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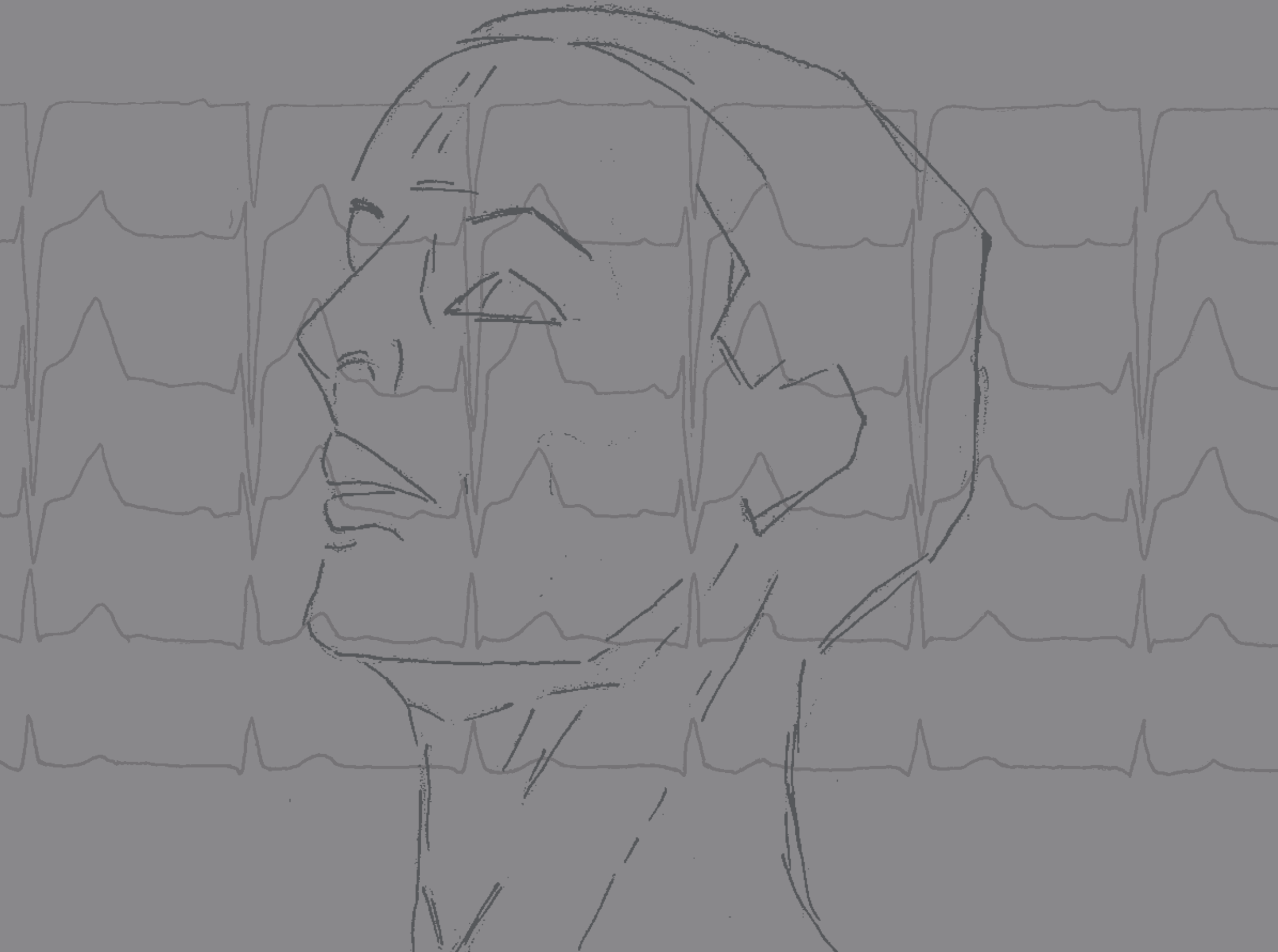

CARDIAC AND CEREBROVASCULAR COMPLICATIONS AND BLEEDING IN HEAD AND NECK CANCER SURGERY

Eeva Haapio

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To Jukka, Meeri, and Iisa

Courage is not the absence of fear; it is the conquest of it.
William Danforth

ABSTRACT

Eeva Haapio

Cardiac and cerebrovascular complications and bleeding in head and neck cancer surgery

University of Turku, Faculty of Medicine, Department of Otorhinolaryngology – Head and Neck Surgery; Doctoral Programme of Clinical Research; Heart Center

Annales Universitas Turkuensis Ser. D, Painosalama Oy – Turku, Finland 2018

In head and neck surgery, there is generally a 1–1.5% risk of cardiac and cerebrovascular complications. However, risk of these events in head and neck cancer surgery is less well established. Smoking and heavy alcohol consumption increase the risk of head and neck cancer, and they are also significant risk factors of cardiac and cerebrovascular comorbidity. There is evidence that age and comorbidity in general increase the risk of major adverse cardiac and cerebrovascular events (MACCE), but the effect of specific comorbidities remains unknown. Furthermore, it would be useful to identify modifiable peri- and postoperative variables in order to decrease the risk of MACCE.

This thesis sought to assess the incidence of MACCE and means to predict adverse events during and after head and neck surgery. Secondly, specific comorbidities and modifiable peri- and postoperative risk factors influencing MACCE risk were identified. This retrospective study included all head and neck patients treated in Turku University Hospital in 1999-2008 (n=456). Data was collected from patient files.

Results of this study support the data that increasing age and comorbidities play a significant role in MACCE, and there is an unmet need for a good predictive tool to assess patients at high risk of MACCE. ASA-classification and CHA_2DS_2-VASc score seemed to predict the risk of postoperative 30-day MACCE. and the easy-to-use CHA_2DS_2-VASc score could be used by the multidisciplinary team to estimate patients' peri- and postoperative risk of MACCE. Futhermore, excessive fluid administration exceeding 4000mL/24h and red blood cell infusion increased the risk of 30-day MACCE nearly 5-fold. Other peri- and postoperative risk factors were microvascular surgery, treatment in the intensive care unit, and tracheostomy, all referring to major surgery. Nevertheless, MACCE also occurred in minor head and neck surgery. However, re-operation due to bleeding did not increase the risk of MACCE, but increased the risk of 30-day mortality more than 5-fold, and in all cases the cause of death was cardiovascular.

By addressing the high-risk patients and controlling the known modifiable risk factors, we might be able to decrease morbidity and mortality due to MACCE in head and neck cancer surgery in the future. For example, and the easy-to-use CHA_2DS_2-VASc score could be used by the multidisciplinary team to estimate patients' peri- and postoperative risk of MACCE.

Keywords: head and neck cancer; MACCE; excessive fluid administration; red blood cell transfusion; CHA_2DS_2-VASc

TIIVISTELMÄ

Eeva Haapio

Sydän- ja verisuonitapahtumat ja vuodot pään ja kaulan alueen syöpäkirurgiassa.

Turun yliopisto, Lääketieteellinen tiedekunta; Korva-, nenä- ja kurkkutautioppi; Kliininen tohtoriohjelma; Sydänkeskus

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Pään ja kaulan alueen kirurgiassa yleisesti on 1-1,5% riski saada vakava sydän- ja verisuonitapahtuma. Pään ja kaulan alueen syöpäkirurgiassa sydäntapahtumien riskiä ei ole kattavasti tutkittu. Tupakointi ja runsas alkoholin käyttö lisäävät pään ja kaulan alueen syövän riskiä ja ovat myös tunnettuja sydän- ja verisuonisairauksien riskitekijöitä. On näyttöä, että ikä ja perussairaudet lisäävät vakavien sydän ja aivotapahtumien (major adverse cardiac and cerebrovascular event – MACCE) riskiä, mutta tietoa yksittäisten perussairauksien vaikutuksista ei ole ollut. Lisäksi olisi hyödyllistä tunnistaa muokattavissa olevia peri- ja postoperatiivisia tekijöitä jotta MACCE riskiä voitaisiin pienentää.

Tämä väitöskirjatyö pyrki selvittämään MACCEn esiintyvyyttä ja arvioimaan työkaluja joilla voitaisiin ennustaa vakava päätetapahtuma Pään ja kaulan alueen kirurgiassa. Toisena tavoitteena oli tunnistaa yksittäiset perussairaudet ja ne peri- ja postoperatiiviset riskitekijät joilla on vaikutusta MACCE–riskiin. Tutkimusaineistona olivat kaikki Turun Yliopistollisessa keskussairaalassa vuosina 1999-2008 hoidetut pään ja kaulan alueen syöpäpotilaat (n=456). Retrospektiivinen aineisto kerättiin potilasasiakirjoista.

Tämän tutkimuksen tulokset tukevat näkemystä siitä, että korkeampi ikä ja perussairaudet ovat merkittävässä roolissa vakavien päätetapahtumien synnyssä ja että tarvitaan työkalu, jonka avulla korkean MACCE–riskin potilaat voidaan tunnistaa. ASA-luokitus ja CHA_2DS_2-VASc–pisteytys ennustavat hyvin MACCEa 30:n päivän kuluessa leikkauksesta. Tulokset osoittavat, että runsas nesteytys (>4000ml/24h) ja punasolusiirto lisäävät 30:n päivän MACCE–riskiä melkein viisinkertaisesti. Muita peri- ja postoperatiivisia riskitekijöitä ovat mikrovaskulaari kirurgia, hoito teho-osastolla ja trakeostomia, eli laaja-alaiseen leikkaukseen viittaavat tekijät. MACCEa esiintyi kuitenkin myös kaikkein pienimmissä pään ja kaulan alueen syövän vuoksi tehtävissä toimenpiteissä. Huomioitavaa on, että uusintaleikkaus jälkivuodon vuoksi ei lisännyt potilaan päätetapahtuman riskiä, mutta lisäsi kuolleisuutta 30:n päivän kuluessa leikkauksesta yli viisinkertaiseksi. Kaikissa tapauksissa kuolinsyy oli sydän- ja verisuoniperäinen.

Osoittamalla suuressa MACCE–riskissä olevat potilaat ja huomioimalla muokattavissa olevat riskitekijät voisimme mahdollisesti tulevaisuudessa vähentää kardiovaskulaarisiin päätetapahtumiin liittyvää sairastuvuutta ja kuolleisuutta pään ja kaulan alueen syöpäkirurgiassa. Esimerkiksi helppokäyttöinen CHA_2DS_2-VASc–pisteytys sopisi preoperatiiviseen riskinarvioon moniammatillisessa hoidonsuunnittelukokouksessa.

Avainsanat: pään ja kaulan alueen syöpä; MACCE; runsas nesteytys; punasolusiirto; CHA_2DS_2-VASc

TABLE OF CONTENTS

ABBREVIATIONS

ACC	American College of Cardiology
ACE-27	Adult Comorbidity Evaluation-27
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA	American Heart Association
ASA	American Society of Anesthesiologists
AUC	Area under curve
BMI	Body mass index
CAD	Coronary artery disease
$CHADS_2$, CHA_2DS_2-VASc	Risk scores for thromboembolic complications in patients with atrial fibrillation
CI	Confidence interval
CVD	Cardiovascular disease
CT	Computer tomography
DNA	Deoxyribonucleic acid
DOI	Depth of invasion
ECG	Electrocardiogram
ENE	Extranodal extension
ESA	European Society of Anaesthesiology
ESC	European Society of Cardiology
GY	Gray
Hb	Haemoglobin
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
ICU	Intensive care unit
IMRT	Intensity-modulated radiotherapy
IQR	Interquartile range
kg	kilogram
MACCE	Major adverse cardiac and cerebrovascular event
MI	Myocardial infarction
mL	Millilitre
MRI	Magnetic resonance imaging
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
ORN	Osteoradionecrosis
OS	Overall survival
PE	Pulmonary embolism
QoL	Quality of life

RBC	Red blood cell
RCRI	Revised cardiac risk index
SCC	Squamous cell carcinoma
SD	Standard deviation
SSI	Surgical site infection
STEMI	ST-elevation myocardial infarction
TIA	Transient ischaemic attack
TLM	Transoral laser microsurgery
TNM	Tumour, Node, Metastases
TOS	Transoral surgery
UICC	Union for International Cancer Control
VTE	Venous thromboembolism

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in text by their Roman numerals.

I Haapio E, Kiviniemi T, Irjala H, Koivunen P, Airaksinen J.K.E., Kinnunen I. Incidence and predictors of 30-day cardiovascular complications in patients undergoing head and neck cancer surgery. *European Archives of Oto-rhinolaryngoly.* 2016 273(12):4601-4606.

II Haapio E, Kinnunen I, Airaksinen J.K.E., Irjala H, Kiviniemi T. Excessive intravenous fluid therapy in head and neck cancer surgery. *Head&Neck.* 2017 39(1):37-41.

