancer treated with a concomitant combination of high-dose radiotherapy and cetuximab compared to radiotherapy alone, there has been growing interest in treatment with monoclonal antibodies [13,69]. However, no patients included in the studies in this thesis received any molecularly targeted agents. Cetuximab, a EGFR-targeting monoclonal antibody, was the first of these drugs to be tested in clinical studies and has been shown to significantly improve survival for advanced head neck cancers and for patients with recurrent disease [70]. These types of drugs are rapidly developing into more specific treatments since it is not yet known which patients will respond best to these drugs [71].

1.1.2 Aspects of complications

Head and neck cancer patients suffer from a number of side effects—of both the treatment and the tumour disease itself. Due to the location of the primary tumours, basal functions such as breathing, swallowing, speech, hearing, vision, smell, and taste are affected in addition to disfigurement [72-78].

1.1.2.1 Complications induced by neck dissection

The incidence and severity of complications after a neck dissection are reported to be related to type of neck dissection and whether it is combined with radiotherapy or not. For example, a selective neck dissection is generally associated with low morbidity [79]. There are a number of different complications of varying severity that can be divided into acute and late complications.

Acute complications are wound infections, chyle leakage, and postoperative morbidity such as cardiac problems and thrombosis [80,81]. The most common late complications are shoulder disability, shoulder pain, reduced cervical mobility, and lymphoedema [82-85]. A more uncommon but severe late complication associated with neck dissection is carotid blow-out bleeding [86]. The rate of complications varies between studies, from 3% to over 50% [87]. These differences are most likely explained by patient selection, type of surgery performed and the skills of surgeons. It appears that many postoperative complications can be predicted by the preoperative status of the patient [88,89].

To reduce morbidity, neck dissection surgery should be as atraumatic and limited as possible without jeopardizing the aim of the surgery, which is to remove the tumour [90]. Also, pre-, peri-, and postoperative care must be optimal [79,84,91]. Patients with increased risk of morbidity, e.g. patients with malnutrion or tracheostomy, could easily be identified preoperatively and precautions taken [92].

In Paper III, morbidity after neck dissection has focused on the following parameters: cervical range of motion, lymphoedema, swallowing, mouth opening, and shoulder disability—which can all be regarded as late complications. None of these parameters appear to be related to reduced survival, but most of them are considered to be associated with reduced quality of life [93-97].

1.1.2.2 Complications induced by radiotherapy – oesophageal stricture

Photon beam irradiation induces a number of side effects such as mucositis, dermatitis, fibrosis, and xerostomia. There are different terms for these complications; they are often called “toxicity” but the term preferred by the National Cancer Institute is “adverse event”. Some are acute, such as mucositis and dermatitis, while others are late, such as fibrosis of soft tissues and oesophageal stricture. The adverse events are graded on different scales according to their severity [98]. However, there is no consensus as to the grade of toxicity that is often referred to as “acceptable toxicity”. Moreover, the level of the adverse event is also poorly reported in many trials [99].

It is not clear why patients react differently regarding the toxicity of radiotherapy. As shown by Taylor *et al*., fractioning and dose is a risk factor for adverse events with

hypopharyngeal and laryngeal tumours but not with oropharyngeal tumours. A general risk factor for adverse events seems to be the size, the T-stage, of the primary tumour [100]. At the cellular level, the acute mucosal reaction in the oral cavity is caused by radiation-induced mitosis of the basal cells in the mucosa. As the turnover of these cells is about two weeks, clinical signs of mucositis will develop after this time lag. However, there is also a more acute reaction in the mucosa—developing within minutes after radiotherapy—that is induced by reactive oxygen species, cytokines, and inflammatory mediators released by cells in the mucosa [101]. In the skin also, the basal cells are destroyed but development of dermatitis is a more long-lasting process due to the slower turnover of skin cells. Hair follicles have a faster turnover, which can explain the rapid loss of hair, something that can be temporary or chronic, starting soon after initiation of treatment. Cytotoxic drugs induce a toxicity to the oral mucosa which is similar to that of ionizing radiation, but this is named stomatitis instead of mucositis. One major clinical problem is that the combination of these two modalities can aggravate the acute mucosal reaction. The acute reaction in skin is characterised by vasodilation and increased vascular permeability. This may lead to reduced perfusion, with development of fibrosis of small vessels and deposits of foam cells and fibrin under the endothelium, similar to arteriosclerosis. The inflammatory state enhances fibroblast proliferation, giving rise to an increase in collagen production that causes fibrosis of the soft tissues and skin. In the salivary glands, there is also an inflammatory response to radiation—causing fibrosis mainly affecting the serous glands—while the mucous glands manage better, which is why the saliva is more viscous after radiotherapy. In bone, the osteocytes and osteoclasts can be damaged by radiation causing osteoradionecrosis, a less frequent but feared and painful complication [102].

Oesophageal pathology such as peptic oesophagitis and candidiasis is common in head and neck cancer patients [103]. The incidence of oesophageal stricture after radiotherapy is below 5% [104,105] whereas it is reported to be around 20% if radiotherapy is combined with chemotherapy [106-109]. Swallowing problems are very common in head and neck cancer patients [110], and can be caused by a number of radiation-induced adverse events such as xerostomia, more viscous mucous production, mucositis, oedema of soft tissues, and later on by fibrosis and rigidity in these soft tissues and loss of function in muscles that are part of the swallowing process [111].

There are several risk factors that are considered to cause oesophageal stricture in head and neck cancer patients after treatment. The aim of Paper II was to further investigate causes that lie behind this adverse event. One factor that has been suggested to be involved is placement of an enteral feeding tube during radiotherapy, either by percutaneous endoscopic gastrostomy (PEG) or with a nasogastric tube (NG-tube) [112,113]. Whether the stricture may be caused by this or whether enteral feeding only indicates patients at risk is not known [114]. It has been speculated that it is gastric reflux due to the gastric tubes that causes the stricture, but there is little evidence for this [115-118]. Other possible risk factors that have been reported earlier are hypopharyngeal primary tumour, female sex, and hyperfractioned radiotherapy [107]. Another risk factor discussed is a high dose of radiation delivered to the upper part of the oesophagus [119-121]. The cause of oesophageal stricture in head and neck cancer patients treated with radiotherapy is most likely multifactorial.

1.1.2.3 Functional impairments

Losses of function are typically late, chronic side effects that are very difficult to treat, and care is directed at alleviation. Xerostomia—dry mouth—is very common in head and neck cancer patients; the incidence rate is reported to be 60–90% [122], due to reduced saliva production after radiotherapy. Xerostomia in turn causes bad oral health, dental problems, changes in taste, speech problems, swallowing problems, and results in reduced quality of life [123-125]. Oral mucositis further enhances these problems; it develops in about 50% of patients [126]. These impairments lead to weight loss and a prolonged need for enteral feeding, they are costly, and they significantly reduce quality of life [127] and need to be studied further [94,128]. The functional impairments that were examined in Paper IV were related to problems affecting speech, swallowing, chewing, motility in the neck and shoulders, mouth opening, and how these problems affected weight loss, working ability, and quality of life.

1.1.3 Aspects of rehabilitation

Rehabilitation may be a feasible way to reduce and alleviate functional impairments in head and neck cancer patients, and requires a multi-professional approach [129]. Further studies on different rehabilitation programmes with evaluation of their outcome are much needed and sought after [130]. In the past, rehabilitation of patients with head and neck cancer has concentrated on a compensatory approach aimed at relieving already established functional losses. Many authors now advocate a preventive approach that is aimed at preventing these functional impairments from developing [131,132].

It is important to consider all aspects of rehabilitation. Hands-on rehabilitation of well-defined functional impairments using newly engineered techniques is obviously a very straightforward and appealing approach. It is, however, just as important to engage in supportive rehabilitation that facilitates the development of a patient's coping skills and confidence. This type of rehabilitation is important, for example, in handling facial disfiguration surgery but should be incorporated into all types of rehabilitation [133]. The reasoning behind this is that rehabilitation is part of our care of the survivors. With every success in improving survival comes a new challenge in the form of handling survivorship. Most institutions have elaborate guidelines concerning diagnosis and treatment of cancer patients, but guidelines for care of the survivors are often lacking. The guidelines on survivorship that actually exist are generally designed for the specialist sector and not for primary care [134]. Focusing on survivorship is at present mainly a question for developed countries, but hopefully survival rates will improve in the developing countries—which might make survivorship care one of the main global tasks in cancer care [135].

1.1.3.1 Rehabilitation of trismus

The rehabilitation for preventing reduced mouth opening mainly concentrates on programmes using different jaw-stretchers or mouth-opening exercises, but there have been few studies [136-139]. Furthermore, there has been no study comparing the different devices available—such as Therabite, the TMJ exerciser [140], and the Acute Medic jaw trainer and stretcher. The latter was used in the study presented in Paper IV. Regarding the actual treatment of trismus, there are different surgical approaches [141,142].

1.1.3.2 Rehabilitation of swallowing

The process of swallowing is complex, and considering the trauma to the upper aerodigestive tract during treatment of head and neck cancer, disturbance of this process is understandable. Once in the oral cavity, food is moved onto the teeth by the tongue, which also brings the food together after the crushing by the teeth; this forms a bolus that can be swallowed. The food is then pushed backward into the pharynx and then the airway has to be sheltered, as well as the entrance to the rhinopharynx. The bolus of food is then pressed down into the oesophagus by the pharyngeal muscles and the base of the tongue at the same time as the upper oesophageal sphincter relaxes. Dysphagia in patients with head and neck cancer is associated with aspiration—with an increased risk of pneumonia [143,144] and a reduced quality of life [145].