III Haapio E, Kinnunen I, Airaksinen J.K.E, Irjala H, Kiviniemi T. Determinants of re-operation for bleeding in head and neck cancer surgery. *The Journal of Laryngology and Otology*. 2018 8:1-5.

IV Haapio E, Kinnunen I, Airaksinen J.K.E, Vahlberg T, Koivunen P, Irjala H, Kiviniemi T. Performance of simple risk score in prediction of adverse cardiac events in head and neck cancer surgery. Submitted.

1 INTRODUCTION

Head and neck cancer (HNC) is a variant group of neoplastic processes, most commonly squamous cell carcinoma (SCC), where smoking and heavy alcohol consumption are the most common predisposing factors.[131] Those are also risk factors for cardiac and cerebrovascular comorbidity.[12]

HNC is treated with surgery or radiation therapy combined with chemotherapy if necessary. In more advanced disease, surgery and oncologic treatment are used together for better locoregional control. Both treatment modalities include a risk of complications. Patient comorbidities (such as cardiac and pulmonary disease) increase the risk of complications and, in the worst case, can compromise the curative intent of the treatment. The impact of increased comorbidity burden include lower overall survival rate, increased short-term mortality, negative influence on disease-specific survival, increase in the number and severity of complications, impaired quality of life (QoL), and functional outcomes and increased cost of treatment.[190] Incidence of complications is reported to be 21–36% in HNC surgical patients, and the incidence of cardiac and cerebrovascular complications in HNC surgery is high, over 5%.[20, 30, 57, 171] Factors predisposing to peri- and postoperative major adverse cardiac and cerebrovascular events (MACCE) are, e.g., age, comorbidity, length of surgery, estimated amount of bleeding, and tumour type.[57, 61, 162] By identifying the high-risk patients preoperatively and taking into account the possible modifiable peri- and postoperative risk factors, we might be able to improve the survival of the patients, and decrease morbidity and cost of the treatment.

There are several risk indices (e.g., American Society of Anesthesiologists (ASA) classification, Adult Comorbidity Evaluation-27 (ACE-27), Revised Cardiac Risk Index (RCRI), Comorbidity Index) to identify patients at risk for cardiac and cerebrovascular complications. Many of them are more suitable for research use, and none of them has become videly popular among head and neck surgeons, possibly because of the abundant number of variables or because of variables that are not known before multidisciplinary planning of the treatment. There is an unmet need for a good predictive index for preoperative use.

2 REVIEW OF LITERATURE

2.1 Head and neck cancer (HNC)

In the anatomically complex head and neck area, a variant group of neoplastic processes with different behaviour and outcome exists. The majority of head and neck neoplasms originate from the mucosa of the upper aerodigestive track, including the oral cavity, pharynx, larynx, nasal cavity, and sinuses, most of them histologically SCC. Malignancies can also arise from salivary glands, soft tissue, bone, thyroid, and parathyroid glands, and skin and can have many different histological types. Neoplasms originating from skin, thyroid and parathyroid glands are not discussed in this thesis.

2.1.1 HNC epidemiology

The worldwide incidence of HNC is more than 550,000 cases annually, causing around 300,000 deaths per year.[104] There are wide geographical differences in the incidence of HNC arising from genetic and environmental factors. According to the Finnish Cancer Registry, there were 840 new cases of HNC in Finland and 293 HNC-related deaths in 2015.[1]

The incidence of HNC increases with age, and the median age at the time of diagnosis is 50 to 60 years, depending on subsite and epidemiological factors.[184] The known epidemiological factors influencing the development of HNC are smoking and heavy alcohol consumption, oncogenic viruses such as human papilloma virus (HPV) and Epstein-Barr virus, local and systematic premalignant conditions, lower socioeconomic status, and occupational exposures to chemicals and hardwood dust.[184, 228, 246]

Smoking is the most important independent risk factor for HNC. The risk of cancer is related to quantity and duration of smoking and the risk is highest for laryngeal cancer.[132] Heavy alcohol consumption is frequently observed among HNC patients. Heavy drinking is associated with increased HNC risk, and the risk is multiplicative if a patient is simultaneously a smoker.[132] Alcohol also has direct harmful effects on multiple organs, including the liver and the heart.

Although alcohol and tobacco consumption have been decreasing in developed countries, the incidence of HNC has been quite stable or slightly increasing due to the rising incidence of HPV infections.[119] HPV infection is strongly linked to oropharyngeal cancer, and the risk of HPV-related HNC SCC is reliant on the number of oral sex partners.[90] An HPV-positive HNC patient is determined by the presence of high-risk types of HPV (HPV-16, HPV-18),[121] and the expression of viral E6 and E7 oncoproteins is obligate to the malignant nature of these tumours.[181] Patients with HPV-positive HNC have improved survival.[8, 64] Smoking increases the risk of oropharyngeal cancer in HPV-positive patients.[7]

2.1.2 Tumour stage and TNM -classification

Head and neck tumours are staged according to their original site: lip and oral cavity, pharynx, larynx, nasal cavity, and paranasal sinuses and salivary glands. The TNM (tumour, nodus, and metastasis) staging system for head and neck tumours uses the size and extension of the primary tumour, its lymphatic involvement, and the presence of distant metastasis to classify the progression of cancer. The staging system is developed and maintained by the Union for International Cancer Control (UICC) and has been updated 3 times in the twentieth century.

TNM -classification is clinically practiced in the treatment decisions and estimation of the prognosis of malignancy. In the classification, T stands for the size of the primary tumour, N indicates the cancer distribution to local lymph nodes, and M represents the possible presence of distant metastasis. An example of TNM -classification is given for oral cavity cancer in Table 1 and tumour staging is introduced through oropharyngeal cancer in Table 2.

The 8th edition brought some notable changes in TNM –classification of HNC. The most significant update is the separate staging for HPV-positive and HPV-negative oropharyngeal cancers, presented in Table 2. Prognosis of HPV-positive cancer is much better and that is taken into consideration in new classification. For oral cavity cancer, the new classification takes into account the depth of invasion (DOI) in addition to greatest surface dimension, and for local lymph node metastasis, the extranodal extension (ENE) of the cancer in non-HPV-positive tumours. For cancer where primary tumour is not known the new classification requires viral examination, if lymph node is HPV p16-positive, cancer is staged as oropharyngeal, and if Epstein-Barr virus is positive, cancer is staged as nasopharyngeal, if both of these remain negative, cancer is staged as unknown primary.[26]

Table 1. Clinical TNM-classification for oral cavity cancer according to the 8th edition of UICC (DOI = depth of invasion, ENE= extranodal extension). [26]

T: Primary tumour		**N: Regional lymph nodes**		**M: Distant metastasis**	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	MX	Distant metastasis cannot be assessed
Tis	Carcinoma in situ	N0	No metastasis in regional lymph nodes	M0	No distant metastasis
T1	Tumour ≤ 2 cm in greatest dimension, and DOI ≤ 5mm	N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE- negative	M1	Distant metastasis
T2	Tumour ≤ 2cm, and DOI > 5mm but ≤ 10mm or Tumour > 2 cm but ≤ 4 cm, and DOI ≤ 10mm	N2a	Metastasis in a single ipsilateral or contralateral lymph node < 3cm in greatest dimension but ENE-positive, or metastasis in single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension, and ENE-negative		
T3	Tumour > 4 cm or DOI > 10mm	N2b	Metastasis in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension, and ENE-negative		
T4a	Moderately advanced disease: Lip: Tumour invades through cortical bone or involves inferior alveolar nerve, floor of the mouth or skin of the face. Oral cavity: Tumour invades adjacent structures only (e.g. trough cortical bone, or involves sinus maxillaris or skin); superficial erosion of bone/tooth socket alone in gingival primary is not sufficient for T4 classification	N2c	Metastasis in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension, and ENE-negative		
T4b	Very advanced disease: Tumour invades masticator space, pterygoid plates, or skull base, and/or encases the internal carotid artery	N3a	Metastasis in a single or multible lymph nodes > 6cm, and ENE-negative		
		N3b	3cm in greatest dimension and ENE-positive, or multiple metastasis with any ENE-positive		

Table 2. Clinical oropharyngeal cancer staging according to the 8th edition of UICC.[26]

a. Stage for HPV- related (p16+) oropharyngeal cancer.

Stage	TNM
I	T0N1 or T1-T2N0-N1
II	T0-T2N2 or T3N0-N2
III	T0-T3N3 or T4N0-N3
IV	Any M1

b. Stage for non-HPV-related (p16-) oropharyngeal cancer.

Stage	TNM
I	T1N0
II	T2N0
III	T1-T2N1 or T3N0-N1
IVA	T1-T3N2 or T4aN0-N2
IVB	T1-T4aN3 or T4bN0-N3
IVC	Any M1

2.1.3 Treatment modalities

Because of the complex anatomy and function of the head and neck area, the type of treatment must be selected carefully to optimise the best possible anatomic and functional outcome, taking cosmetic issues into account. The treatment typically involves surgery and/or radiotherapy combined with systemic chemotherapy if needed. Selection of the treatment is made by a multidisciplinary team based on, e.g., patient-related factors, TNM–classification, and HPV status. The rising incidence of HPV-positive HNC has an influence on the development of new treatment modalities.[8]

The basic principle in the treatment of HNC is that small (T1-T2) tumours are treated with single modality, surgery, or radiation alone. In more advanced disease, the combined treatment is often needed: surgery followed by postoperative radiation, often combined with chemotherapy.[105]

2.1.3.1 Surgical treatment

In many cases, surgery is the first line of the treatment for HNC. Surgery is also crucial in situations where the oncologic treatment has failed or where the patient has had previous radiotherapy to the head and neck region. Surgical alternatives depend on the site of the primary tumour and include endoscopic and open resection as well as robotic surgery. Surgery includes the resection of the primary site with reconstruction on demand and treatment of the neck if necessary. In small tumours, the resection of the primary tumour can be followed by primary closure, healing by secondary intention, local flap, or split thickness skin graft. In more advanced disease, reconstruction is made with pedicled or microvascular flaps. Commonly used pedicled flaps are the pectoralis, latissimus dorsi, and temporalis muscle flaps. Microvascular free tissue transfer is selected according to the tissue needed: when soft tissue, like skin and muscle are needed, the radial-forearm, anterolateral thigh, transverse rectus abdominis, and latissimus dorsi flaps are often used, and when the bone is needed as well, reconstruction is usually made with free tissue transfer from the fibula, scapula, or crista iliaca, depending on the amount of tissue needed.[198] According to study amongst European maxillofacial surgeons the most commonly used flaps in head and neck area were radial forearm flap (32%), fibula flap (18%), and pectoralis major flap (11%).[110] Major surgery, like surgery including raising the microvascular free flap, carries a higher complication rate.

In hypopharynx and larynx the organ preservation is preserved when possible to maintain the function. Both endoscopic and oncologic treatment options are used depending on the tumour. In more advanced stages of the hypopharyngeal and laryngeal cancer, and in situations where oncologic treatment has failed, total laryngectomy or laryngopharyngectomy is often required to control the disease, and reconstruction with a microvascular or pedicled flap may be needed.[71]

Nasal and sinonasal cancer is treated with primary surgery when possible. Adjuvant radiation is needed in most cases and chemoradiation is used when there are high-risk features. In more advanced disease, surgery can be excluded and those cases are treated with chemoradiation if possible. Surgical options include endoscopic resection, but open surgery is often needed, with possible hemimaxillectomy or maxillectomy.[138] The sinonasal area is highly vascular, and abundant bleeding can occur.

Cancer distribution to regional lymph nodes of the neck is the single most important prognostic factor in HNC. When the first line of treatment is surgery, the treatment of neck is determined based on the risk of nodal metastasis influenced by site, size, T-stage, location and histomorphological features of the primary tumour. The main goal of the treatment is regional control of the disease, and neck dissection remains to be the buttress of the treatment of cervical lymph node metastasis.[53, 193] In small T1/2 clinically N0 SCC located in the oral cavity, or in selected cases the oropharynx sentinel node biopsy and accurate histopathological assessment may be considered as an alternative to elective neck dissection.[5] Radical neck dissection is the gold standard procedure, but modifications that spare non-lymphatic structures or lymph node levels are used to decrease morbidity. Types of neck dissection are presented in Table 3.

Table 3. Neck dissection types.[189]

Term	Anatomical structures removed
Radical	Lymph nodes from levels I–V, the sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve
Modified	Lymph nodes from levels I–V but at least one non-lymphatic structure is preserved (sternocleidomastoid muscle, internal jugular vein, spinal accessory nerve)
Selective	In comparison to radical neck dissection, one or more lymph node levels are preserved
Extended	An additional lymph node level or group or a non-lymphatic structure is removed in comparison to radical neck dissection (e.g., superior mediastinal lymph nodes, external carotid artery, hypoglossal nerve)

The six different neck dissection levels are presented in Figure 1. Clear surgical and anatomical landmarks are used to determine the borders of different levels.

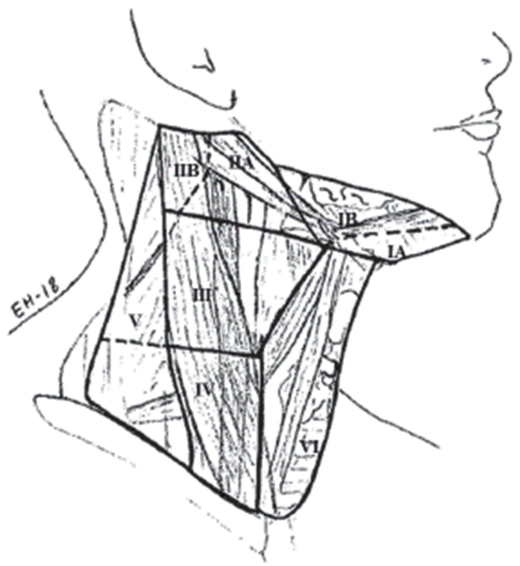

Figure 1. Neck dissection levels I-VI.

When the primary tumour is treated with radiotherapy, cervical metastasis can be treated with radiotherapy and supplemented with neck dissection if necessary.[178, 237]

With new developments in transoral surgery (TOS), such as transoral laser microsurgery (TLM), transoral robotic surgery (TORS), it has become possible to treat previously awkwardly available tumours, especially in the oropharyngeal region including the tonsillar region, the base of the tongue, and the hypopharynx. TOS suites best for early stage (T1-T2) disease that has been previously treated by (chemo)radiation therapy[95, 156] or with advanced surgery. It can also be considered as the treatment modality for young HPV-positive patients due to the absence of late toxicity burden. It is also an option for patients with tobacco- and alcohol-induced cancers, saving the radiation for further possible second primaries (8–27% risk[107, 224]).

Salvage surgery is needed when there is residual or recurrent disease.[194] Salvage surgery can include the treatment of the primary site or neck dissection for occult metastasis or both. In salvage surgery, anatomical landmarks can be changed due to the previous treatment and scarring, and tissues can be fragile, especially after chemoradiation. Salvage surgery is related to a high complication rate, i.e., wound, infection and bleeding complications, even with modern surgical technology [200, 221].

Palliative surgery can be required for large ulcerative tumours or to control painful symptoms of the patient, even when curative surgery is not possible. The aim of the palliative treatment is to restrain tumour growth, relieve symptoms, and restore breathing and swallowing. Surgeons dealing with the palliative treatment should be familiar with the pros and cons of different procedures and carefully consider patient's symptoms and needs case by case as well as the causation to QoL, and of equal importance, the quality of their death.[244] Other palliative treatment options are radiation, reradiation, chemotherapy, and in selected cases photodynamic therapy.

2.1.3.2 Oncologic treatment

The oncologic treatment can be designated as a first line curative treatment in the case of small (T1-T2) HNC, especially in subsites where organ preservation is important to maintain speech, swallowing, and breathing. Radiotherapy damages cellular DNA and cell membrane structures and is used alone or in many cases in combination with chemotherapy and as adjuvant therapy before or more often after surgery. Adjuvant radiation or chemoradiation therapy is needed when there is insufficient or positive resection marginal, more than five positive lymph nodes, extranodal extension or advanced tumour stage. The most commonly used chemotherapeutic agents are cisplatin and fluorouracil.[242] When radiotherapy is use alone or with chemotherapy, the standard treatment dose is 70 grey (Gy) for primary tumour and 66Gy for metastases. When given as adjuvant treatment after surgery, the dose is 60–66Gy for primary tumour and for possible metastasis. The elective dose for the neck is 50Gy.[105]

The complication of the oncologic treatment is the immediate and late toxicity. The side effects of the oncologic treatment at the head and neck region include, e.g., xerostomia, dysphagia, osteoradionecrosis of the mandible, trismus, and ischaemic stroke. There has been constant ambition to improve the treatment modalities to reduce toxicity. The intensity-modulated radiotherapy (IMRT) technique introduced in the early 2000s, offers the opportunity to diminish the dose of healthy tissue and spare functionally crucial organs and structures.[102, 130] IMRT is ideal for the head and neck region due to the regions's complex functional anatomy and it offers improved tumour control through delivery of high radiation doses to the target tissue.[126] With IMRT, the incidence of severe complications such as xerostomia and dysphagia has diminished.[67, 109, 161]

Other methods designed to diminish toxicity are proton therapy, stereotactic radiation, and three-dimensional conformal radiation therapy. Proton therapy has rapidly generalised in the head and neck region for the same reasons as IMRT, and it has the potential to further reduce complications. Proton therapy offers a low-energy deposition on entrance, a rapid rise in deposition in target tissue followed by a non-existent dose on exiting tissue.[10] The restrictive factor for the use of proton therapy at the moment is high cost and lack of proton facilities in Finland. Stereotactic radiation is given at four university hospitals in Finland, mainly in brain tumours and skull base tumours. It sends very narrow, high-dose radiation beams to cancer tissue. In three-dimensional conformal radiation, reconstructed matched computer tomography (CT) or magnetic resonance imaging (MRI) images are used, allowing for more precise targeting of radiation and saving the healthy tissues.[105]

For organ preservation, hyperfractionated and accelerated radiotherapy has been studied in more advanced disease. In hyperfractionated radiation, the patient gets a higher dose in a shorter time, 1.2Gy dose twice a day in comparison to the traditional 2.0Gy daily dose,[3, 249] and in acceleration the weekly dose exceeds 10Gy to shorten the treatment time. With hyperfractionation, the survival benefit is 8% and with acceleration it is 5.4% in relation to standard fractionation. In addition to hyperfractioning concomitant chemotherapy brings little or no advantage.[74] One problem with these radiotherapy modalities is the balance between benefits and increased local side effects.

HPV-positive HNC is detected as more radiosensitive compared to HPV negative.[116, 185] De-intensification of radiation for HPV-positive patients is under investigation, and the challenge is to find suitable low-risk patients.

The novel type of HNC treatment is immunotherapy. The objective of immunotherapy is to delete those derangements in the immune system and alterations in transformed cells that have allowed the immune scape and manifestation of cancer. In head and neck SCC, the best studied agents are cetuximab (Immunoglobulin G1 antiepidermal growth factor receptor [Ig-G1-anti-EGFR]) and ipilimumab (anticytotoxic T-lymphocyte antigen 4 [anti-CTLA-4]), but there is extensive research going on in this field of science.[16]

2.2 Peri- and postoperative management and complications

It is a well-known fact that surgery includes a risk of complications both peri- and postoperatively, which was already published inter alia by Thomas in 1914.[227] There are many factors influencing the occurrence of complications, and some of them can be modulated to lower the complication rate. Careful preoperative patient selection, preparation, and treatment planning can lower the complication rate, but does not erase the problem.

Previously, the term "comorbidities" has often been used as a group of long-term diseases in head and neck surgery literature. This definition, however, is problematic because it contains many diseases with a different survival pattern and mode of treatment. Patient comorbidities have a crucial impact on peri-and postoperative complications and overall survival. Increased comorbidity burden leads to increased short-term mortality with head and neck SCC patients, lower overall survival (OS) in head and neck SCC, impaired disease-specific survival, high incidence of and more severe complications, impaired QoL and functional outcomes, and increased costs of treatment.[190] Picciorillo et al. (2000) showed that in HNC patients, there is a significant causal relation with severity of comorbidity and overall survival.[171] Further studies have amplified these results and have shown that the total burden of comorbidities is a major univariate predictor of perioperative risk and the optimisation of comorbidities should be included in the treatment of HNC patients. Incidence of comorbidities (such as chronic pulmonary disease, congestive heart failure, and cerebrovascular disease) in HNC patients is reported to vary from 21% to 36%.[20, 171] There is also evidence that the relation between comorbidity and survival is not related to age, but comorbidity is also a risk factor for patients under age 45-years with head and neck SCC.[215]

The type and length of surgery[122] and the possible treatment in the intensive care unit (ICU)[11, 23] are also associated with peri- and postoperative complications. Continuation of smoking is known to increase the complications during anaesthesia and after operation. It will slow the wound healing process and can compromise the flap survival.[180, 226] Therefore, the discontinuation of smoking is recommended to patients. The most common complications are evaluated in the upcoming chapters.

2.2.1 Perioperative bleeding and transfusion

Perioperative bleeding is related to tissue injury made by the surgeon. Major surgery is often associated with more abundant bleeding. Because of the direct approximation of the carotid artery and jugular vein in the head and neck area, the surgeon and anaesthesiologist should be prepared for massive bleeding.

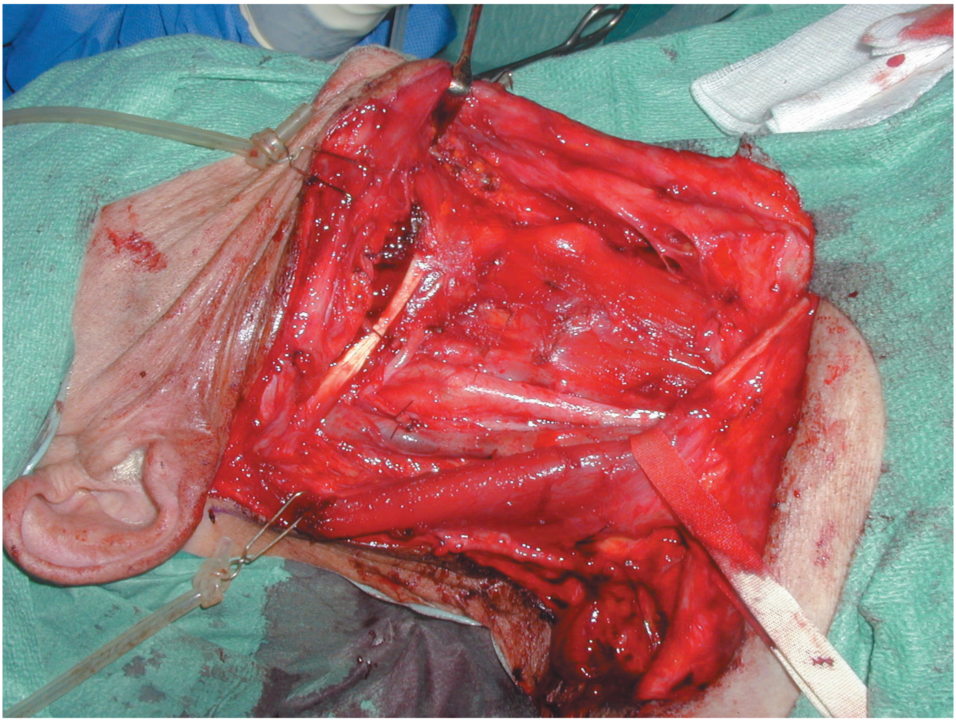

Figure 2. Neck dissection level I-V. (Photo by Ilpo Kinnunen)

In cancer surgery there is evidence that profuse bleeding and need of transfusion is related to higher tumour stage and T-classification.[4, 134, 239] Higher stage and T-classification are related to more invasive cancer with angioneogenesis,[69] and deeper resection is usually needed. In a study of Weber et al., 11.7% of patients undergoing head and neck surgery required blood transfusions; factors likely to lead to transfusion were advanced T-classification, low preoperative (haemoglobin) Hb level, flap reconstruction, and prior chemotherapy.[239]

Profuse bleeding is also related to the risk of re-operation due to bleeding.[245] There are not many studies about postroperative bleeding complications in HNC surgery. Studies available are mostly related to transoral surgery, and thyroid surgery. In transoral surgery of the oropharynx, the incidence of postoperative bleeding was 3.6–5.4% with 67.3% of those needing operative intervention.[123, 176] Moreover, in thyroid surgery, the need for re-operation for bleeding ranges from 1.2% to 4.2%. Factors increasing the risk of re-operation include age, male gender, magnitude of surgery, malignant histology and more advanced tumour stage.[81, 195]

In a large multicentre randomised controlled clinical trial of transfusion requirements in critical care (TRICC), the difference between the liberal (transfusion limit Hb ≤10g/dL) and restricted (Hb ≤7g/dL) transfusion strategies was studied. There was no difference in mortality.[89] In line, the FOCUS study (Transfusion Trigger

Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) found no difference in mortality between patients having liberal transfusions (Hb ≤10g/dL) versus restricted (Hb ≤8g/dL). Moreover, young (<55 years) and less ill patients had significantly lower 30-day mortality in the restricted transfusion group.[37] Two large observational studies, CRIT (Anemia and Blood Transfusion in Critically Ill– Current Clinical Practice in the United States) and ABC (Anemia and Blood Transfusion in the Critically Ill), stated that transfusion increased mortality and decreased OS.[51, 235] These results have led to recommendations of a more restrictive transfusions strategy based on patients' individual needs.