The main reasons for swallowing problems in head and neck cancer patients after radiotherapy are thought to be reduced tongue strength, reduced laryngeal elevation, reduced tongue base retraction during swallowing, and fibrosis of the muscles involved in swallowing [130,131]. Thus, most rehabilitation programmes concentrate on maintaining tongue strength, tongue mobility, and the mobility of the larynx [132]. In the rehabilitation programme presented in Paper IV, the exercises consisted of tongue mobility and stretching and the Mendelson´s manoeuvre (holding the larynx in its most supine position during swallowing, for 2–3 seconds during each swallow).

1.1.3.3 Rehabilitation of speech

As the voice is produced at the level of the vocal cords and then transformed into speech by articulators, such as the tongue and soft palate, these are differently affected by head and neck cancer disease and treatment. Obviously the voice is severely reduced by a laryngectomy or radiotherapy to the larynx, while speech can be more affected by treatment and disease in the oral cavity. Many studies on voice and speech have not been conclusive and have lacked the proper instruments for evaluation [146]. Most of these studies have focused on maintaining the voice in laryngectomy patients [147-149]. For this reason, a specific rehabilitation programme for head and neck cancer patients other than larynx patients is difficult to construct. In Paper IV, the exercises for swallowing were also thought to affect speech.

1.1.3.4 Rehabilitation of cervical range of movement

Figure 3. Measurement of cervical range of movement with a Myrin device.

Neck and shoulder stiffness in head and neck cancer patients is probably due to both EBRT and surgery, in particular neck dissection. The rationale for rehabilitation of these patients with stretching exercises, as in Paper IV, is the same as for neck and shoulder stiffness for other reasons [150] and there have been studies indicating an effect of these types of exercises [95].

1.1.3.5 Rehabilitation of lymphoedema

Oedema in the head and neck region causes a dull pain and facial disfigurement, and in extreme cases lips and eyelids can be so swollen that vision and eating is impaired [151]. Lymphoedema therapy consists of sequential manual lymphatic drainage of the oedematous region according to Vodder's technique [152,153]. This can be combined with compression garments [154]. The effect of manual therapy for lymphoedema is poorly evaluated in head and neck cancer patients and there is a need for prospective studies and clear definitions of different levels of oedema [155]. In Paper III, lymphoedema was evaluated as a dichotomous variable, without grading, by one physiotherapist who is an experienced lymphotherapist.

1.1.3.6 Rehabilitation of shoulder disability

Shoulder disability refers both to impaired mobility in the shoulder joint and to pain in the shoulder region after neck dissection. This is a well-known and common morbidity that is induced by injury to the accessory nerve, leading to denervation of the trapezius muscle and neuropathic pain with secondary effects in the shoulder such as adhesive capsulatis and myofascial pain in muscles around the shoulder [85]. This leads to problems in daily activities and a reduced quality of life [96]. There are different rehabilitation approaches to relieve shoulder disability, but there have been few prospective randomised studies on these different techniques. The techniques that are used are, for example, progressive resistance exercise training [156] and preventive exercises to maintain shoulder mobility and strength [157]. In this thesis, the impact of rehabilitation on shoulder disability was not assessed but such exercises are part of the regular physiotherapy at our institution.

2 AIMS

The aim of the work described in this thesis was to investigate the outcome of treatment for cervical metastasis, to study some severe complications after treatment, and to investigate rehabilitation based on self-care for head and neck cancer patients. It was my intention throughout the thesis work to perform clinical trials and cohort studies to enable direct clinical implementation of the results.

The specific aims of the four papers were:

I. To investigate whether there is a need for a planned neck dissection in the N+ patient after full-dose radiotherapy, regardless of the clinical response in the neck.

II. To identify and evaluate the risk factors for developing an oesophageal stricture after radiotherapy for head and neck cancer.

III. To determine what possible morbidities two different neck dissection procedures might add to those induced by radiotherapy for head and neck cancer patients.

IV. To implement an early rehabilitation programme and to determine whether it could reduce functional impairments and improve quality of life in head and neck cancer patients.

3 MATERIAL AND METHODS

3.1 PAPER I – PLANNED NECK DISSECTION

Study design: a cross-sectional observational study

3.1.1 Patient material

Five hundred and fifteen consecutive patients treated between 1998 and 2002 in the well-defined county of Stockholm, Sweden, with squamous cell carcinoma of the head and neck and neck metastasis could be identified. Those who had received EBRT of > 60 Gy with a complete response at the primary site followed by a planned ND were included in the study. The patients' medical records were reviewed. Patients treated with chemotherapy (induction and/or concomitant) were excluded, as were patients whose medical record was incomplete regarding information about the clinical outcome after EBRT or if the pathology report was missing or incomplete.

3.1.2 Treatment

Radiotherapy was given either at Karolinska Hospital, Södersjukhuset or Karolinska Hospital, Radiumhemmet. The doses were planned according to the local guidelines in Stockholm.

ND was performed according to the local guidelines in Stockholm, at a single institution (the ENT clinic at Karolinska University Hospital in Solna). Patients were operated four to six weeks after termination of EBRT if there was a complete response at the primary tumour site according to an endoscopic examination with the possibility of taking biopsies. A planned ND was carried out in all patients who had metastasis in the neck at the time of diagnosis, irrespective of the clinical response to EBRT. The regions included in the ND normally depended on the site of the primary tumour and the extent of disease in the neck before EBRT, and were not dependent on the clinical response.

3.1.3 Clinical outcome

Palpatory findings in the neck 4–6 weeks after radiotherapy were used as a parameter for evaluation of the clinical response to EBRT. Patients were categorised either as having no response/partial response (NR/PR) or a complete response (CR) depending on whether a palpatory mass was found or not found in the neck. During the period 1998–2002, no regular radiology examinations after EBRT were included in the follow-up protocol. If the pathology report stated that there were viable malignant cells in the neck specimen, the patient was recorded as being histopathologically positive (PAD+); if not, the patient was histopathologically negative (PAD-). Data concerning recurrence, site of recurrence, death, and cause of death were correlated to the clinical response and histopathology report.

Patients with primary tumour in the tonsillar fossa or the base of the tongue were analysed separately because of earlier studies showing that tumours arising from

Waldeyer´s ring might be more readily controlled by radiotherapy than those originating from other sites in the head and neck region.

Follow-up time in this material was between two and seven years with a median follow-up time of 4.4 years.

3.1.4 Statistical methods

The comparisons of differences in proportions were made using the chi-square test for independence, and with Fisher's exact test when necessary.

Survival time was calculated from the date of diagnosis to the date of death, or if the patient was still alive, to 31 December 2004. Survival curves were estimated using the Kaplan-Meier method.

In the analysis of cause-specific survival, deaths due to causes other than head and neck cancer were treated as censored observations at the time of death. Tests for differences in survival times were performed using the log-rank test.

3.2 PAPER II – OESOPHAGEAL STRICTURE

Study design: a nested retrospective case-control study

3.2.1 Patient material

We continuously identified and registered all patients with upper oesophageal stricture after external beam radiotherapy (EBRT) at our department during the years 1992 to 2005. All the patients included were initially diagnosed as having head and neck cancer at the Department of Otolaryngology and Head and Neck Surgery, Karolinska University Hospital, Solna, Sweden, between 1987 and 2005. The study sample was divided into two time periods based on the year of the EBRT, 1987–1999 and 2000–2005, as there was a change in EBRT treatment between 1999 and 2000. Calculation of incidence was based on the time period 1992–2005 due to lack of earlier data. The population base during this time period consisted of 1,805 patients.

Patients with swallowing difficulties and clinical signs of an oesophageal obstruction were examined with conventional swallow X-ray using barium contrast and endoscopy. Diagnosis of stricture of the upper oesophagus was made by an endoscopic procedure under general anaesthesia, except in one case in whom only an X-ray examination with swallowing of barium contrast was performed. A control group of patients without any reported swallowing problems was constructed. This was done by sending a short questionnaire to all the patients without documented stricture or dysphagia in the medical files from three different time periods, spread out over the same time period as that of the inclusion period of patients with stricture.

In order to make a general description of the strictures of the upper oesophagus, these were classified into three subgroups according to the findings at endoscopy for diagnosis of dysphagia or treatment of stricture. When more than one endoscopy was performed, the patient was classified according to the highest grade of stricture found. In grade I, the stricture could be passed with a rigid oesophagoscope 7 × 10 mm wide and the stricture could be dilated. In grade II, the stricture could not be passed by the 7 × 10 mm scope but could be dilated, and after dilatation the oesphagoscope could pass the stricture. In grade III, there was total obliteration of the oesophagus.

The medical records of all patients were collected and analysed according to a data matrix including the following parameters: EBRT dose (the given dose), survival, tumour localization and stage, use of NG tube and PEG, weight changes during EBRT, oral mucositis, and treatment of the stricture. In order to make a general description of the strictures of the upper oesophagus, these were classified into three subgroups, grades I–III, according to the findings at endoscopy for diagnosis of swallowing disorder or treatment of stricture.

3.2.2 Exclusion criteria

Patients treated with chemotherapy were excluded, as were patients with incomplete medical records. Patients who had had swallowing disorder(s) before diagnosis of the present tumour disease were also excluded. Fourteen patients were excluded as a result of these criteria.