One specific group of patients concerning transfusion is patients with cardiovascular disease (CVD). CVD patients may have an impaired ability to compensate for myocardial oxygen deficiency due to anemia. Anemia is associated with unfavourable clinical outcomes and higher mortality in acute coronary syndrome (ACS), [202, 248] and in patients with heart failure. [99, 142] A Hb level of 10g/dL has often been considered the cut-off for RBC infusion in patients with CVD,[36] but FOCUS study demonstrated that a more liberal transfusion (Hb≤10g/dL) did not decrease mortality in patients with high cardiovascular risk compared to more restrictive transfusion (Hb ≤8g/dL).[37]

More abundant perioperative bleeding and the need for transfusion are connected to decreased overall survival and recurrence of the cancer.[32, 112, 134] There are several studies demonstrating lower survival and increased recurrence rates for patients needing transfusion during head and neck surgery.[13, 106, 169, 223] Marquet et al. (1986) demonstrated modulation on tumour growth when giving an allogenic blood transfusion.[146] Overall, transfusion is more often needed in major surgery with more advanced stage of the disease.

2.2.2 Perioperative fluid management

Perioperative intravenous fluid administration is part of the care of the patient undergoing surgery. The goal of perioperative fluid therapy is often the maintenance of normovolemia and adequate perfusion pressure to vital organs such as the brain, heart, and kidneys.[41, 153]

Normal daily fluid demand for a healthy 70kg adult is approximately 2600mL. Regarding elective surgery, one must consider preoperative 8h fasting, tissue vaporisation, replacement of "third space" fluid loss, and normal bleeding during operation. Thus, the perioperative daily fluid demand for a healthy adult is around 4000mL/day.[234]

In the human body, two-thirds of fluid is located in intracellular space, and remaining extracellular fluid is distributed into the interstitial compartment and blood plasma. The positive intravascular pressure continuously forces fluids towards the interstitial space. In a healthy body, the vascular barrier keeps large molecules in intravascular space and controls the shift of fluids. Any damage on the vascular barrier can lead to an uncontrolled fluid shift towards the extravascular compartment, leading to inadequate circulating volume.[220] Furthermore, hypervolaemia causes impairment in the vascular barrier and leads to tissue oedema.[29, 40]

Excessive perioperative fluid administration and transfusion increase the risk of peri- and postoperative complications.[66, 160, 177] In a randomised observer-blinded multicentre trial, Branstrup et al. could demonstrate that restrictive intraoperative fluid administration (aiming to euvolaemia) was associated with lower incidence of complications after elective colorectal resection.[25] Meta-analysis of perioperative goal-directed fluid administration in noncardiac surgery supported that result.[188] In head and neck surgery, excessive fluid therapy was associated with a higher complication rate in patients with major head and neck surgery, but these studies are limited with relatively small sample sizes and include only patients undergoing major head and neck surgery.[87 66]

2.2.3 Infections

Postoperative infections complicate the recovery of patients after surgery by prolonging the hospital stay and wound healing and increasing morbidity and mortality. Due to infection, the cosmetic and functional result may deteriorate and the patient's QoL may worsen. Postoperative infection may also prolong the initiation of postoperative oncologic treatment. There is evidence that patients who had postoperative infection had a higher incidence of the recurrence of cancer.[84]

In head and neck surgery, 10–45% of patients suffer from postoperative wound infections.[59, 80, 84, 128, 139, 168] Risk factors for postoperative wound infections are comorbidities (e.g., diabetes), high body mass index (BMI), malnutrition, heavy alcohol consumption and smoking, poor oral hygiene, tumour location (clean–contamined wound), advanced tumour stage, preoperative oncologic treatment, high ASA classification, flap reconstruction, need of tracheostomy, extent of the surgery, blood loss, and individual skills of the surgeon.[28, 59, 80, 84, 128, 139, 168, 206] Infection in the head and neck area can be just a superficial surgical site infection (SSI), deep SSI, organ or space SSI, or infection leading to fistula formation by wound disruption.

Surgical wounds have been classified by the Centers for Disease Control and Prevention according to the risk of postoperative infection. Risk is based on the extent of contamination present at the time of surgery.[213]

1) Clean wounds – wounds are made in ideal conditions with no failure in sterile technique occur during the surgery and no infection is present, i.e., parotid or submandibular gland excision or neck dissection.

2) Clean-contaminated wounds – these wounds are originally sterile, but the mucosal barrier is penetrated or the hollow viscus is entered during the operation, i.e., laryngectomy and surgery in oral cavity.

3) Contaminated wounds – these wounds are a consequence of major error in sterile technique or exposure to acute infection, i.e., fresh traumatic wounds.

4) Dirty wounds – infected and/or traumatic wounds with bacteria or environmental debris.

Wounds in head and neck oncologic surgery are mostly in classes 1 or 2 and sometimes in class 3 or 4, especially in revision surgery.

Prophylactic antibiotics are mandatory for clean-contaminated wounds for 24h after the operation. There is no evidence to support longer use of antibiotics as a prophylactic manner.[214] The use of prophylactic antibiotics in clean-contaminated wounds has been proven to reduce the incidence of postoperative infection in several studies.[78, 128, 214, 216, 238] In clean wounds in major head and neck oncologic surgery (i.e., neck dissection), postoperative infections are shown to be reduced when prophylactic antibiotics are used, especially when extensive or radical lymphadenectomy is done or the operation is taking a long time.[52, 145] Antibiotics should cover the basic flora of the upper aerodigestive track, both aerobic and anaerobic.

Pneumonia is a well-known postoperative complication also affecting HNC patients.[39] Infective pneumonias, pneumonias due to aspiration, and ventilator-associated pneumonias can occur. In general surgery, risk factors for pneumonia are advanced age, need for transfusion, poor pulmonary function, prolonged time of surgery (>3 hours), and higher ASA classification.[45, 118, 247] The incidence of postoperative pneumonia in HNC surgery is 1.4–6% [31, 158, 208] and even higher (7.2%) with patients with free tissue transfer surgery.[33] Moreover, many patients need tracheostomy after surgery and the risk of pneumonia is higher (19.7%) for those patients; the predisposing factors include male gender, prolonged need of tracheostomy and smoking.[133] Furthermore, risk factors for pulmonary complications in head and neck surgery are prolonged need for ventilation, ASA >2, BMI >30, male gender, advanced age, smoking, alcohol abuse, history of pulmonary disease, preoperative medication for hypertension, and more frequent admission to ICU.[55, 137] In a large nationwide retrospective database study in the United States (2012), HNC patients who had postoperative pneumonia were more likely to develop other acute medical comorbidities and postoperative surgical complications than patients who did not suffer from pneumonia, and mortality was higher in the group of patients with postoperative pneumonia.[208] In another large national register study from the United States (2017), postoperative pneumonia was associated with 7.2% mortality.[158]

2.2.4 Treatment-specific complications

The HNC treatment can include treatment-specific complications, which can be caused by surgery or oncologic treatment and vary in incidence and in severity as well as how they impact to QoL.

Dysphagia is one of the most common complications in HNC patients. In a large study, containing 8,002 patients, 40% of head and neck patients treated with different modalities experienced dysphagia and the stricture rate was 7–7.2%, respectively.[72, 236] Patients treated with chemoradiation had a 2.5-fold higher incidence of dysphagia compared to those treated with surgery only.[72] Irradiation of the lower neck with IMRT -technique has increased the incidence of dysphagia compared to conventional raditherapy (16.7% vs. 5.7%) due to higher dose delivered to inferior pharyngeal constrictors and cervical esophagus.[236] Dysphagia is associated with morbidity and it has high impact on emotional and physiological health. There are several conservative interventions to improve swallowing inluding modifications to bolus, jaw mobilization devises, swallowing exercises (e.g. effortful swallow), and nonswallow exersises (e.g. headlift).[120] If there is severe dysphagia due to stricture surgical interventions may be needed. Strictura is generally treated with esophageal dilatations with a high success rate (73%), but the result is often transient, and repetitive dilatations are needed.[157]

Free flap success rate is reported to be approximately 95%.[207, 243] Nevertheless, there can be problems jeopardising the flap survival. The independent risk factors related to the increased risk of severe complications include the type of flap used, higher ASA classification, advanced T-stage, and high-volume surgery.[27] Most often, the problems with free flap are related to developed vascular compromise and the flap can be salvaged with early detection and prompt re-exploration if needed.[44] Flap infections with possible necrotic tissue should be treated aggressively with antibiotics and expedient resection of necrotic tissue. However, if the flap is lost, the options are replacement of a second free flap or use a pedicled flap or conservative wound care, possibly followed by closure by secondary intention or with delayed local or skin graft.[243] Exposure of the carotid artery or dura is potentially life-threatening and should be adequately covered by vascularised tissue.

Salivary fistula is a serious complication that can occur after major head and neck surgery. In the head and neck area it can complicate any surgery. It is most often seen in surgery involving oropharyngeal, and hypopharyngeal region where connection to the neck is compounded. It usually occurs in 1-4 weeks after surgery. The breakdown of musculature closure allows saliva to leak into soft tissues causing local infection and fistula formation.[62] The incidence of pharyngocutaneus fistula ranges from 9% to 23% according to the literature.[9, 92, 149, 167] Factors predisposing the patient to fistula formation include patient-related factors, i.e., diabetes, malnutrition, low Hb levels, and peripheral vascular disease, and local factors, i.e., tumour site and stage, pre- or postoperative radiotherapy, and the extent and technique of surgery.[144] Fistula can be treated conservatively but if that is not effective surgical treatment is needed, often with vascularised flap.[62]

Oral mucositis is a common complication after radiotherapy and systemic therapies due to HNC. This adverse event affects approximately 90% of patients treated with radiotherapy due to HNC.[24, 229] The intensity of mucositis defines the magnitude of symptoms. Mild mucositis causes soreness and erythema. Severe mucositis will interfere with oral food intake and cause ulcerations, severe pain, infections, high rates of hospitalisation, decreased QoL, and breaks in treatment, ultimately causing a worse outcome.[21, 60]

Xerostomia or inadequate salivary function is a common complication after head and neck radiotherapy affecting patients' QoL by causing difficulties in speech, swallowing, chewing, and impaired dental health.[241] The generalisation of IMRT in the treatment of HNC has reduced salivary gland toxicity significantly.[38]

Radiotherapy causes tissue toxicity and one of the infrequent manifestations of late toxicity is osteoradionecrosis (ORN). After the introduction of IMRT the incidence of ORN has declined, and reported to be 1.2–6.3%, respectively.[43, 83, 231] ORN is followed by tissue damage and distinguished by necrosis: hypoxic, hypocellular, and hypovascular tissue.[58] The most important counteractive action to prevent ORN is prophylactic oral care prior to, during and after radiotherapy.[103] Treatment of ORN consists of antibiotic use, surgical removal of necrotic tissue and reconstruction with a vascularised flap (if needed), and hyperbaric oxygen.[103]

Furthermore, in the head and neck area, radiotherapy increases the risk of cardiovascular complications mediated via extracranial vascular injury leading to carotid stenosis and damage to the hypothalamus-pituitary sector, causing metabolic syndrome. Radiation can also cause straight injury to brain tissue, leading to haemorrhage, seizures, and cognitive changes.[14, 143] The risk of stroke and transient ischaemic attack (TIA) is at least doubled in patients after head and neck radiotherapy due to the damage of medium- and large arteries[46, 174] and evidence-based guidelines on how to treat asymptomatic and symptomatic radiation-induced vasculopathy of the head and neck are missing.