3.2.3 Radiotherapy

EBRT was given at two different treatment centres in Stockholm, Södersjukhuset and Radiumhemmet (parts of Karolinska University Hospital) and dose plans were constructed according to local guidelines. After 1998, the target delineation was changed according to new guidelines from the Swedish ARTSCAN study group. These guidelines were then gradually implemented for all head and neck cancer patients. It was decided that the irradiation volumes and the total dose given to unaffected tissue, e.g. the contralateral neck, should be 46 Gy. Earlier, the dose given to elective nodes was the same as given to macroscopic tumour. As a result of this change, smaller volumes were treated with high doses and a larger proportion of normal tissue could be spared. In addition, the larynx was blocked from the anterior-posterior fields if it was not included in the planning target volume.

Patients had a CT scan done in supine position at 10- or 5-mm intervals covering an area from the base of the skull down to the chest. The CT scans were transferred to the treatment-planning system (TMS; Nucleotron, Veenendaal, the Netherlands) in which the target and critical structure volumes were delineated. Dose-planning treatment data were stored for all patients.

Data for a subgroup of patients with stricture and for the control group treated at Radiumhemmet were retrieved from the archive in the TMS system. The oesophagus was delineated on each CT image for each patient. The differential and cumulative dose volume histograms (DVHs) of the upper 5 cm of the oesophagus were assessed for each patient. From the cumulative DVHs, it was possible to calculate the mean dose delivered to the upper 5 cm of the oesophagus for this subgroup of patients.

3.2.4 Statistical methods

Test of equality of distribution was done with the chi-square test, or Fishers's exact test when appropriate. Difference of means was tested with Student's t-test after assessing the normality assumption. Odds ratios (ORs) for potential risk factors in developing a stricture were estimated using logistic regression. In the logistic regression analysis, the categories of stage and site were analysed as separate indicator variables. A multivariate analysis was done with the most interesting and important factors from the univariate analysis. All analyses were done using SPSS for Windows version 17.0.1 (SPSS Inc., Chicago, IL).

3.3 PAPER III - MORBIDITY OF NECK DISSECTION

Study design: a prospective cohort study

3.3.1 Patient material

Patients included in the early-rehabilitation study described in Paper IV served as the population base for this study. From this cohort, patients who had met with the physiotherapist (PT) were retrieved; most of these patients had also met with the speech-language pathologist (SLP). These patients were then divided into three groups according to the treatment given:

- external beam radiotherapy (EBRT) + supraomohyoidal neck dissection (SOND)
- EBRT + modified radical neck dissection (MRND)
- EBRT only

These groups were then compared concerning cervical range of motion (CROM), mouth opening, lymphoedema, shoulder disability, and swallowing.

The head and neck range of movement and mouth opening (interincisial distance between upper and lower left front teeth) were measured before the start of treatment and at all follow-ups. The CROM (flexion-extension, rotation, and lateral flexion) was measured with a Myrin device (an inclinometer) [158] that measured grades of movement, which is a well-established method [159]. Range of motion was measured in full range, i.e. rotation all the way from left to right, from full extension to full flexion, and from lateral flexion to the left to lateral flexion to the right.

Lymphoedema was evaluated clinically as a dichotomous variable (yes/no) by the PT who is an experienced lymph therapist.

Shoulder disability was also evaluated clinically by the PT within 2 months after the ND, and was considered established in cases of obvious weakness when the patient was asked to lift his/her shoulder to the ear and abduct and flex his/her extended arm, or in the case of an obvious shoulder droop.

The following swallowing parameters were clinically evaluated: oral manipulation and transport of bolus, presence of aspiration, laryngeal elevation, need for several swallows, delayed initiation of swallowing, and nasal regurgitation. Aspirations were noted as cough, need to clear the throat, wet voice, or sudden breathing difficulties.

3.3.2 Surgery

Surgery was done according to local guidelines at the Department of Otolaryngology and Head and Neck Surgery at Karolinska University Hospital where all surgical procedures were performed.

Neck dissection was done either as MRND or SOND. In MRND as classified in the present study, the accessory nerve is mostly spared but the sternocleidomastoid muscle

is sacrificed and nodal levels I–V are removed. In SOND as classified in the present study, both the accessory nerve and the sternocleidomastoid muscle are spared, with removal of nodal levels I–III and in this study level IV also in some cases, which is referred to as extended SOND [41]. The extended SOND patients were analysed together with the SOND patients.

Patients underwent EBRT before or after neck dissection, i.e. preoperatively or postoperatively. Patients with the primary tumour in the oral cavity or salivary glands were mainly treated with ND before EBRT. They were therefore evaluated by the PT or SLP for the first time 4–6 weeks after surgery in connection with the start of EBRT. In patients who underwent EBRT before surgery, ND was performed in cases of suspected or manifest residual tumour in the neck. These patients were evaluated for the first time by the PT and SLP before the start of any treatment.

3.3.3 Statistical methods

Differences in distribution between the three treatment groups and nominal variables were compared using the chi-square test for independence or, when appropriate, Fisher's exact test. Continuous variables were modelled using linear regression. In these models, the treatment effect was estimated using two dummy variables. When baseline values were available, these were included in the regression models to control for potential initial imbalances. Results from these models are presented as mean differences together with 95% confidence intervals. P-values from the models refer to F-tests.

3.4 PAPER IV - EARLY REHABILITATION

Study design: a prospective cohort study

3.4.1 Patient material

This study was based on a clinical development programme financed by the Swedish Cancer Society and structured as a prospective non-randomised study comparing two parallel groups, one group undergoing experimental early preventive rehabilitation and the other group not being offered a systematic rehabilitation programme. Patients were included consecutively into both groups over 3.5 years and the first year of inclusion, 2004, functioned as a pilot study. Thus, no selection of patients was done.

Patients diagnosed with head and neck cancer in Stockholm from 1 January 2004 to 31 July 2007 who were to receive EBRT with curative intent were included in the study. The patients receiving EBRT at the southern unit (Södersjukhuset) were included into the rehabilitatiton programme and those treated at the northern unit (Radiumhemmet) served as a control group.

Patients included in the study group met before the start of treatment with an SLP and a PT who were also part of the research team. Patients included were sent a letter about the study directly after diagnosis, to make sure they received information about the study before the start of treatment.

3.4.2 Speech-language pathologist intervention and evaluation

All the patients in the study group were examined by the SLP before EBRT and 3 months after completion of therapy. The patients were instructed, both verbally and with written information, on how to perform mobility exercises for the tongue and larynx (Mendelson's manoeuvre) at least once and preferably twice a day at home during the course of EBRT, and for 3 months after termination of treatment. At the clinical screening of swallowing, the patient was asked to complete one swallow of two bolus sizes (5 ml and 15 ml) of four consistencies: thin liquid, thick liquid, paste, and cookie. Movement of the floor of the mouth, and hyoid and thyroid cartilage was evaluated by manual palpation during the act of swallowing. Voice and articulation were perceptually assessed by the SLP and the motility of the tongue was assessed with tongue exercises.

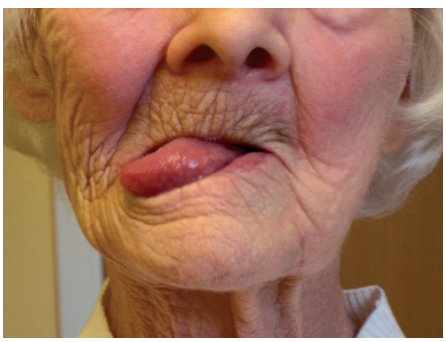


Figure 4. Tongue exercises

3.4.3 Physiotherapy intervention and evaluation

The patients had an appointment with the PT before the start of EBRT and follow-ups were performed at 2, 6, and 12 months after termination of treatment. The patients received written and verbal instructions about exercises and stretching of muscles of the head and neck in order to maintain mobility in the EBRT-exposed areas. The

prevention of trismus consisted of exercises with the "Acute Medic jaw trainer and stretcher" (www.acutemedic.com, Sweden).

3.4.4 Effect of treatment and rehabilitation

Since patients in the control group did not meet the SLP or PT for evaluation of functional loss, all patients in both cohorts who were planned for curative EBRT at the weekly multiprofessional treatment meeting were sent a set of questionnaires before the start of treatment and 6 months after termination of treatment, i.e. last surgery or last day of EBRT or brachytherapy. The questionnaires used were EORTC-QLQ-C30, EORTC-H&N35 (the European Organisation for Research and Treatment of Cancer), HADS (Hospital Anxiety and Depression Scale), and a project-specific questionnaire.

3.4.4.1 Key measure for integration of the programme

The key measure used to evaluate the integration of the intervention was the length of time between the date of diagnosis and the start of EBRT.

3.4.4.2 Key measures for improvement and study endpoints

Weight loss and 2-year survival were chosen as the principal measures of effect. Secondary outcome measures were sick leave, self-reported loss of function, HRQOL, and anxiety/depression.

3.4.4.3 Treatment

EBRT was given at two different radiotherapy centres in Stockholm and dose plans were constructed according to local guidelines. Chemotherapy was given either as induction treatment or as concomitant treatment. Brachytherapy was mainly used for patients with tumours at the base of the tongue and for some cases with tumour in the mobile part of the tongue or the floor of the mouth.

Surgery was performed according to local guidelines at the Department of Otolaryngology and Head and Neck Surgery at Karolinska University Hospital following the same guidelines for both groups.

3.4.4.4 Follow-up

All patients were followed up for at least two years according to set guidelines, with visits every third month for the first 2 years and every six months thereafter.

3.4.5 Statistical methods

Survival time was calculated from the date of the multi-professional treatment meeting to the date of death, or until the common date for the end of survival follow-up, 1 August 2009. Survival was estimated according to the Kaplan-Meier technique and differences in survival times were tested using log-rank test. Confidence interval for the reported survival differences refers to the fixed 2-year time point.

Continuous variables were analysed using linear regression models. In these models, intervention was included in the model as a categorical variable taking the value of 0

for the control group and 1 for the study group. For some continuous outcome variables, baseline values were available. In these cases, models were estimated including the baseline values as well as the intervention variable. Differences in categorical variables were tested using Fisher's exact test. Binary outcomes were modelled using ordinary logistic regression models. For ordinal variables, distributional comparisons were performed using the Mann-Whitney U-test and the ordinal outcomes were modelled using the proportional odds model. The exponentiated intervention coefficient in these models can be interpreted as the ratio (between the study group and control group) of the odds of being in a higher (worse) rather than lower (better) category. All effects from the regression models are presented together with 95% confidence intervals.

3.5 ETHICS

All studies included in this thesis were conducted according to the declaration of Helsinki. The study in Paper II on oesophageal stricture was approved by the the Research Ethics Board of Stockholm. Concerning the studies in Paper I on planned neck dissection and in Papers III and IV on morbidity of neck dissection and rehabilitation, the Research Ethics Board of Stockholm judged that no ethical approval was required as they were regarded as clinical development programmes. Such assessments by ethical boards can be troublesome when papers are submitted to peer-review journals, as these often demand approval by an ethical board.

4 RESULTS

4.1 PAPER I – PLANNED NECK DISSECTION

A total of 156 patients were included in the study.

4.1.1 Histopathological outcome

One third of the patients (52/156) had viable tumour cells in the neck specimen after EBRT. There was a CR in 40% (63/156) of the patients, and among these 24% (15/63) had viable tumour cells in the neck. In patients with palpable mass in the neck, 40% (37/93) were found to have viable tumour cells. There was no significant difference in incidence of viable tumour cells between the N1 group with CR (10%, 5/51) and the N2–3 group with CR (10%, 10/105). In N1 patients with viable tumour cells in the neck, there was no significant difference between those with a CR (5/51) and those with residual disease (5/51). However, the incidence of viable tumour cells was significantly lower ($p = 0.012$) in N1 patients (20%, 10/51) than in the N2–3 group (40%, 42/105).

Among patients with the primary tumour in the tonsil or base of tongue 26% (22/85) had viable tumour cells, 16% (5/31) of those with CR had viable cells. This is significantly lower when compared to all other sites (30/71, 42% and 23/71, 32%, respectively). (These figures differs from line 2, table VII in Paper I where there is an error.)

4.1.2 Clinical outcome

The incidence of ipsilateral recurrences with or without another recurrence site in patients with viable tumour cells in the neck specimen was 15% (8/52), and it was 2% (2/104) in patients without viable tumour cells in the neck specimen. The risk of an ipsilateral recurrence was almost the same in patients with a CR (6%, 4/63) as in those with PR/NR (6%, 6/93).

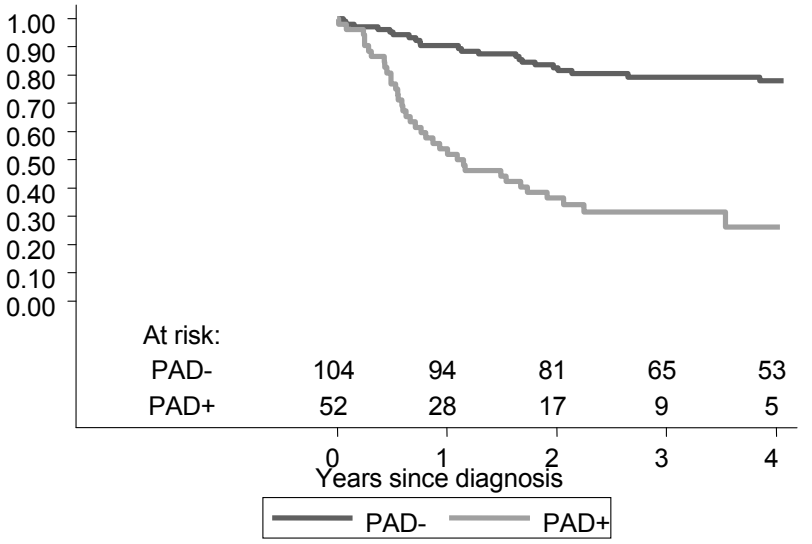
The incidence of ipsilateral and overall recurrences in patients with viable tumour cells in the neck specimen was more than doubled in patients with a CR after EBRT (80%, 12/15) compared to those who still had a palpatory mass in the neck (41%, 15/37). There was a significant difference when these two groups were compared regarding cause-specific deaths ($p = 0.014$). The incidence of cause-specific deaths was 73% (11/15) in patients with a CR and viable tumour cells as compared to 43% (16/37) when there was a PR/NR and viable tumour cells.

Overall survival was 62% and disease-specific survival was 76% in this material. There was no significant difference in disease-specific survival between N1 patients (25%, 13/51) and patients with N2–3 (24%, 25/105) ($p = 0.91$). There was also no difference between the groups when comparing only those with a CR (N1: 27%, 7/26; and N2–3: 24%, 9/37) ($p = 0.95$).

Patients with tumours arising from the tonsils or base of the tongue had a significantly better outcome with a disease specific survival of 88% (70/85) compared to 68% (48/71) for patients with tumours at all other sites.

Viable tumour cells in the neck specimen following EBRT indicated a poor prognosis with a disease-specific death rate of 52% as compared to 10% in patients with no viable tumour cells in the neck (Figure 5).

Figure 5. Deaths according to histopathological findings in neck specimens.



4.2 PAPER II – OESOPHAGEAL STRICTURE

Seventy patients with irradiation-induced stricture of the upper oesophagus were identified and evaluated between 1992 and 2005. All patients had undergone EBRT for head and neck cancer between 1987 and 2005. Sixty-six patients were included in the control group. Cases and controls were well-matched for age and gender, but not for year of diagnosis.

The total number of patients irradiated with curative intent for head and neck cancer during the two periods was calculated. Based on this calculation, the total incidence of irradiation-induced oesophageal stricture in patients treated with radiotherapy for head and neck cancer during 1992–2005 was 3.3% (59/1,805). A subgroup analysis of patients treated between 1992 and 1999, and between 2000 and 2005, showed an incidence of irradiation-induced oesophageal stricture of 3.8% (28/740) and 2.9% (31/1065), respectively. Thus, the difference in incidence was not statistically significant ($p = 0.316$).

4.2.1 Stage and site as risk factors

Tumour stage and primary site of the tumour are presented in Table 1. The stricture group and reference group were similar with regard to stage. There was no significant difference in median survival time between cases (9.2 years, 95% CI: 6.7–11.7) and controls (12.3 years, 95% CI: 8.7–160). Univariate analysis of risk parameters for developing a stricture showed a numerical but non-significant increase in odds ratio for patients with oral tumours and oropharyngeal tumours. The risk of developing a stricture was not related to having a primary tumour in the hypopharynx or epipharynx. There was a significant reduction in odds ratio for patients with primary tumour in the larynx.

Patients with primary tumour in “other sites” (involving a number of different sites) appeared to have a lower risk of developing a stricture. We repeated all calculations with such patients excluded from both the controls and cases, to make sure that this group did not confound the outcome. There was no significant difference in the results, however, except for wider confidence intervals.

4.2.2 NG tube and PEG as risk factors

There was a high incidence of patients receiving tube feeding among the stricture patients. In patients using enteral nutrition in the stricture group, 67% (31/46) used only an NG tube and 33% (15/46) used the combination of an NG tube followed later by a PEG; two of these patients received PEG before the start of EBRT.

There was higher loss of weight in the stricture group than in the reference group during EBRT, even though most patients in the stricture group had an NG tube and PEG. In the stricture group, only 4.9% (2/41) gained weight during EBRT as compared to 26% (9/34) in the reference group.

4.2.3 Surgery as a risk factor

In the stricture group, 44 patients (63%) underwent a surgical procedure, as compared to 37 patients (56%) in the reference group. There was an increased odds ratio for development of stricture in patients who received preoperative EBRT compared to patients who received postoperative EBRT. There was a significantly higher incidence of tongue and/or base-of-tongue resections in the stricture group than in the reference group.

4.2.4 Radiotherapy as a risk factor

It was possible to retrieve the complete dose plans and EBRT records for 26 patients in the stricture group and for 37 patients in the reference group. Dose-volume histograms for the upper 5 cm of the oesophagus are presented in Figure 6. Patients receiving a mean dose of over 45 Gy to the superior 5 cm of the oesophagus had a significantly higher risk of stricture.

With stratification of the patients according to the two treatment periods, 1987–1999 and 2000–2005, as shown in Figure 6, the differences in average mean dose and the mean percentage DVHs were statistically significant between the cases and the controls for 2000–2005 but the differences were not significant for the period 1987–1999.

4.2.5 Multivariate regression analysis of risk factors

A multivariate logistic regression analysis was conducted for the following parameters: mean dose to the oesophagus, NG tube and/or PEG, surgery or no surgery, and primary site. This analysis showed that there was a significantly increased risk of stricture in patients with NG tube and/or PEG and for patients who received a mean dose of > 45 Gy to the upper part of the oesophagus. For all other parameters, odds ratios were not significant when adjusted for in the multivariate analysis.