2.2.5 Major adverse cardiac and cerebrovascular events (MACCE) in non-cardiac surgery

Surgery is always a risk for complications, and even non-cardiac surgery increases the risk for cardiac and cerebrovascular complications[122]. In this thesis, MACCE included acute coronary syndrome (ACS), decompensated heart failure, new onset of atrial fibrillation (AF), TIA, stroke, pulmonary embolism (PE) and venous thromboembolism (VTE), and all-cause mortality. General, non-cardiac surgery causes a 3-4.3% risk for MACCE.[201, 217] Non-cardiac surgery is divided into three classes according to the risk for MACCE in American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA) 2014 guidelines (Table 2.2.5-1).[68, 122]

Table 4. Cardiac risk stratification for non-cardiac surgical procedures modified from ACC/AHA and ESC/ESA guidelines.[68, 122]

High cardiac risk >5%	Emergent major operations, particularly elderly Aortic or major vascular surgery Peripheral vascular surgery Upper abdominal surgery
Intermediate cardiac risk 1-5%	Intraperitoneal and intrathoracic surgery Carotid endarterectomy **Head and neck surgery** Gynecologic surgery Neurosurgery Orthopaedic surgery Urologic surgery
Low cardiac risk <1%	Endoscopic procedures Superficial procedures Cataract surgery Breast surgery Ambulatory surgery

Perioperative risk depends on the magnitude and duration of surgery, the prevalence of comorbidities, and the general condition of the patient prior to surgery.[22, 175]

Smoking and heavy alcohol consumption are the main epidemiological factors for HNC and are also important risk factors for coronary artery disease (CAD). Allready in 1964, Doyle et al., showed a strong connection between smoking and CVD.[63] Smokers have a higher incidence of acute myocardial infarction (MI) and sudden death as well as higher overall mortality due to CAD.[12, 63] Heavy alcohol intake alters the coagulation cascade and can increase the risk of thromboembolic as well as haemorrhagic complications by platelet hyperaggregation, variable effect on fibrinogen concentration, and increasing platelet apoptosis.[94, 141]

Cancer increases the risk of thromboembolic complications, from VTE and arterial thrombosis to disseminated intravascular coagulation.[65, 219] The first publication on the connection between VTE and cancer dates back to 1865.[230] A thromboembolic complication is reported in 1–11% of cancer patients,[96, 219] but there is great variance between cancer sites and types of complication. Coagulation disorders related to cancer are due to tumour cells ability to interact with host cells' and produce and release procoagulant and fibrinolytic substances as well as inflammatory cytokines.[65]

In major HNC surgery, including microvascular reconstruction the risk of MACCE is 12–25% based on the literature.[30, 47, 56, 61] Previous studies have shown that patients' total burden of comorbidities is the most important single risk factor for cardiac complications.[47] Moreover, in two large population-based surveys, both including approximately 35,000 patients with HNC, the most frequent non-cancer-related cause of death was CAD (21–28%).[17, 196]

ACS is a condition where blood supply to myocardium is suddenly blocked, totally or partly, due to plaque rupture or erosion in an epicardial coronary artery. This results in myocardial damage ranging from a few myocardial cells to complete areas of the myocardial wall. Clinical findings and patient symptoms are related to the affected coronary artery. Incidence of acute MI (significant troponin release) in non-cardiac surgery is reported to be 7–35%.[2, 93, 163] MI with ST-elevation (STEMI) is related to 29% 30-day mortality rate in non-cardiac surgery.[163] Early percutaneous coronary intervention has been reported to significantly reduce 30-day mortality due to surgery-related MI.[101] Nevertheless, secondary myocardial damage can also occur because of a mismatch of oxygen demand and supply in the absence of new plaque rupture or erosion in the coronary artery. Major surgery, anaemia, or tachyarrhythmia may account for secondary MI peri- and postoperatively. In these cases, the treatment is focused on the reversal of the primary cause of oxygen demand and supply mismatch, such as treating anaemia and tachyarrhythmia.

Heart failure is a general term for conditions where the heart is not able to pump enough blood to meet the organ's needs. Common causes of heart failure include CAD, hypertension, valvular heart disease, and AF, and it occurs in 3–4% of patients aged 65 and over; 5-year mortality is highly dependent on the aetiology of heart failure, and it ranges from 25% to 75%.[150] Acute decompensated heart failure is diagnosed when there is congestion of fluids in multiple organs due to impaired circulation. A stable situation may become decompensated due to infection, fluid overload (e.g., due to operation), cardiac brady- or tachyarrhythmia, MI, uncontrolled high blood pressure, or failure to maintain diet and medication. Patients operated with diagnosed heart failure have 11.7% 30-day mortality and experience a significant morbidity postoperatively.[91]

AF is the most common cardiac arrhythmia characterised by an irregular and often rapid rhythm. The most common causes of AF are hypertension and valvular heart disease, but there are many factors that can contribute to AF, including MI. The frequency of new-onset AF after non-cardiac surgery is reported to be 2.5%, and independent risk factors include advanced age and type of the surgery.[6]

TIA is a transient deficiency in blood supply to the brain. It causes transient symptoms similar to stroke, but they usually will pass within 24 hours. It needs immediate evaluation, as patients suffering from TIA have a 5.2% risk of stroke within 7 days.[79] Stroke is diagnosed with symptoms (such as motoric or sensoric hemiparesis, difficulties in speech or swallowing, or double vision) due to icshaemia in brain tissue from insufficient blood supply. Clinical characteristics and patient symptoms are related to the area of damage. Aetiological risk factors of stroke include age, genetic factors, physical inactivity, dyslipidaemia, hypertension, obesity, diabetes mellitus, smoking, AF, CVD, and carotid artery stenosis.[151] Perioperative stroke risk is reported to be 0.1–0.7% [15, 108, 148] and as much as 5.4% when patient has had prior stroke.[108] Perioperative stroke involves 16-21% risk for mortality within 30 days.[15, 148] In general, head and neck radiation at least doubles the risk of stroke and TIA.[174]

VTE includes deep venous thrombosis, meaning a blood clot formation in a deep vein usually in the leg, and PE, where the clot detaches and travels to the lungs. The risk of VTE 30 days after operation in otorhinolaryngology is reported to be 1.3%,[211] and in a large retrospective cohort of patients undergoing general surgery, it has been 0.96%.[114] In HNC surgery, the incidence of VTE is relatively low (1–4.8%),[42, 225] and the risk is highest with patients undergoing resection with simultaneous microvascular reconstruction.

2.2.6 Complications in elderly

In a large retrospective study including 594,911 patients, Hamel et al.[86] showed that the incidence of postoperative complications increases with age. However, it is important to distinguish chronological age and biological age. It seems that complications are related to comorbidity increased with age than to the age itself.[56, 170, 192] The patient’s chronological age, physical status, and possible reduced treatment tolerance should be considered in a multidisciplinary team when treatment is planned.

There are many recent studies about the effects of age and comorbidity in HNC surgery but cohorts are often retrospective or quite small. Peters et al.[170] showed that there were slightly more complications in the elderly, but those were more related to comorbidity and type and length of surgery, not significantly to age. No significant difference in infective complications [152, 170] or surgical complications[209, 233] were seen with respect to age in HNC surgery. However, the rate of medical complications increased with age, especially in patients with a history of CVD.[77, 170]

In radiotherapy and chemotherapy, complications are more related to physical health and comorbidities than to age.[70, 173]

2.3 Risk indices

The aim of risk indices is to evaluate the patient's current medical status, enable recommendations to optimise cardiac problems, support the surgeon with treatment decisions, and enhance peri- and postoperative treatment of the patient.[97]

Several risk indices have been developed during the past 40 years to predict peri- and postoperative adverse events, i.e., ACE–27, Charlson Index, and the Cumulative Illness Rating Scale. The best-known and widely used in daily practice is ASA classification.[85] In 1977, Goldman was the first to introduce the risk index for prediction of cardiac complications in patients undergoing surgery.[82]

Prediction of intermediate to high cardiovascular risk in non-cardiac surgery is important. Identification of patients at risk and optimisation of their treatment preoperatively aims to reduce risk.[122] ESC/ESA[122] and ACC/AHA[68] recommended the use of risk indices in preoperative assessments of patients undergoing non-cardiac surgery. Moreover, the United Kingdom national multidisciplinary guidelines for pre-treatment assessment of HNC patients recommends the use of risk indices to predict cardiovascular morbidity.[191] In Finnish university hospitals treating HNC, there is a growing interest on comorbidity evaluation as part of the treatment.

Three different risk indices will be introduced in following chapters. ASA was selected due to its long history in perioperative use. RCRI was selected because it is introduced in United Kingdom national guidelines for HNC. CHA_2DS_2-VASc score was selected because it is commonly used in prediction of thromboembolic complications for patients with AF, and its ability to predict MACCE in preoperative setting has not been evaluated.

2.3.1 ASA classification

The ASA Physical Status Classification was introduced in 1941 by Skalad.[203] The intent of this classification is to describe the general condition of the patient and not the specific anaesthetic or surgical risk. In 1961, the current classification was proposed by Dripps et al. There are different variations of the classification, clinical use containing 5–7 classes; one used in this thesis is introduced in Table 4.[205] Patients with ASA class ≥3 are considered as high risk patients.

ASA classification is widely used and well validated. Sankar et al. (2014)[205] showed in their large cohort of 10,864 patients that ASA classification has moderate inter-rater reliability in clinical practice, as well as, the ability to predict in-hospital mortality and cardiac events. However, in two smaller studies there has been wide variation in ASA classification between the anaesthesiologists.[88, 182] Moreover, non-anaesthesia providers assign ASA with significantly lower accuracy[54] and the result can be biased by the general frailty of the patient. ASA classification is rarely used outside the operating theatre in the preoperative outpatient department.

Table 5. ASA classification.

Class 1:	A normal healthy patient
Class 2:	A patient with mild systemic disease
Class 3:	A patient with severe systemic disease that limits activity but is not incapacitating
Class 4:	A patient with an incapacitating systemic disease that is a constant threat to life
Class 5:	A moribund patient who is not expected to survive for 24h with or without the operation
Class 6:	A patient, declared brain-dead, whose organs are being removed for donor purposes

2.3.2 Revised cardiac risk index

Goldman et al. introduced the first cardiac risk index in 1977[82] and that index was revised by Lee et al. in 1999 to create the RCRI.[127] RCRI is extensively validated and evaluated amongst many clinicians and researchers to be the best currently available cardiac risk predictor index in non-cardiac surgery.[122] This index was designed to predict postoperative MI, pulmonary oedema, ventricular fibrillation, or complete heart block and cardiac arrest. Table 5 presents the six variables the risk index is composed of.[127] The presence of ≥2 variables indicates moderate (7%) to high (11%) complication rate.[127] In HNC surgery, RCRI ≥2 has been reported to be a risk factor for higher 2-year mortality after treatment.[212] RCRI is introduced in the United Kingdom national multidisciplinary guidelines to be used in pre-treatment clinical assessment in HNC.[191] However, it characterises high-risk surgery only as intraperitoneal, intrathoracic, and suprainguinal surgery, and includes some subjective variables sensitive to interpretation.

Table 6. Revised cardiac risk index. (ECG= electrocardiogram, dL=desilitre)

	Lee variables
1.	High-risk surgical procedures (intraperitoneal, intrathoracic, suprainguinal vascular)
2.	History of ischaemic heart disease (history of myocardial infarction, history of abnormal exercise ECG, current complaint of chest pain considered secondary to myocardial ischaemia, use of nitrate therapy, ECG with pathological Q-waves)
3.	History of congestive heart failure (history of congestive heart failure, pulmonary oedema, paroxysmal nocturnal dyspnoea, bilateral rales or S3 gallop, chest radiograph showing pulmonary vascular redistribution)
4.	History of cerebrovascular disease (history of transient ischaemic attack or stroke)
5.	Preoperative treatment with insulin
6.	Preoperative serum creatinine >2.0 mg/dL

2.3.3 CHA_2DS_2-VASc score

The previously used Cardiac Failure, Hypertension, Age, Diabetes, Stroke [doubled] ($CHADS_2$) score was developed from known risk factors for stroke in patients with AF to predict thromboembolic comlications.[75] Because of the simplicity of the $CHADS_2$ score, it rapidly found its place in clinical practice, but over the years some limitations were identified.[111, 113]

In 2010, Lip et al. introduced CHA_2DS_2-VASc score modified from $CHADS_2$. They showed that CHA_2DS_2-VASc score better distinguished patients who were at high vs. low risk for stroke, compared to prior $CHADS_2$. CHA_2DS_2-VASc was validated in a study of patients with non valvular AF followed for 1 year without anticoagulation. Variables included in CHA_2DS_2-VASc score are presented in Table 6.[135] The ESC guideline for the management of patients with atrial fibrillation defines a high-risk patient when score is ≥ 2 for men and ≥ 3 for women.[117] CHA_2DS_2-VASc is widely used in daily clinical practice by general practitioners and cardiologists, which implicates that it is straightforward to use.

There has been growing interest to evaluate the ability of CHA_2DS_2-VASc and its derivates to identify other thromboembolic events in variable patient groups, especially in predicting the risk of acute MI and CAD.[115, 155] The limitation of this score is the lack of some factors predictive to CAD i.e. smoking, and family history of CAD. However, in a prospective study by Modi et al. CHA_2DS_2-VASc score was proven to predict the severity of CAD.[154] CHA_2DS_2-VASc has not previously been used as risk score in preoperative evaluation, and its ability to predict MACCE in HNC surgery has not been studied.

Table 7. CHA_2DS_2-VASc score.

	CHA_2DS_2-VASc score.	**Points**
C	History of congestive heart failure	1
H	Untreated hypertension, or medication for hypertension	1
A_2	Age ≥75 years	2
D	Diabetes mellitus	1
S_2	Prior stroke or transient ischaemic attack or thromboembolism	2
V	Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74	1
Sc	Female sex	1

3 AIMS OF THE STUDY

The general objective of this study was to identify patients at risk for MACCE during the treatment of HNC and to find modifiable factors that could lower the incidence of adverse events.

The specific objectives were:

1. To study the incidence and preoperative risk factors of 30-day MACCE.
2. To assess modifiable peri- and postoperative risk factors of 30-day MACCE.
3. To assess the effect of re-operation due to bleeding on postoperative recovery.
4. To test the predictive performance of risk assessment tools to preoperatively identify patients at high risk for MACCE.