4.2.6 Treatment of oesophageal stricture

The duration between termination of EBRT and diagnosis of stricture ranged from one to 132 months, with a mean time of 22 months and a median time of 8 months. Oesophagoscopy under general anaesthesia showed grade-II stricture in 41 patients (59%). Grade I stricture was found in 19 patients (27%), and grade III stricture in 10 patients (14%). There was no significant association between the grade of stricture and the primary site or tumour stage.

Treatment of the stricture of the upper oesophagus was generally performed by endoscopic dilatation under general anaesthesia. In 63 patients, dilatation was performed using Savary wire-guided bougies; 53 (84%) could swallow after dilatation but in 45 of these patients dilatation had to be repeated. The average number of dilatation procedures per patient (according to grade of stricture) was 3.3 for grade I, 3.0 for grade II, and 4.5 for grade III. Endoscopic dilatation using Savary wire-guided dilatations failed to offer any improvement of the swallowing function in 10 patients (16%). One patient with grade-II stricture developed a perforation after dilatation with Savary-guided bougies.

Five patients underwent dilatation using the through-the-scope balloon dilators; two of these patients were also dilated with Savary bougies. Four of them could swallow after the procedure, but three had to undergo dilatation more than once.

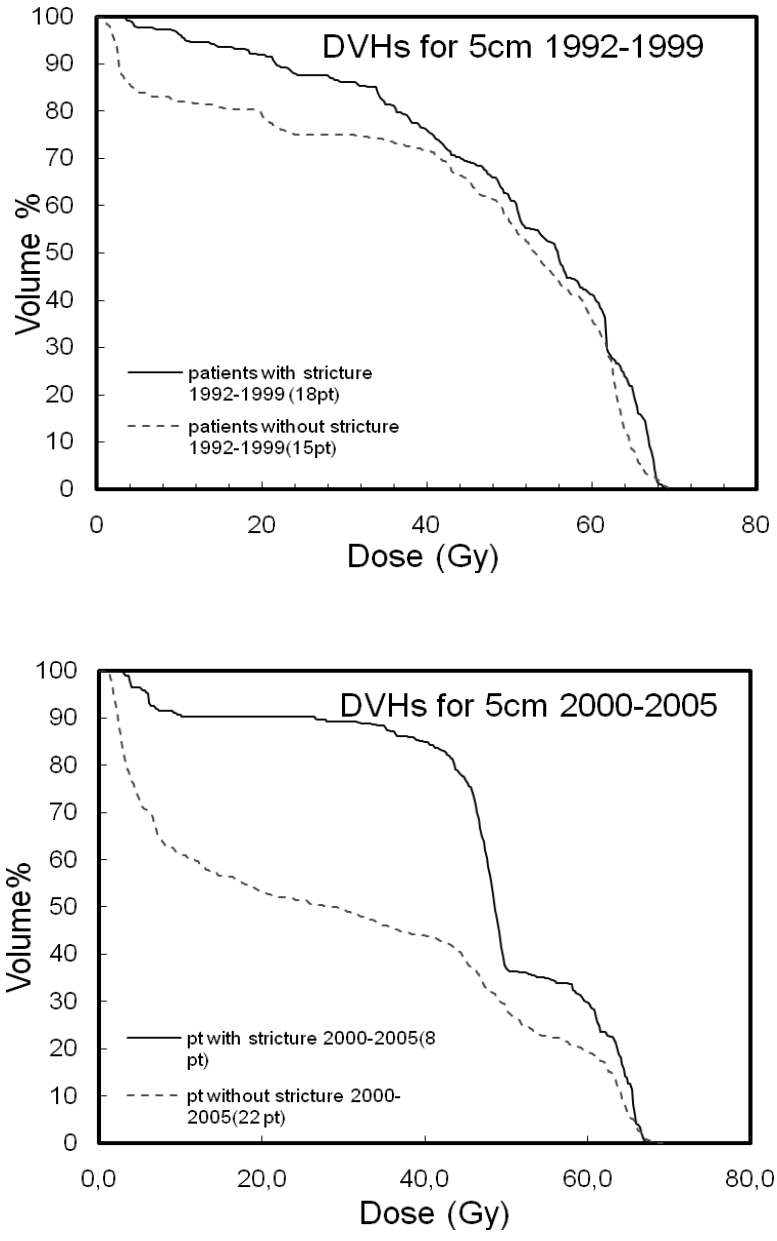
Two patients (grade III) were operated with a resection of the stricture and reconstruction with a free vascular flap. One of these patients could swallow after the surgical procedure while the other had a postoperative infection and was unable to swallow.

Table 1. Analysis of risk parameters

	With stricture (n=70)	No stricture (n=66)	OR (univariate)	OR (multivariate)
Stage:				
Stage I	9 (13%)	17 (26%)	0.43 (0.17–1.04)	
Stage II	19 (27%)	10 (15%)	2.09 (0.89–4.90)	
Stage III	20 (29%)	10 (15%)	2.24 (0.96–5.24)	
Stage IV	22 (31%)	22 (33%)	0.92 (0.45–1.88)	
No stage	0 (0%)	7 (11%)	.	
Primary site of tumour:				
Oral	21 (30%)	11 (17%)	2.14 (0.94–4.89)	1.36 (0.33–5.67)
Oropharyngeal	22 (31%)	13 (20%)	1.87 (0.85–4.11)	1.76 (0.43–7.19)
Epipharyngeal	5 (7%)	6 (9%)	0.77 (0.22–2.65)	
Hypopharyngeal	5 (7%)	2 (3%)	2.46 (0.46–13.15)	
Laryngeal	14 (20%)	24 (36%)	0.44 (0.20–0.95)	0.58 (0.13–2.54)
Other sites	3 (4%)	10 (15%)	0.25 (0.07–0.96)	0.22 (0.03–1.49)
Mucositis:				
Mucositis during EBRT[1]	49 (70%)	31 (47%)	2.63 (1.30–5.32)	
Enteral feeding:				
Only NG[4] tube	31	6		
PEG[5] and/or NG[4] tube	15	3		
Total incidence of NG[4] tube and/or PEG[5]	46 (66%)	9 (14%)	12.14 (5.14–28.66)	11.93 (4.56–31.21)
Weight:				
Mean weight loss during EBRT[1]	5.8% (n =41)	3.5% (n =34)		
< 5 % (ref)	16 (23%)	20 (30%)		
> 5 %	25 (36%)	14 (21%)	2.23 (0.88–5.64)	
Missing	29 (41%)	32 (49%)	1.13 (0.50–2.59)	
Surgery:				
No surgery (ref)	26 (37%)	29 (44%)		
Surgery	44 (63%)	37 (56%)	1.33 (0.67–2.63)	1.78 (0.57–5.55)
Postoperative EBRT [1] (ref)	13 (19%)	19 (29%)		
Preoperative EBRT[1]	31 (44%)	18 (27%)	2.52 (1.01–6.28)	
Hemigloss-tongue[2]	16 (23%)	3 (5%)	6.22 (1.72–22.50)	
Radiotherapy:				
Mean dose to upper oesophagus				
< 45 Gy[3] (ref)	7 (10%)	25 (38%)		
> 45 Gy[3]	19 (27%)	12 (18%)	5.65 (1.87–17.10)	7.01 (1.63–30.27)
Missing	44 (63%)	29 (44%)	5.42 (2.07–14.16)	5.49 (1.60–18.88)

Abbreviations: [1]external beam radiation therapy. [2]Hemiglossectomy, tongue resection, base-of-tongue resection. [3]Gray. [4]Nasogastric tube. [5]Percutanous endoscopic gastrostomy.

Figure 6. DVH for patients with and without stricture, stratified according to year of treatment. All patients in the first time period were treated during 1992–1999.



4.3 PAPER III – MORBIDITY OF NECK DISSECTION

A total of 234 patients were included in this study. Patients with major surgery to the primary tumor—i.e. laryngectomy or resection followed by reconstruction with a vascularised free flap—were excluded (n = 13), as were patients with missing baseline data (n = 15). Of the 206 patients remaining, 98 were treated with EBRT as single-modality treatment, 25 were operated with SOND in combination with EBRT, and 83 were operated with MRND in combination with EBRT. As expected, the groups differed concerning stage and primary site since these parameters are decisive in the indication for neck dissection and for the type of neck dissection. The groups also differed with regard to gender, with a higher proportion of females treated with SOND. Concerning the other clinical parameters collected, the groups were well-matched.

4.3.1 Acute morbidity of ND as single-modality treatment

To investigate the acute morbidity of neck dissection alone, the neck-dissected patients were analysed according to whether they had undergone EBRT preoperatively or postoperatively. Of the 108 patients in the neck dissection group, 33 were neck-dissected before EBRT (postoperative EBRT) and 75 patients were neck-dissected after EBRT (preoperative EBRT). No significant differences between the postoperative EBRT group and the preoperative EBRT group were found concerning age, gender, site, stage, radiotherapy treatment, or chemotherapy treatment. When comparing the baseline data for CROM, trismus, and lymphoedema for the postoperative EBRT group after surgery to those of the preoperative EBRT group before any treatment was given, no significant differences between the two groups were found and due to this finding the groups were amalgamated in the ensuing analysis comparing ND patients treated with EBRT to patients treated only with EBRT as single-modality treatment. Significantly more patients in the postoperative EBRT group (15/33) suffered from swallowing disorders than in the preoperative EBRT group (15/75) ($p = 0.032$).

4.3.2 Morbidity outcomes

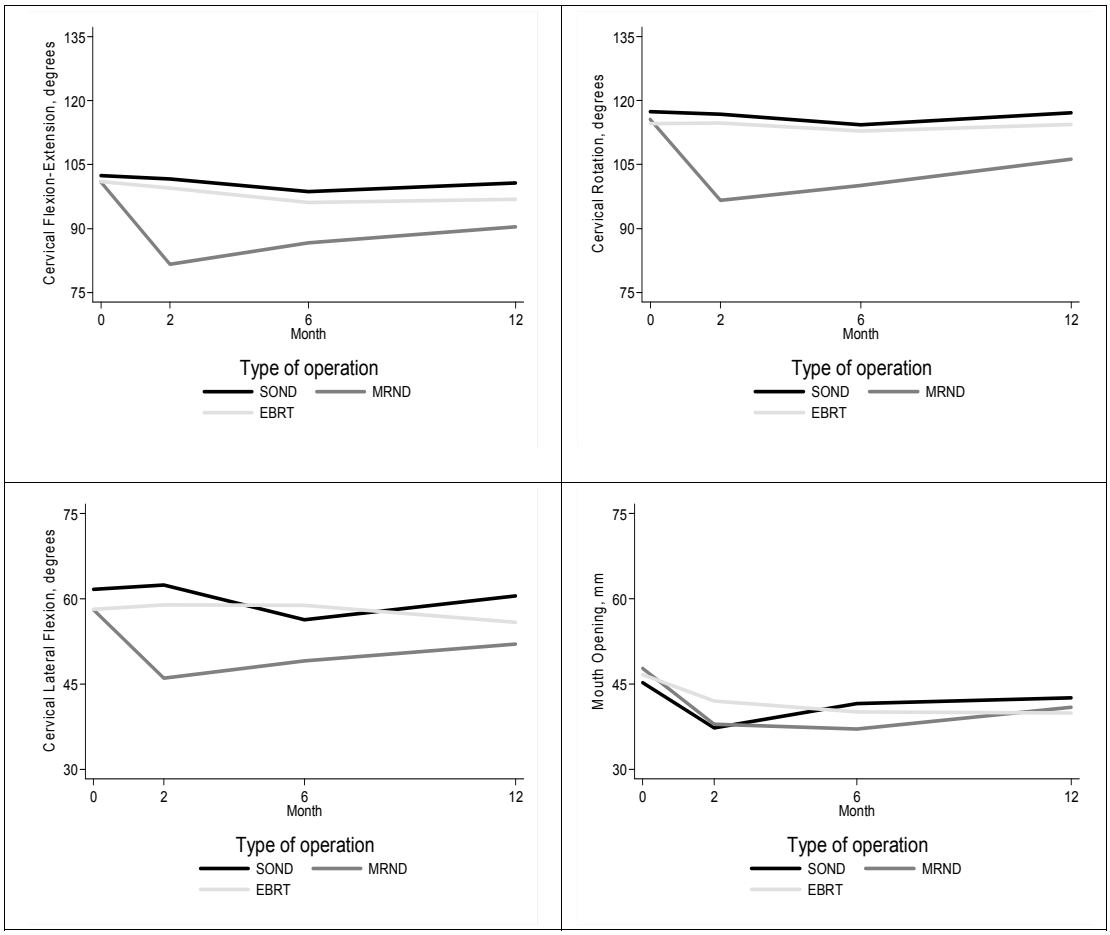
In Figure 7, the difference in CROM and mouth opening between the SOND and MRND patients and the patients who were not neck-dissected is shown over time: from baseline prior to EBRT to 12 months after treatment. There was a significant reduction in all three parameters of CROM and in mouth opening in patients who were operated with an MRND two months after treatment ($p < 0.001$). At 12 months after treatment, there was still a significant reduction in cervical rotation but the effect on the other parameters had declined to a non-significant level. There was no effect of the SOND on the evaluated parameters at any time point during the first year. Furthermore, no significant difference in lymphoedema was found between the three groups at 12 months.

The patient groups compared at 12 months were smaller than at baseline, due to loss of patients from recurrences or deaths (n = 53) and for unknown reasons (n = 44).

The total incidence of shoulder disability in neck-dissected patients was 18% (18/102; altogether, 6 patients were missing for unknown reasons). Even though a large numerical difference, there was no significant difference between patients who were

operated with MRND (16/78, 20%) and those who were operated with SOND (2/24, 8%) (p = 0.23). There was no significant difference in the incidence of swallowing disorders between the patients who were not neck-dissected (47/67, 70%), the SOND patients (14/20, 70%), and the MRND patients (53/68, 78%) (p = 0.53).

Figure 7. Comparison of CROM and mouth opening between SOND patients, MRND patients, and patients who were not neck-dissected.



Data regarding CROM at 0, 2, 6, and 12 months were available (all three groups combined) for 206, 146, 137, and 109 patients. For mouth opening, data were available for 200, 140, 135 and 108 patients over time.

4.4 PAPER IV – EARLY REHABILITATION

In total, 456 patients were included in the study, 82 in the pilot study and 374 in the prospective study. Of these 374 patients, 205 answered the project-specific questionnaire at 6 months after termination of treatment, 84 in the study group and 121 in the control group. The basic characteristics of the 205 patients were not significantly different from those of the 169 patients who did not answer the project-specific questionnaire. The groups were well-matched except for a significant difference in the number of patients who received chemotherapy ($p = 0.004$).

4.4.1 Incorporation of the rehabilitation programme

All patients undergoing EBRT at the southern unit could be included in the clinical development programme. There was no difference in time from diagnosis to start of treatment between the study group (25.9 days, SD = 30.5) and the control group (25.9 days, SD = 30.4) ($p = 0.99$).

4.4.2 Weight loss, survival, and working ability

There was no significant difference in weight loss between the study group (-5.9 kg) and the control group (-6.2 kg) (Table 2). The difference in the incidence of patients with weight loss of > 10%, although higher in the control group, was not significant. Overall 2-year survival for all patients in the study (n = 374) was 76% (95% CI: 71–80). There was no significant difference in 2-year survival between the study group (n = 190) and the control group (n = 184) (log rank, $p = 0.49$).

As shown in Table 2, a significantly higher number of patients in the control group who had been working before diagnosis had returned to work by 6 months after treatment, i.e. more patients in the study group were still on sick leave and had not returned to work.

4.4.3 Functional losses

Patients in the control group reported significantly less swallowing difficulties than those in the study group, with a proportional odds ratio (OR) of 2.3 (95% CI: 1.3–4.0). In the control group, 58% answered that they could swallow all consistencies of food as compared to 35% in the study group ($p < 0.001$; data not shown in tables). There were a significantly higher number of patients using high-kilocalorie/protein supplement in the study group (60%) than in the control group (32%) ($p < 0.001$). Overall incidence of swallowing problems was 61% (114/185) and the incidence of patients reporting any level of dryness of the mouth was 92% (184/201); incidence of “very great” problems with dryness of the mouth was 41% (82/201).

There was a significant difference in the degree of speech problems, with an OR of 2.5 (95% CI: 1.4–4.4) and an increased risk of being at a worse level in the study group. In the total material, the incidence of chewing problems was 61% (113/186); 57% (106/186) reported a reduced ability to open the mouth and 70% (133/189) reported stiffness of the neck and shoulders 6 months after termination of treatment. There was an OR of 1.9 (95% CI: 1.1–3.3) with an increased risk of reduced ability to open the mouth in the study group relative to the control group.

4.4.4 Quality of life and depression

Response frequency was lower in EORTC questionnaires than in the project-specific questionnaire. No parameters in the EORTC questionnaires or the HADS showed any significant difference between the two groups at 6 months after termination of treatment. Six months after treatment, the total incidence of depression at any level (mild to severe) was 27% (50/183).

Table 2. Comparison of outcome between study group and control group

Characteristics (%)	n[a]	Study group	Control group	p-value	Difference (95% CI)
Weight loss[a]:	197				
Stable or increase		17 (21)	15 (13)		
Decrease < 5%		18 (22)	27 (24)		
Decrease 5–10%		27 (33)	30 (26)		
Decrease > 10%		21 (25)	42 (37)	0.23	
Mean weight loss[b] in kg [SD]		-5.8 [7.8]	-6.2 [5.8]	0.68	-0.4 (-1.5–2.3)
On sick leave at baseline:	22				
Situation unchanged at 6 months		7 (64)	7 (64)		
Situation better at 6 months		4 (36)	4 (36)	1.0	
					-
Not on sick leave at baseline:	133				
Situation unchanged at 6 months		29 (55)	64 (80)		
Situation worse at 6 months		24 (45)	16 (20)	0.003	25.2 (9.3–41.3)
Total number of patients	205	84	121		

[a]Number of patients included in the analysis.

[b]The difference in weight loss after controlling for baseline weight was not significant (p = 0.42) and was estimated to be 0.7 (-1.0 to 2.4).

5 DISCUSSION

This thesis is based on four studies using three different study populations. All patients were part of the ordinary clinical pathway at our institution and they were included in a non-selective manner avoiding experimental set-ups.