4 MATERIALS AND METHODS

All data for these retrospective studies were collected from a single tertiary care centre at the Turku University Hospital Department of Otorhinolaryngology–Head and Neck Surgery. The catchments area of the hospital is about 1 million residents and the centre takes care of all HNC patients irrespective of ages and comorbidities. This study is part of a wider protocol assessing thrombotic and bleeding events in patients undergoing surgery.[125, 129] The study is registered in Clinical Trials.gov (identifier NCT02563470).

This study was conducted in accordance with the Helsinki Declaration as revised in 2002. The study protocol was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland. Informed consent was not required because of the registry nature of the study.

4.1 Patients and source of data

Inclusion criteria consisted of all consecutive patients (n=456) diagnosed with HNC at Turku University Hospital from 1999 to 2008. The study also included patients who received the palliative treatment. All HNC operations (n=591) were evaluated and included in studies I, II, and III. The patients' first operation due to HNC (n=456) was analysed for study IV. If the treatment fo the patient started in another institute or was not finished in our institute, the patient was excluded from the study. Information was collected by the author from patient files, referral letters, anaesthesiology reports, ICU reports, radiology database, laboratory database, electrocardiograms (ECG), pathology reports, and national Statistics Finland (information about mortality at long-term follow-up). During the study period the 6th and 7th edition of TNM–classification were in use, and preoperative oncologic treatment was normal practice in our clinic.

4.2 Cardiac and cerebrovascular endpoints

Study I assessed the incidence and preoperative risk factors for MACCE 30 days after HNC operation. In study II, we evaluated peri- and postoperative risk factors for MACCE and modifiable factors were searched. Study IV looked for new tools to preoperatively predict adverse cardiac and cerebrovascular events.

Regarding cardiac and cerebrovascular complications, the primary endpoint was a composite of MACCE including ACS, decompensated heart failure, new onset of AF, TIA, stroke, PE, venous embolism, and all-cause mortality; during 30 days after treatment in studies I–IV, and death due to MACCE in the 5-year follow-up in study IV.

Endpoints were adjudicated case by case by a committee consisting of a cardiologist and an otorhinolaryngologist. The criteria for endpoints were as follows. Perioperative MI was verified if a troponin level was >3x the normal 99th percentile level and when there were either symptoms or ST-segment changes in ECG. ST elevations, ST depressions, and T wave inversions were classified according to the guidelines of the ESC. TIA was defined as a focal transient (<24h) neurological deficit adjudicated by a neurologist and stroke as a permanent focal neurological deficit adjudicated by a neurologist and confirmed by CT or MRI. Venous embolism was defined as signs/symptoms of peripheral ischaemia associated with a positive imaging test. Decompensated heart failure was documented if clinical evidence of dyspnoea, and positive findings were discovered in chest X-ray and/or diagnosis confirmed by a cardiologist. AF was diagnosed when new onset of AF was seen in ECG.

4.3 Bleeding-related endpoints

Study III evaluated the re-operation for bleeding and its influence on postoperative recovery. The primary endpoint was re-operation for bleeding. Estimated intraoperative bleeding was a secondary endpoint. The study population was divided into two groups based on the amount of median bleeding, and operations with bleeding equal to or higher than the median were evaluated separately. Re-operation for bleeding as a risk factor for MACCE was evaluated in the 30-day follow-up period.

Major bleeding was defined when a patient received 4 or more red blood cell (RBC) units or had a fatal bleeding event. In studies II–III, patients were studied in two groups based on the amount of intravenous fluids they received on the operation day (≥4000mL vs. <4000mL). Normal daily fluid demand for a healthy adult is 25–35mL/kg (e.g, 1750-2450mL for a 70kg patient), and if the 8h preoperative fasting is considered, the need is ~3300mL. A limit of 4000mL considers the possible tissue vaporisation and normal bleeding during operation. A history of heavy alcohol consumption was defined as the use of ≥20 doses of alcohol weekly.

4.4 Risk indices

Preoperative risk evaluation to find patients at high risk for MACCE during and after operation was studied in work IV. Three different risk scores were evaluated.

Scores included were selected by the criteria presented in the review of the literature section. ASA is a preoperative tool for anaesthesiologists to evaluate patients' risk for complications during anaesthesia. RCRI is validated to evaluate patients' risk for cardiac complications in non-cardiac surgery. The CHA_2DS_2-VASc score is validated to evaluate AF patients' risk for thromboembolic complications. All scores are presented more specifically in the review of the literature section. All scores are well validated although used for different purposes, but RCRI is the only one validated to predict cardiac complications. The preoperative ability of CHA_2DS_2-VASc score to predict MACCE has not been studied.

To investigate how different indices work, we studied their performance to identify MACCE 30 days after treatment, death due to MACCE in the 5-year follow-up, and overall survival in the 5-year follow-up. The primary endpoint was MACCE 30 days after treatment. Study IV was designed to compare CHA_2DS_2-VASc to ASA and RCRI as a predictor of MACCE in HNC procedures. The limits for high risk patients were set according to the limits presented in review of the literature section.

4.5 Statistical analyses

Data are presented as count, frequencies (%), means ± standard deviations, and median [interquartile range] where appropriate. Independent samples t-test were used to analyse continuous variables, and Chi-square test and Fisher's exact for categorical variables as appropriate. Univariate and multivariate logistic regression analyses were used to evaluate the possible predictors of MACCE and death 30 days postoperatively, mortality in the 5-year follow-up, and death due to MACCE in the 5-year follow-up. For each predictor, adjusted odds rations (OR), 95% confidence intervals (CI), and *p*-values were calculated. Significance was set at p-value <0.05.

Kaplan-Meier survival analysis was used in study II. In study IV, Cox -regression was used for survival analysis, and ROC -analysis for sensitivity and specificity of the scores. Analysis was performed with SPSS-statistics 22.0 software for MAC (SPSS Inc., Chicago, Illinois) by the author with a tutorial of the statistician.

5 RESULTS

5.1 Epidemiological aspects

Between 1999 and 2008, a total of 456 patients were treated for HNC at Turku University Hospital, and a total of 591 operations were performed. From all operations, 195 (33%) were performed on females, and the mean age was 62 years. In the study population, 141 patients had the oncologic treatment (81 had only radiation therapy and the rest chemoradiation therapy). Characteristics of the study population are presented in Table 7. During the study period, HPV was not routinely determined.

Table 8. Baseline clinical characteristics and 30-day MACCE in the study population. (Data are presented as median [IQR], count, and percentage). Modified from study I.

Variable	All operations n=591	30-day MACCE n=33	*p*-value
Age (years)	**62 [18]**	**76 [13]**	**<0.001**
Women	**195 (33%)**	**16 (8%)**	**0.041**
Tobacco	369 (62%)	18 (5%)	0.401
Alcohol use	308 (52%)	11 (4%)	0.063
Hypercholesterolaemia	46 (8%)	2 (4%)	0.703
History of heart failure	**22 (4%)**	**4 (18%)**	**0.015**
Coronary artery disease	**57 (10%)**	**9 (16%)**	**0.001**
Prior myocardial infarction	**32 (5%)**	**6 (19%)**	**0.002**
Prior coronary revascularisation	12 (2%)	2 (17%)	0.113
Hypertension	**152 (26%)**	**15 (10%)**	**0.010**
Diabetes mellitus	60 (10%)	6 (10%)	0.123
Atrial fibrillation	29 (5%)	4 (14%)	0.059
Mechanical heart valve	1 (<1%)	0	1.000
Prior transient ischaemic attack or stroke	36 (6%)	2 (6%)	0.994
Prior aspirin medication	**106 (18%)**	**14 (13%)**	**<0.001**
Prior warfarin medication	26 (4%)	1 (4%)	0.695
Prior betablocker medication	**118 (20%)**	**15 (13%)**	**<0.001**
Prior statin medication	72 (12%)	5 (7%)	0.595
Prior cancer	40 (7%)	1 (3%)	0.394

5.2 Incidence and preoperative risk factors for MACCE

In the whole study group, the incidence of 30-day MACCE was 33/456 patients (7.2%), and 12/103 (11.7%) with patients undergoing microvascular surgery. The distribution of operations is presented in Table 8. Median time from operation to MACCE was 3 days.

Table 9. Performed surgery (data presented as count, median, IQR, and percentage). Modified from studies II and III.

Operation	**No. of operations N= 591**	**Median Stage [IQR]**	**Median bleeding (mL) [IQR]**	**No. of re-operations due to post-operative bleeding**	**MACCE n=33**
Panendoscopy ± Tonsillectomy	132 (22%)	-	400 [-]	5	5 (15%)
Local resection in oral cavity	119 (34%)	2 [-]	30 [180]	0	4 (12%)
Local resection + neck dissection	33 (6%)	2 [1]	400 [500]	4	3 (9%)
Neck dissection	68 (12%)	2 [2]	500 [375]	1	2 (6%)
Removal of submandibular or parotic gland + neck dissection	5 (1%)	3 [3]	1000 [2075]	0	0
Resection + temporal plasty	15 (3%)	4 [1]	1000 [988]	1	2 (6%)
Resection + temporal plasty + neck dissection	6 (1%)	4 [1]	2000 [500]	1	1 (3%)
Resection + pectoral plasty + neck dissection	11 (2%)	2.5 [1]	1300 [1238]	1	1 (3%)
Resection + microvascular reconstruction + neck dissection	109 (18%)	3 [1]	1200 [1050]	15	12 (36%)
Laryngectomy	18 (3%)	2 [1]	500 [425]	1	1 (3%)
Laryngectomy + neck dissection	6 (1%)	3 [1]	550 [225]	1	0
Laryngopharyngectomy + neck dissection + microvascular reconstruction	9 (2%)	3 [2]	1400 [1200]	0	1 (3%)
Sublabial rhinotomy	19 (3%)	3 [1]	800 [600]	0	1 (3%)
Other operation	41 (7%)	-	300 [-]	0	0

A number of adverse cardiac and cerebrovascular events as well as their derivatives at a 30-day follow-up are presented in Table 9.

Table 10. Adverse events at 30-day follow-up. (Published with permission)

Endpoint	**n=591**
Acute cardiac or cerebrovascular event	40 (6.8%)
Decompensated heart failure	16 (2.7%)
Acute coronary syndrome	12 (2.0%)
NSTEMI	10 (1.7%)
STEMI	2 (0.3%)
Atrial fibrillation (requiring specialist consultation)	8 (1.4%)
Stroke / transient ischaemic attack	2 (0.3%)
Pulmonary embolism	1 (0.2%)
Venous embolism	1 (0.2%)
Cardiovascular death	6 (1%)

In a binary logistic regression analysis, the univariate predictors of MACCE at the 30-day follow up were use of prophylactic low-molecular weight heparin (LMWH) (OR 5.01, 95% CI 2.37–10.62, p<0.001), history of MI (OR 4.56, 95% CI 1.73–11.97, p=0.002), history of heart failure (OR 4.14, 95% CI 1.32–13.02, p=0.015), pre-existing CAD (OR 3.98, 95% CI 1.75–9.06, p=0.001), prior aspirin medication (OR 3.73, 95% CI 1.81–7.71, p<0.001), prior betablocker medication (OR 3.67, 95% CI 1.79–7.51, p<0.001), hypertension (OR 2.55, 95% CI 1.25–5.19, p=0.010), and increasing age (OR 1.08, 95% CI 1.05–1.12, p<0.001). Independent predictors of MACCE were pre-existing CAD (OR 2.45, 95% CI 1.03–5.80, p =0.042) and increasing age (OR 1.08, 95% CI 1.04-1.11, p<0.001) in a multivariate logistic regression analysis including all the significant univariate predictors in the model.

Patients with pre-treatment evaluation of HNC distributionusing panendoscopy examination as the only form of surgery were analysed separately to evaluate whether MACCE also occurred after minor head and neck oncologic surgery. It was discovered that 5/33 adverse events (including 2 strokes, 1 MI, 1 decompensated heart failure, and 1 AF) occurred after pre-treatment evaluation. All the patients were women with a history of smoking and alcohol use, but only one of them had a history of cardiac comorbidity.

5.3 Peri- and postoperative risk factors for MACCE

MACCE was more often encountered at the 30-day follow-up with patients who received fluids liberally >4000mL/24h compared to those who had ≤4000mL of fluids (10.8% vs. 2.4%, p=<0.001). Moreover, statistically non-significant, slightly increased mortality was seen in patients who received over 4000mL fluids in 24h (3.9% vs. 1.6%, p=0.088). No differences in comorbidities or prior medications were observed, but lower preoperative Hb values were found in patients receiving fluids liberally. They were also younger and more often women.

The median volume of intravenous fluid administration on operation day (24h) was 3000mL [IQR=4000]. Perioperative bleeding rates were higher in patients receiving fluids liberally compared to those with moderate fluid administration (1000mL [IQR=975] vs. 300mL [IQR 350]). However, major bleeding occurred in only 33% of patients hydrated liberally. Patients undergoing microvascular reconstruction surgery (57%) or neck dissection (26%) were the main patient subsets for liberal fluid administration.