The aim was to conduct the studies in such a way that the interpretation of findings could easily be incorporated into the existing clinical setting. All four studies reached this goal, and have influenced patient care at our institution. Unfortunately, this clinical approach causes several methodological problems. For instance, patient material is not uniform and relationships between key measures and outcomes might be hard to establish. However, these problems have to be faced and handled in order to further improve treatment, complications, and rehabilitation of head and neck cancer patients.

5.1 PLANNED NECK DISSECTION

The basic question of the planned neck dissection is to weigh the probability of a reduced risk of recurrence in the neck against the probability of morbidity caused by surgery. In this work, a third of all patients and a quarter of the patients with a complete response in the neck had viable cancer cells in the neck specimen. This is well in line with earlier studies and can be interpreted as an indication for planned neck dissection for N+-patients after preoperative oncological treatment, regardless of outcome [160-162]. Other guidelines of today advocate a neck dissection only in patients who do not achieve a complete response in the neck, and suggest that patients who are not operated on might be controlled with PET-CT 2–3 months after termination of radiotherapy [81,163]. An alternative to PET-CT is diffusion-weighted MRI, which has the advantage of not being disturbed by surrounding inflammation and which allows control of tumor effect during the course of radiotherapy [164,165]. Another alternative is to control the neck after radiotherapy with ultrasound with the possibility of fine needle aspiration for cytology. This technique has a rather high sensitivity on not irradiated N0 necks but studies are lacking on sensitivity in the irradiated neck [166-168]. Not to perform a neck dissection in patients with a complete response in the neck is the predominant line of treatment today [31] and this is also the existing guideline today at our institution for oro- and rhinopharyngeal tumours. As shown in this thesis, histopathological outcome and disease-specific survival after radiotherapy for patients with tumours of the tonsils or base of the tongue were significantly better than in other sites.

The high incidence of viable tumour cells in the neck specimen—as found in many studies—might be due to the fact that the neck dissection is often performed six weeks after radiotherapy. Many speculate that tumour cell death is not complete at this time, and that many of these cells could have undergone cell death at around 12 weeks after radiotherapy [169]. This would also allow a PET-CT to be performed at 12 weeks, which seems to be the best timing to be able to separate inflammation from residual tumour [31]. The disadvantage would be that the optimal “surgical window” at 4–6 weeks after termination of radiotherapy is missed. Quality of radiotherapy might also have an influence on differences in anti-tumour activity between studies.

We found an overall risk of regional recurrence of around 6%, but the risk was doubled if there were viable tumour cells in the neck specimen; these figures are also supported in other studies [170]. The risk was the same in the group with complete response in the neck as for those with palpable residual disease.

In the present study, no comparison between different types of neck dissections was done but findings in other studies suggests that less extensive surgery, such as supraomohyoidal neck dissection, is as effective as more extensive surgery [171]. As shown in Paper III, the late morbidity of a supraomohyoidal neck dissection appears to be low [90,91,172]. We did not do any analysis of acute complications in Paper I and in Paper III such as bleeding, wound infection, chyle leak, or delayed healing. The incidence of acute morbidity reported in other studies is highly variable, from below 10% to over 20% [100,160,173-175], and since we lacked a complete morbidity analysis in our own material we have had to rely on the findings of other studies.

We found a poor prognosis for patients with viable tumour cells in the neck specimen after full-dose radiotherapy. Currently, the most sensitive way to find these cells is a neck dissection with histological examination but established methods such as PET-CT and ultrasound-guided examination with the possibility for fine-needle aspiration can most likely be improved further. Unfortunately, apart from surgery there are no additional curative therapies for patients without a complete response to radiotherapy at the moment. In our material, a group of 15 patients achieved a complete response in the neck but had viable tumour cells in the neck specimen, and this group had a much worse outcome than patients with palpable residual disease and viable cells. It does seem that these patients were not helped by the neck dissection. A possible reason might be that a palpatory residual mass is easier to remove radically than a non-palpatory one.

So, should a planned neck dissection be performed in all N-positive patients? The question remains unsatisfactorily answered by this study—as well as by earlier studies. Obviously further studies are needed, preferably a prospective randomised study—but such a study is difficult to perform today due to the changed attitude to neck dissection. Instead, at our institution we accomplished a thorough retrospective analysis (after the present results had been published) of the outcome in our patients according to primary site (unpublished data). From these analyses, it appears that there have to be different guidelines for different sites, and even for sub-sites like the mobile part of the tongue and the floor of the mouth. As the oncological treatments improve, there is a trend towards less surgery, and the trials on radiotherapy and chemotherapy appear to be superior in their design to trials on surgical methods. However, surgical methods are also developing and some studies using techniques such as robotic surgery show less need of additional oncological treatment and also less morbidity [176]. At the same time, there is a lack of comparisons between adverse events induced by radiotherapy or chemotherapy and surgery. These treatment modalities must be evaluated concerning outcome and adverse events according to the same standards, in order to provide patients with the best possible treatment with the lowest possible morbidity.

5.2 OESOPHAGEAL STRICTURE

As shown in this thesis, the incidence of oesophageal stricture at our institution has not changed significantly over the time period 1992-2005 and remains around 3%. Even though it is a rare complication, it is associated with considerable morbidity and repeated interventions. We identified the use of enteral feeding tubes and a mean dose of > 46 Gy to the upper oesophagus as independent risk factors for stricture formation. Due to the low incidence of oesophageal stricture, it is difficult to achieve high significance for these ratios. Still, the patient material in the present study, 70 cases and 66 controls, was comparatively large.

In this work, patients treated with chemotherapy were excluded. In studies on patients treated with chemoradiotherapy, the incidence of stricture has been reported to be around 20% [107,109]. There have been few prospective studies, but in the study on chemoradiation by Farwell *et al*. [103], 23% of the patients were found to have oesophageal stricture. However, there may have been a selection bias in that study, as only 15% of the patients included reported no dysphagia at all. In our material in Paper IV, 38% of the patients reported no dysphagia six months after termination of treatment, and the speech-language pathologist found no clinical signs of swallowing disorders in 26% of the patients. In the study by Francis *et al*. [109], 60% were found not to be suffering from dysphagia. Obviously, patients reporting dysphagia are more likely to have an oesophageal stricture.

The relationship between enteral feeding and stricture can be interpreted in different ways. It can either be a warning sign for patients who are likely to develop a stricture, or the percutanous endoscopic gastrostomy (PEG) or nasogastric-tube (NG-tube) might induce stricture formation—directly or indirectly. The possible direct negative effect could be oesophageal regurgitation due to the NG tube [177,178]. There is evidence that PEG placed before the start of treatment prolongs enteral feeding dependency [179] and is associated with a reduced quality of life [180]. Still, many advocate a prophylactic PEG placement before therapy starts to avoid weight loss [181,182] and enteral feeding is generally considered to be favourable for patient care [183]. Our hypothesis is that continued swallowing during and after treatment might prevent stricture formation [184]. Factors that might prevent patients from swallowing are mucositis, surgery in the oral cavity or base of the tongue, and PEG or NG tube; all of these parameters were found to be significant risk factors in the univariate analysis. The NG tube itself disturbs swallowing, and if patients have a PEG they might be less inclined to swallow. As shown by Ryu *et al*. [185], it is possible to maintain good nutritional status for shorter periods using intravenous total parenteral nutrition instead of enteral nutrition. Patients who received total parental nutrition had a reduced incidence of aspiration pneumonia compared to patients on enteral feeding, although instead there is a risk of catheter-related infections. The increased risk of pneumonia is most likely related to gastro-oesophageal reflux, as there does not appear to be an increased risk of aspiration during oral intake with an NG tube in place [186].

One interpretation of the results could be that the physician should be more selective before equipping patients with tools for enteral nutrition. Instead, some of these patients might be better of with total parenteral nutrition—or even just swallowing training and

nutritional supplements. Questions can also be raised about the value of nutrition support, considering studies such as that of Rabinovitch *et al*. showing a poorer loco-regional control in patients receiving nutritional support, even though these patients did have less weight loss and a better quality of life [187].

At our institution, dilatation with Savary-guided bougies is still the most common way to treat oesophageal strictures. According to the results in this thesis, the procedure is safe and successful but often has to be repeated, which is in accordance with the results of Piotet *et al*. [188]. The number of patients treated with through-the-scope balloon dilatation was low, but in our material it seemed to be just as good as the Savary technique. Even though the radial force of a balloon dilatation would appear to be better than the combined longitudinal and radial force of the Savary dilator, the outcomes of these methods are comparable [189,190].

In our material, no difference in survival was found between the groups in spite of the fact that patients in the stricture group went through a number of dilatation interventions and suffered from dysphagia. No analysis of quality of life was performed in this work, but based on other studies patients with oesophageal stricture can be expected to suffer from a reduced quality of life due to dysphagia [191]. To reduce the risk of stricture formation, radiotherapy at our institution is being continuously developed in order to spare organs at risk, such as the upper oesophagus. However, the number of patients receiving prophylactic PEG and NG tube is increasing (unpublished data), and a thorough discussion on the use of enteral nutrition is needed.

5.3 MORBIDITY OF NECK DISSECTION

This study complements the study from Paper I in order to evaluate some of the morbidity parameters induced by neck dissection combined with radiotherapy, and to compare supraomohyoidal neck dissection (SOND) to modified radical neck dissection (MRND). As stated in section 5.1, the choice of treatment is always taken by balancing the risk of leaving residual tumour after radiotherapy and reducing the risk of recurrence with the possible morbidity induced by ND. Most earlier studies on morbidity and clinical outcome from neck dissection are retrospective and therefore have a low level of evidence while our study is prospective, including longitudinal data, making it possible to adjust for baseline values. The chosen morbidity parameters studied were cervical range of motion (CROM), trismus, lymphoedema, dysphagia, and shoulder disability. According to our findings, the risk of causing a surgical injury by SOND is low and the only morbidity found was shoulder disability in 2/24 patients. For patients who had gone through a MRND, there was a slight but significant reduction in cervical rotation and 16/78 patients suffered from shoulder disability 2 months after surgery. An important observation was that morbidity after MRND was significant for most of the evaluated parameters two months after treatment, but declined during the first post-treatment year. The low rate of objective measurable stiffness in the neck contradicts the high rate of self-reported stiffness in the neck and shoulders found in Paper IV (70%). The reduced morbidity after a selective ND and the decline over time is in line with the findings of Shah *et al*. [192], even though their study lacked the longitudinal approach of the present study. Studies focusing on quality of life also show an improvement during the time period from 3 months after treatment to 12 months

after treatment [193]. There is some evidence of a relationship between reduced quality of life and neck dissection [96], but quality of life was not assessed in the present study.

The fact that SOND induced shoulder disability in 2/24 patients (as the only morbidity found in this study) does not give a complete picture. For instance, we did not look for acute complications to surgery; thus, the incidence is not known for this material. However, the incidence of acute post-surgical complications other than shoulder disability after a SOND is low according to other studies [79,91]. More extensive neck dissections, such as the MRND, may be associated with a higher incidence of acute post-surgical complications [32]. As mentioned in section 5.1, however, there is a need to compare oncological treatment to surgery concerning treatment outcomes and associated morbidity. A SOND alone does achieve sufficient prevention for regional metastasis in N0 oral cavity tumours, but with less morbidity than radiotherapy [194-196]. Perhaps SOND could replace radiotherapy concerning other diagnoses also—such as small oropharyngeal tumours [196,197], but there has to be a proven benefit in morbidity outcome.

5.4 EARLY REHABILITATION

We integrated a programme for early preventive rehabilitation into the clinical pathway that is presently in use as a clinical routine. This was achieved without delaying the start of treatment, mainly due to our organisation with a coordinating oncology nurse making the time schedule for the clinical work-up for every new patient. However, no positive outcomes were demonstrated by this programme when comparing patients receiving early preventive rehabilitation with patients from the same institution who had not been included in the programme. The hard objective outcome measures compared were 2-year survival and weight loss. A comparison of functional impairment was done by questionnaire; thus, only data concerning the patients' self-perceived impairment were collected in this analysis.

There are several possible explanations for the lack of evidence of positive effects of the programme. One is simply that the programme itself did not offer any positive outcomes. Other rehabilitation programmes using similar exercises to ours but different outcome measures have shown positive results [136]. Van der Molen *et al*. were able to show improvement concerning dependence of tube-feeding but not in swallowing and trismus [198]. Carroll *et al*. compared nine patients who underwent rehabilitation to nine patients in a control group, and found improved swallowing in the study group from a video-fluoroscopic examination but no improvement in tube-feeding dependency [199]. Kulbersh *et al*. used the M.D. Anderson Dysphagia Inventory (MDADI) questionnaire to assess patients receiving pre- or post-treatment rehabilitation, and found results in favour of the pretreatment group [200]; however, objective parameters such as weight loss and tube-feeding dependency were lacking. In our work, we found no significant difference in tube-feeding dependency but significantly more patients in the intervention group used nutritional drinks (data not shown). This finding may reflect better-informed patients in the intervention group regarding the importance of nutrition.

Another explanation for the absence of positive results in the rehabilitation programme could be low compliance. This was not thoroughly assessed by us, but 37% of the

patients in the intervention group answered that they had rarely or never performed the exercises provided by the speech-language pathologist (data not shown). Based on this figure, low compliance might be a bias that was not adjusted for in this analysis; instead, the analysis was done according to intention-to-treat. Perhaps a rehabilitation programme like this one should be more intense, with frequent appointments to motivate patients better. The patients in our study were meant to start different rehabilitation exercises just after their cancer diagnosis and to perform these on a daily basis while receiving radiotherapy and in some cases extensive surgery also. It is understandable that many of these patients did not follow the rehabilitation programme and it remains a challenge to motivate patients with cancer burden during and after treatment.

Concerning quality of life, depression, and anxiety, the response frequency was too low to be able to interpret these questionnaires. However, no significant difference between the intervention and control groups was found. When analysing the total material, there was a significant decrease in patients scoring > 7 in anxiety from diagnosis to 6 months after treatment: 33% scored > 7 at 6 months as compared to 50% at diagnosis. There was the same pattern for depression, but this decrease was not significant: 33% scored > 7 at 6 months after treatment as compared to 38% at diagnosis. Similar figures have been found in previous studies [201].

The EORTC-QLQ-C30 and EORTC-H&N35 questionnaires were used in this study. The patients who answered these seem to have had slightly higher morbidity than expected when comparing our results to the results of Hammerlid *et al*. [202]. In our material, the mean score for swallowing in EORTC-H&N35 was 25 (95%CI: 20–31); the score was exactly the same for pain. For social eating, the mean score was 36 (95%CI: 29–42). This might partly be explained by the fact that 71% of the patients in the present study were at stages III–IV, as compared to 45% in the study by Hammerlid *et al*. The high incidence of stages III–IV in the present study can be explained by the fact that radiotherapy was our basic inclusion criterion.

We could not show any positive effects of our intervention with early rehabiliation, which might initially seem negative. Instead, we consider this a very important finding. Rehabilitation is often presented as a solution to many of the complex problems that cancer patients suffer from [129,203]. Despite our negative findings, rehabilitation with a multidisciplinary approach might be one important part of the care of these patients. However, new rehabilitation programmes must be evaluated according to the same standards as are new techniques for treatments. There are indications of positive outcome regarding well-being from meeting rehabilitation staff, without any measurable improvement in functional impairments, but this effect is not enough to justify such interventions [157].

Based on the results of the studies described in this thesis, our programme for early rehabilitation should be subject to further analysis and modifications.

5.5 FUTURE PERSPECTIVES

There are indications that rehabilitation of selected patient groups is one important way to reduce morbidity for head and neck cancer patients. As mentioned above, we will further analyse the data from the early rehabilitation project. Firstly, an analysis on selected subgroups will be performed. The probable subgroups will be according to primary site, sex, age, and pre- or postoperative radiotherapy. More parameters than those presented in this thesis will also be assessed. After the analysis of outcomes for the subgroups is completed, adjustment of the rehabilitation programme will be done. We also intend to present the programme to the patients in a different way, in order to improve compliance. These changes will have to be evaluated. Since all patients at our institution are now offered rehabilitation, a control group not receiving any rehabilitation will be difficult to construct. Instead, changes in the programme for specific subgroups will have to be compared to the outcome for the same subgroup earlier. Another possibility is to compare outcomes from patients treated at different institutions.

Since 2008, the Swedish Head and Neck Cancer Quality Register (SHNC-OR) has been operating with a high rate of inclusion. It is possible to connect modules for different evaluation parameters to this register. We hope to connect modules for specific questionnaires to evaluate the effects of different ways of rehabilitation. These might be questionnaires for quality of life (EORTC), depression and anxiety (HADS), and swallowing (MDADI). We are investigating the possibility of having data automatically transferred from the medical files from the physician, the speech-language pathologist, and the physiotherapist concerning mouth opening, aspiration, and speech. This approach of collecting data will provide us with large populations and with the possibility of performing a multi-centre study.

Patients with oesophageal stricture formation will continue to be identified at our institution. As there are unpublished data showing increased use of PEG, an increased incidence of stricture might be anticipated in accordance with our findings. However, as part of the rehabilitation programme patients will be encouraged to continue to swallow to the best of their ability even though they receive tube feeding. There are also changes in the oncological treatment with chemotherapy and EGFR at our institution that might affect the incidence of stricture formation.

As mentioned earlier, we are continuously investigating outcomes for the patients treated at our institution and guidelines are adjusted according to these evaluations. The need for neck dissection and the levels that have to be included in the neck dissection for each primary site is one important issue. Some of these investigations will soon be submitted to peer-review journals. The author of this thesis has analysed the outcome for patients with tumours in the floor of the mouth, and will continue with cancers of the lip.

6 CONCLUSIONS

- Our study showed that a clinical evaluation alone was not sufficient to determine if a neck dissection was necessary after definitive radiotherapy.

- Viable tumour cells in the neck specimen indicated a poor prognosis, especially if there was a clinically complete response in the neck.

- There was an increased risk of development of oesophageal stricture after radiotherapy if more than 45 Gy was delivered to a large volume of the upper 5 cm of the oesophagus. The risk was also increased if the patient used a percutanous endoscopic gastrostomy or a nasogastric tube for enteral nutrition during or immediately after radiotherapy.

- Treatment of an oesophageal stricture with Savary-Gilliard bougienage or through scope balloon dilatation was safe and successful, but it often had to be repeated.

- A supraomohyoidal neck dissection had no effect on cervical range of motion, trismus, or lymphoedema, while a modified radical neck dissection induced a slight reduction in cervical rotation.

- The incidence of shoulder disability after a supraomohyoidal neck dissection was approximately 8%, as compared to 20% after a modified radical neck dissection.

- We could not show any positive effects of early preventive rehabilitation starting before radiotherapy on patient survival, weight loss, functional impairment, or quality of life.

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