Furthermore, incidence of 30-day MACCE was higher for patients receiving RBC transfusion peri- and postoperatively (11.4% vs. 2.7%, p=<0.001), and they also had higher 30-day mortality (3.9% vs. 1.7%, p=0.132). The risk of MACCE increased 18% per unit/litre when analysed per units of RBC transfused or per litres of fluid administered over 4000mL/24h (RBC OR 1.18, 95% CI 1.08–1.30, p<0.001; fluids OR 1.18, 95% CI 1.04–1.34, p=0.012).

All univariate peri- and postoperative predictors of MACCE are presented in Table 10.

Table 11. Univariate predictors of MACCE at 30-day follow-up.

Predictor	OR	95% CI	*p*-value
Excessive fluid administration >4000mL/24h	4.84	2.18–10.75	≤0.001
Red blood cell infusion	4.63	2.18–9.84	≤0.001
Treatment in intensive care unit	2.65	1.28–5.47	0.009
Tracheostomy	2.34	1.13–4.88	0.023
Microvascular reconstructive surgery	2.28	1.07–4.88	0.033

The only independent predictor for 30-day MACCE was >4000mL fluid administration/24h (OR 4.84, 95% CI 2.19–10.75, p<0.001) when analysed in a multivariate model.

Predictors of decompensated heart failure were analysed separately. Total amount of fluids (24h) >4000mL (OR 7.64, 95% CI 2.13–27.42, p=0.002), RBC infusion (OR 7.03, 95% CI 2.24–22.10, p=0.001), use of papaverin (OR 6.74, 95% CI 2.40–18.93, p<0.001), and treatment in ICU (OR 5.65, 95% CI 2.02–15.83, p=0.001) were univariate predictors of MACCE. Furthermore, predictors of ACS were RBC infusion (HR 6.93, 95% CI 1.85–25.89, P=0.004), total fluids (24h) > 4000mL (OR 4.99, 95% CI 1.31–19.03, p=0.019), and treatment in ICU (OR 4.65, 95% CI 1.45–14.89, p=0.010).

5.4 Re-operation for bleeding and its effect on postoperative recovery

Of all operations, the rate of re-operation for bleeding was 31/591 (5%) and it occurred within the first 2 days in 58% of cases (18/31). Older age, gender, comorbidities, smoking, or prior antithrombotic medication (including aspirin and oral anticoagulation) or other patient-related factors had no effect on re-operation risk. Moreover, if the patient had pre-operative oncologic treatment prior to microvascular surgery, the risk of re-operation was significantly higher (18% vs. 6%, p=0.001).

The univariate predictors of re-operation due to bleeding in a binary logistic regression analysis are presented in Table 11.

Table 12. Univariate predictors of re-operation induced by bleeding.

Predictor	OR (95% CI)	*p*-value
Fluids ≥4000mL/24h	4.88 (2.20–10.81)	≤0.001
Intraoperative bleeding ≥700mL	3.55 (1.70–7.41)	0.001
History of heavy alcohol consumption	2.67 (1.23–5.92)	0.014
Preoperative oncologic treatment	2.46 (1.17–5.15)	0.017
Advanced tumour stage	1.42 (1.06–1.90)	0.020
Increasing T classification	1.42 (1.03–1.97)	0.034

Re-operation induced by bleeding turns out to be an independent risk factor for 30-day mortality (OR 5.27, 95% CI 1.39–19.96, p=0.014). For all re-operated patients, the cause of death at 30 days was cardiovascular (CAD or heart failure), and one-third of patients who died had a history of heart failure. However, for 30-day cardiac and cerebrovascular events, re-operation for bleeding was not an independent risk factor.

During the operations, the median estimated bleeding was 700mL [IQR 800]. Increased risk for re-operation induced by bleeding was associated with operations with more excessive (≥700mL) bleeding (p=0.001). Characteristics of operations are presented in Table 5.2-1. Operations predisposing the patient to higher risk for intraoperative bleeding were microvascular reconstruction (82 radial forearm flap, 16 latissimus dorsi flap, 14 fibula flap, 1 crista iliaca flap) or reconstruction using pedicled regional muscle flap (12 pectoral flap, 9 temporal flap, 1 sternocleidomastoids flap, 1 trapezius flap), salivary gland operation with neck dissection, and major sinonasal surgery. Higher tumour stage (p<0.001) and T classification (p<0.001) were also associated with more profuse bleeding intraoperatively.

5.5 Identification of patients at high risk for MACCE by risk indices

From 456 patients undergoing the first procedure for HNC, 213 (46.6%) patients died during the 5-year follow-up, and for 25 (5.5%) patients the primary cause of death was MACCE. Mean follow-up time in study IV was 5.6 [SD 4.3] years. After the index operation, the incidence of MACCE within 30 days was 4.6% (21/456).

In our study, the performance of the CHA_2DS_2-VASc score was compared to ASA-classification and RCRI. Distinction in action of different scores is presented in Table 12.

Table 13. Performance of ASA, RCRI and CHA_2DS_2-VASc score.

	ASA	**RCRI**	**CHA_2DS_2-VASc**
Information available n/456 (%)	440 (93.6)	322 (70.6)	455 (99.8)
Median score [IQR]	1 [1]	0 [0]	1 [3]
High score n/456 (%)	215 (47)	**9 (1.9)**	170 (37)
Risk of 30d MACCE	OR 2.80 (1.50–5.22) p=0.001	OR 2.50 (1.24–5.06) p=0.010	OR 1.67 (1.30–2.14) p<0.001

The rate of 30-day MACCE for a patient who had a low vs. high score in ASA, RCRI, and CHA_2DS_2-VASc score was 1.3% vs. 8.4% (p=0.001), 5.7% vs. 22.2% (p=0.102) and 1.7% vs. 9.4% (p≤0.001), respectively. In ROC –analysis, the AUC (area under curve) value for 30-day MACCE was 0.71 for ASA (highest specificity value 3), 0.62 for RCRI (highest specificity for value 1), 0.70 for CHA2DS2-VASc for women (highest specificity for value 3), and 0.72 for CHA_2DS_2-VASc for men (highest specificity for value 2). The AUC values for ASA and CHA2DS2-VASc were in line with published thresholds but AUC value for RCRI did not meet the published treshold.

Cox regression for overall survival and death due to MACCE in the 5-year follow-up compared to the ASA classification with standardisation to age is presented in Figure 5.5-1 and compared to CHA_2DS_2-VASc in Figure 5.5-2.

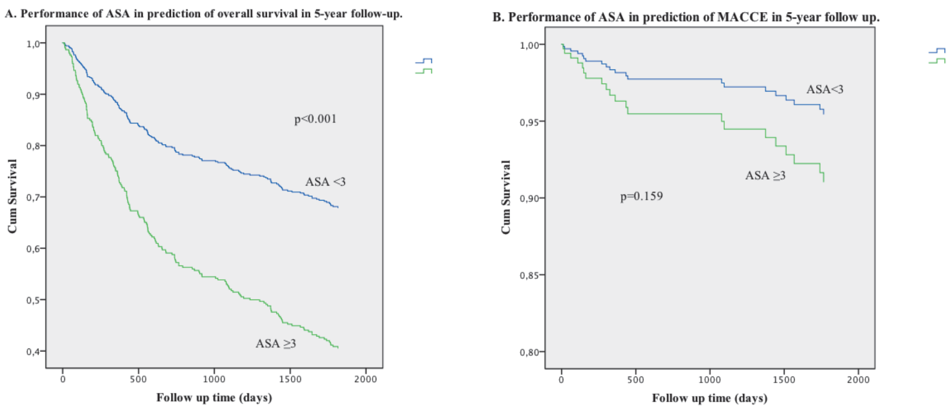

Figure 3. Performance of ASA. Modified from study IV.

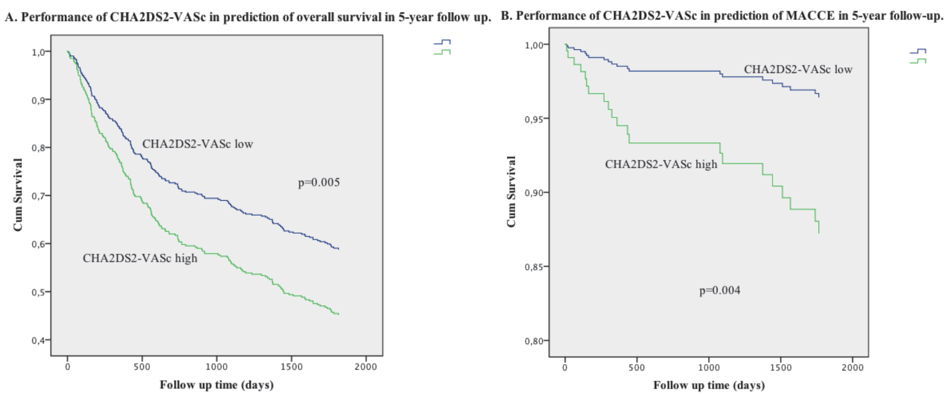

Figure 4. Performance of CHA_2DS_2-VASc (Low: women < 3, men < 2, high: women ≥3, men ≥2). Modified from study IV.

6 DISCUSSION

6.1 Baseline characteristics

Characteristics of HNC patients in this thesis are comparable to those presented earlier in the review of the literature. Overall, males are overexpressed in HNC patients, which was also seen in our population, as only 33% of patients were female. The mean age (62 years) was well in line with national and international statistics.[104] Patients were distributed as younger patients with a history of smoking, heavy alcohol consumption, and possibly HPV, which was not determined at the time, and as older people with increasing incidence of cancer due to age. Smoking and alcohol consumption were the main predisposing factors, and many patients had comorbidities, including CVD such as hypertension, heart failure and CAD. Thirty-one percent of patients had definitive oncologic therapy or adjuvant to surgery.

6.2 Comorbidity and HNC

Cancer-related mortality of HNC has decreased, especially in the past decade, probably because of the increase in HPV,[222] and HNC related mortality is reported to be 48%.[131] Median survival time in patients with HNC varies according to cancer sites. The worst prognosis is in hypopharyngeal cancer (5-year OS 41%) and best in laryngeal cancer (5-year OS 71%).[131] Furthermore, non-cancer-related mortality of patients with non-metastatic SCC of the head and neck was 13% in the 5-year follow-up according to a large population-based cohort study. The most common non-cancer-related causes of death were CAD (28%), obstructive pulmonary disease (8.5%), and cerebrovascular disease (5.6%).[197] Piccirillo et al.[171] studied different cancer sites in a cohort of 3,378 patients and showed that comorbidity displayed an important role in HNC, as a significant percentage of patients (21%) had moderate or severe comorbidities. The burden of comorbidity was higher only in patients with lung and colorectal cancers. Moreover, as diminished toxicity of chemoradiotherapy and overall improved disease control makes HNC prognosis better, a substantial proportion of patients experience non-cancer-related deaths.[210]

In earlier head and neck literature, comorbidity has been used to describe a wide concept of illnesses of variable severity. Because cardiac comorbidities have different aetiologies and treatment modalities and survival, study I focused on the influence of specific comorbidities. Hypertension, CAD, and history of heart failure were significant predictors of 30-day MACCE. Moreover, other severe diseases such as diabetes and history of stroke were not associated with increased risk of MACCE in this material.

Cardiac and cerebrovascular events complicate recovery after surgery and increase mortality and medical cost. Thus, prevention of those events is critical.[165] In major head and neck surgery, the incidence of cardiovascular complications has shown to be as high as 12–25%.[30, 57, 61] In our real world cohort of all HNC patients, incidence of MACCE was 7.2%, and in our subgroup of patients undergoing microvascular surgery it was 11.7%. It is worth noting that MACCE also occurred after minor head and neck surgery: 3.8% of adverse events occurred after pre-treatment endoscopic evaluation. The identification of high-risk patients could improve HNC patient outcome and enable the prevention of adverse events. Therefore, means to better identify patients at high risk for cardiac events after HNC surgery are clinically needed.

6.3 Risk indices

There is an unmet need for an effective tool to preoperatively predict cardiovascular complications in HNC surgery. Many risk indices have been introduced to identify patients at high risk for complications. The most commonly used index is the ASA classification, which intends to describe the general condition of the patient rather than any specific complication. It is widely used, but probably due to its subjective nature[182, 186, 205] and poor performance in the hands of surgeons,[54] it has not really emerged out of the operating theatre. In our study, ASA performed well in the prediction of 30-day MACCE after treatment and overall survival, but was not specific to death due to MACCE in 5-year follow-up. Furthermore, in this study the ASA class information was collected from anaesthesia reports and were therefore originally assessed by anaesthesiologists. There is a large retrospective study of 10,864 patients showing that the ASA rating in the operation theatre predicts significantly better myocardial injury compared to preoperative clinical ratings, even though it had only moderate inter-rater reliability.[205]

In comparison to ASA, RCRI is well validated in non-cardiac surgery[19, 127] and is recommended to predict cardiovascular complications,[191] but in the present data, the lack of information prevented a real evaluation of its performance mostly due to a lack of preoperative laboratory tests and recently analysed ECG needed for RCRI. An easy-to-use index should include only routinely collected elements in the pretreatment evaluation of a multidisciplinary team. The other weakness of

RCRI is that it identifies only a limited number of high-risk procedures (intraperitoneal, intrathoracic, and suprainguinal vascular surgery), and all others are classified as low-risk procedures.

It is even suggested that comorbidity burden should be integrated in the TNM-classification system to increase the predictive value of staging the disease. ACE-27 and Comorbidity Index are both validated in HNC to predict survival and complications, but include over 20 elements and are not easily incorporated into daily practice but serve well in scientific use.[164, 171, 204, 215]

Study IV introduced a well-validated CHA_2DS_2-VASc score and studied its performance in predicting MACCE in the HNC population. The CHA_2DS_2-VASc score is validated for predicting stroke and thromboembolic complications in patients with AF[135] and is widely used in daily practice by cardiologists and general practitioners.

Equally to ASA, CHA_2DS_2-VASc had good predictive value for 30-day MACCE, overall survival, and death due to MACCE in 5-year follow-up. In addition to anaesthesiologists' ASA, CHA_2DS_2-VASc could improve the preoperative identification of patients at high risk for cardiovascular complications during surgery. With assistance of CHA_2DS_2-VASc, patient comorbidities could be easily evaluated by a multidisciplinary team. Consciousness of the comorbidity burden would help optimise the patient perioperatively and guide treatment choices in the peri- and postoperative period.

It is commonly agreed that comorbidity burden is relevant for the evaluation of prognosis, and head and neck surgeons should routinely pay attention to this matter before treatment and during follow-up to decrease non-cancer-related mortality. CHA_2DS_2-VASc could be used in addition to anaesthesiologists' ASA to highlight the risk of cardiac complications and optimise treatment.

6.4 Peri- and postoperative predictors of MACCE

6.4.1 Excessive fluid administration

Findings in study II provide evidence that, despite the comorbidities, operated HNC patients receiving more than 4000mL fluids perioperatively (24h) clearly had an elevated risk for 30-day MACCE. Patients receiving excessive intravenous fluid administration had nearly 5-fold risk for MACCE. Strikingly, every administered litre of fluid exceeding 4000mL increased the risk of MACCE by 18%.

In patients undergoing head and neck surgery, the incidence of cardiovascular complications is highest within the first days after operation,[30] in our study, the median was 3 days. Consequently, it is likely that the amount of fluids given peri- and postoperatively is one of the important contributors of this finding. Postoperative weight increase up to 3–4kg is likely with standard fluid administration,[25, 136] and increased fluid load is connected to pulmonary oedema.[25] In randomised observer blinded multicentre trial by Brandstrup et al.,[25] increase in the amount of fluid given and increase in body weight on the day of operation were both predictors of higher complication rate. Moreover, complication rate was significantly higher in the standard fluid administration group compared to the restrictive group (51% vs. 33%).[25] Previous literature has failed to set the limit for liberal fluid transfusion; in study II, fluid administration exceeding 4000mL was connected to an increased risk of MACCE. Additionally, when perioperative risk factors were evaluated in a multivariate model, administration of fluids >4000mL (24h) remained as the only predictor of MACCE (OR 4.84). These results support the data that adequate replacement of fluids seems to have the power to improve patient outcome.[41]

The amount of fluids given to a patient is self-evidently dependent on the type of surgery. In major head and neck surgery, the operation usually takes many hours and fluids are needed to replace blood and evaporation of tissue fluid and to maintain adequate perfusion pressure levels. According to the results of study II, in univariate analysis, microvascular surgery increased the risk of MACCE 2.3-fold and operations including microvascular reconstruction included increased MACCE risk compared to the whole study population (11.7% vs. 7.2%). In our study, the main subset for liberal fluid administration consists of patients undergoing microvascular surgery (57%) and neck dissection (26%), supporting the fact that increased risk of MACCE in major HNC operations is partly due to fluid overload.

Furthermore, in previous studies of major head and neck surgery, excessive intraoperative fluid administration was associated with higher complication rate.[66, 87] Complications related to excessive fluid administration include bleeding, pneumonia, renal failure, and wound infection.[25] When the risk of re-operation due to bleeding was investigated in study III, there was a 4.8-fold increase in risk with fluid administration >4000mL/24h. Postoperative fluid overload increases mortality risk,[140] but with goal-directed fluid therapy it is possible to significantly reduce the risk.[187] Our results indicate a tendency towards higher mortality 30 days after operation with excessive fluid administration, but the difference is not statistically significant.

HNC patients receiving excessive intravenous fluid administration peri- and postoperatively were at high risk for cardiac complication, especially decompensated heart failure. Perioperative fluid administration should be considered more carefully, especially in patients with prior CAD or congestive heart failure.

6.4.2 Bleeding and transfusion

In surgery, there is always a risk for major bleeding. British obstetrician James Blundell made the first successful human-to-human blood transfusion in the 1820s for a woman who suffered post-partum haemorrhage.[18] This was decades before Nobel winner Landsteiner identified different blood groups.[124] Since then, we have made great progress in transfusion safety and one can only guess how many lives have been saved. However, there are still many unsolved problems connected to transfusion, especially concerning patients with ACS, due to lack of randomised trials.

The head and neck area gets its blood supply from the arteria subclavia and common carotid artery, and the area is highly vascular. In our cohort, major bleeding was reported in 12% of HNC operations. In the current study, re-operation due to bleeding occurred in 5% of all operations and within the first 2 days in 58% cases. Re-operation due to postoperative bleeding is related to higher mortality, complicates the recovery, and can increase the cost due to longer hospital stay.[73, 147, 240] In study III, re-operation due to bleeding increased the risk of 30-day mortality. Oncologic treatment prior to surgery, especially chemoradiation, weakens the anatomical structures and induces scarring, which complicates operations. We reported the risk of re-operation to be significantly higher in patients who underwent microvascular surgery with pre-operative oncologic treatment compared to those without pre-operative oncologic treatment (18% vs. 6%, $p=0.001$). More advanced tumour stage and increased T classification were also risk factors for re-operation due to postoperative bleeding, both referring to more extensive surgery. Heavy alcohol consumption has both increasing and decreasing effects on coagulation and increased risk for bleeding complications as well as for MACCE.[172] In study I, heavy alcohol consumption did not increase the risk of MACCE, but did have a 2.7-fold increase in the risk of re-operation due to bleeding in study III. Re-operation due to bleeding was not an independent predictor of MACCE.

In recent years, there has been a growing interest in RBC transfusion and whether we should be more restrictive with it. Several studies have been conducted to compare mortality and complications in restrictive and standard transfusion groups.[37, 89] A systematic Cochrain review of 12,587 patients showed no increase in 30-day mortality or in cardiac complications with a more restrictive transfusion strategy (Hb threshold 7g/dL to 8g/dL) compared to the standard transfusion threshold (Hb 9g/dL to 10g/dL).[35] The same result was reported in a large meta-analysis by Holst et al.[98] Flap-related complications did not increase with the restrictive transfusion treshold nor with the standard, but other perioperative complications increased with the standard transfusion and a more restrictive strategy is recommended in free flap surgery.[179, 199]

In 2016, the AABB (American Association of Blood Banks) provided guidelines for RBC transfusion thresholds. They recommend with strong evidence that restrictive transfusion strategy, threshold 7g/dL, is preferred for hospitalised haemodynamically stable adult patients including critically ill, and with moderate evidence that Hb threshold 8g/dL is preferred for those with pre-existing CVD. Due to insufficient evidence, no formal recommendations for patients with ACS are presented in the current guidelines.[34]

The association between mortality and blood transfusion is controversial. In a multicentre, randomised trial of critically ill patients, Herbert et al. did not find any difference in overall 30-day mortality between liberal and standard transfusion groups. However, mortality was significantly lower in the restrictive group with patients <55 years and less ill.[89] We could not indicate higher 30-day mortality for patients who received RBCs, but there was a tendency towards higher mortality (3.9% vs. 1.7%, p=0.132). Nevertheless, in patients undergoing vascular surgery, there is an independently increased risk of all-cause mortality with perioperative transfusion,[232] and in Corwin et al., mortality risk was increased by the number of RBC units transferred.[50]

Patients with cardiac comorbidity such as CAD and heart failure are prone to events if blood transfusion is needed. Blood transfusions may also increase thrombogenecity. Nevertheless, anaemia is reported to increase mortality and serious morbidity for patients with CVD.[36, 100, 248] Especially in patients with ischaemic heart disease, sufficient oxygen supply should be secured to avoid ischaemia. Moreover, patients with heart failure are sensitive to circulatory overload,[49, 159] which may result in decompensated heart failure. Significantly, in this study of the HNC population, RBC transfusion increased the risk of MACCE more than 4-fold, and every unit of RBC transfused increased MACCE by 18%. Previously, it was suggested by Sunil et al. and by Garfinkle et al. that blood transfusion to patients with acute ischaemic heart disease increases mortality and more conservative transfusion strategies should be considered.[76, 183]

This thesis provides evidence that more restrictive transfusion strategies could also be beneficial in HNC patients who undergo surgery.

6.4.3 Other factors increasing the risk of MACCE

Patients undergoing surgery which included postoperative treatment in the ICU, had a 2.75-fold increase in the risk of MACCE in univariate analysis and ICU treatment was also an independent predictor of ACS and heart failure. In Boss et al., overall mortality for cancer patients treated in the ICU after operations was 1.4%.[23] The mortality rate for patients treated in the ICU was as high as 4.4% in our cohort. It is obvious that it included patients with more advanced disease. However, according to literature, death for cancer patients treated in the ICU is more often caused by multi-organ failure, overall performance status, and need of mechanical ventilation than by the severity of cancer.[218] Early extubation, spontaneous breathing, and treatment in a non-ICU unit should also be considered for HNC surgery patients after complex microvascular surgery according to some preliminary studies.[11, 48, 166] Other risk factors were microvascular surgery and need of tracheostomy. All these factors refer to major HNC surgery.

6.5 Limitations

This study has all the limitations that come with its retrospective nature and its being a single-centre cohort, including individual risk-based decisions in the treatment planning. Nevertheless, the strength of this thesis is the inclusion of a real-world cohort of all HNC patients with a wide variety of operations. That gives us information about the unselected population similar to our daily practice. The retrospective nature of the study excluded some variables that we would have liked to include in our analyses, e.g., urine outcome (measured only for patients undergoing microvascular surgery). However, we had access to all patient files, including referral letters, anaesthesiology reports, ICU reports, laboratory database, radiology database, ECG, transfusion reports, pathology reports, and national Statistics Finland, as well as notifications from the ward to utilise a wide quantity of information. Furthermore, all adverse events were re-evaluated case by case by an adjudication committee consisting of cardiologist and otorhinolaryngologist to verify the diagnoses. Results of this thesis are well in line with previous publications and bring new information to use in daily clinical practice.

7 CONCLUSIONS

On the basis of the retrospective clinical study the following conclusions are drawn:

1. Incidence of MACCE was 7.2% in 30-days in patients treated for HNC, with the highest incidence in patients undergoing microvascular surgery. Increasing age and history of CAD, hypertension, and heart failure were significant preoperative risk factors of 30-day MACCE.

2. Excessive fluid administration (>4000mL/24h) and RBC transfusion increased the risk of 30-day MACCE nearly 5-fold and every litre of fluids exceeding 4000mL and every unit of RBCs increases the risk by 18%. Excessive fluid administration was an independent predictor of 30-day MACCE postoperatively. These results suggest that more restrictive fluid admission could be beneficial to HNC patients undergoing surgery. Moreover, individualised transfusion strategy with consideration of pros and cons might be beneficial to HNC patients.

3. Re-operation due to bleeding increases the risk of 30-day mortality more than 5-fold, but did not increase the risk of 30-day MACCE. This finding underscores the need for careful haemostasis during index surgery.

4. The CHA_2DS_2-VASc score reliably predicted the risk for 30-day MACCE and could be used as a preoperative risk index in multidisciplinary treatment planning of HNC patients to highlight patients at risk and to optimise their treatment.

8 FUTURE PROSPECTS

Following to the results of study II, there has been a growing awareness in our hospital considering fluid and blood transfusion to patients undergoing HNC surgery. In the following years, it would be of great interest to make a follow-up study and see if we have been able to introduce more restrictive fluid strategy, and if so, study its effects on the incidence of 30-day MACCE after surgery.

Based on the findings of this project, we have started a multicentre prospective study concerning surgery-related bleeding in HNC patients. It will provide more information about the effect of acetylsalicylic acid on surgical bleeding and post-operative bleeding complications.

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