Complications After Thyroid Surgery

Salem, Farhad

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

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Farhad A. Salem MD.

LUND UNIVERSITY

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Prof. Oliver Gimm
Linköping University

LUND UNIVERSITY
Faculty of Medicine

Department of Clinical Sciences

Author: Farhad A. Salem

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Abstract

Background: Thyroidectomy is a common surgical procedure performed worldwide. Postoperative complications can be life-threatening. Many efforts have been made during the last century to reduce the burden of postoperative complications, with remarkable achievements. However, there are still many patients suffering.
Aims: the main aims of the first three studies were to understand risk factors for infection, postoperative bleeding, and hypocalcaemia after thyroidectomy. The fourth study aimed to understand the life expectancy in elderly patients (80 or older) undergoing thyroid surgery for benign thyroid disorders.
Methods: The Scandinavian Quality Register for Thyroid, Parathyroid, and Adrenal Surgery (SQRTPA), a nationwide database for thyroid surgery, was used for patient data collection. Studies I and II used a nested case-control design, and attending surgeons were asked to add further data on cases and controls. For studies III and IV, data from the SQRTPA were used along with data from the National Health Care Registers; the Swedish Prescribed Drug Register, and the Swedish Cause of Death Register.
Results: In study I, multiple regression analysis showed that risk factors for postoperative bleeding were male gender, high age, and use of a drain, with odds ratios (ORs) and corresponding 95 % confidence intervals (95 % CIs) of 2.2 (1.6-3.0), 3.6(1.8-7.4), and 1.7(1.1-2.7) respectively. In study II, adjusted multiple regression showed that risk factors for postoperative surgical site infection were lymph node dissection and use of a drain, with OR (95 % CI) 3.2(1.3-7.8) and 1.8(1.04-3.2) respectively. In study III, central lymph node dissection was an independent risk factor for postoperative permanent hypoparathyroidism in patients operated for papillary thyroid cancer with OR (95 % CI) of 3.7(1.5-9.6). In patients operated with total thyroidectomy and central lymph node dissection, node-negativity was a risk factor for permanent hypoparathyroidism and had an OR (95 % CI) of 3.1(1.3-7.2). In study IV, apart from age, no other risk factors were found for death after thyroid surgery for benign thyroid disease. The median (IQR) follow-up time was 4.5 (2.9-7.2) years, and the median (IQR) survival time was 8.0 (4.1-12.5) years. The standardised mortality ratio was 0.76 for women and 0.67 for men.
Conclusions: In thyroid surgery, high age, male gender, and the use of a drain are independent risk factors for postoperative bleeding. Lymph node dissection and the use of a drain are independent risk factors for surgical site infection. Central lymph node dissection is an independent risk factor for postoperative permanent hypoparathyroidism in patients operated for papillary thyroid cancer; those with negative lymph nodes have a higher risk. Mortality in patients aged 80 years or older undergoing thyroid surgery for benign thyroid disease is lower than the general population, with no specific risk factors apart from age.

Keywords: Thyroid Surgery, Risk factors, Complications, Mortality, Aged patients

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Farhad A. Salem MD.

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to my beloved family

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Abbreviations

APTT	Activated Partial Thromboplastin Time
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CI	Confidence Interval
CLND	Central Lymph Node Dissection
IONM	Intraoperative Nerve Monitoring
IQR	Interquartile Range
NIM	Nerve Integrity Monitor
OR	Odds Ratio
PT-INR	Prothrombin Time – International Normalised Ratio
SQRTPA	Scandinavian Quality Register for Thyroid, Parathyroid, and Adrenal Surgery
SSI	Surgical Site Infection
TSH	Thyroid-Stimulating Hormone
TT	Total Thyroidectomy

Thesis at a glance

Paper	Title	Type of study	Conclusion
I	Evaluating risk factors for re-exploration due to neck haematoma after thyroid surgery.	Multi-centric Retrospective Nested case-control Observational	High age, male gender, and the use of a drain are independent risk factors for bleeding after thyroid surgery. Even with careful patient selection for day surgery, prolonged observation might be necessary.
II	A nested case-control study on the risk of surgical site infection after thyroid surgery.	Multi-centric Retrospective Nested case-control Observational	Lymph node dissection and the use of a drain are independent risk factors for surgical site infection after thyroidectomy. Antibiotic prophylaxis might be considered in patients with these risk factors.
III	Central lymph node dissection and permanent hypoparathyroidism after total thyroidectomy for papillary thyroid cancer. Population-based study.	Multi-centric Retrospective Observational	Central lymph node dissection is an independent risk factor for permanent hypoparathyroidism. Node-negativity is associated with a higher risk of permanent hypoparathyroidism compared with node positivity.
IV	Mortality in patients 80 years or older after thyroid surgery for benign thyroid diseases.	Multi-centric Retrospective Observational	Mortality after surgery for benign thyroid disease in patients 80 years or older was lower than the general population with no specific risk factors for death except for age.

Introduction

Historical background

Thyroid surgery was practised as far back as 500 A.D[1]. Historical documentation from Salerno, Italy shows that in the 12th and 13th centuries, surgeries were performed on patients with enlargement of the thyroid gland. Most of the patients who underwent surgery died or had complications[1,2]. With a very high mortality rate due to per- and postoperative haemorrhage, thyroid surgery was banned by the French Academy of Medicine as late as the mid 19th century[3,4]. Many surgeons, such as Diffenbach from Germany, Liston from the United Kingdom, and Gross from the United States criticised thyroid surgery as “horrid butchery” and demanded that surgeons performing such operations should be rebuked. They declared that “no honest and sensible surgeon would ever engage in it”[5,6]. Meanwhile, surgeons such as Theodor Billroth and his brilliant student Theodor Kocher (Figure 1) changed thyroid surgery. By introducing antisepsis and haemostasis in thyroid surgery, Billroth succeeded in minimising the mortality rate in thyroid surgery to around 10%. Kocher developed the surgical technique, and lowered the mortality rate from 12.6% in 1870 to 0.2% in 1898[1]. He was later praised as “The Father of Modern Thyroid Surgery”[7] and awarded the Nobel prize in 1909[8,9]. Bern, the city where Kocher lived, became the world’s capital for thyroid surgery. Kocher also discovered the endocrine function of the thyroid gland together with Jaques-Louis Reveridin of Geneva. In 1883 Kocher presented a paper on adverse effects after thyroidectomy, which he termed c*achexia strumiprivia,* showing that the thyroid gland has a function that is important for the metabolism in the whole body. William Halsted, who observed both Billroth´s and Kocher´s operations, described Kocher´s operative technique on thyroid as bloodless with the removal of most of the thyroid tissue and preserving the surrounding structures, whereas Billroth´s operation technique used a more rapid approach resulting in the injury of surrounding structures and larger retained segments of the thyroid gland. The latter resulted in Billroth’s patients having fewer problems with myxoedema (severe hypothyroidism) postoperatively compared to Kocher's patients[1]. At the end of the 19th-century thyroid surgery was no longer “horrid butchery” nor “deserving of rebuke and condemnation”.

It is also worth recalling the surgeons William Halsted, Johann von Mikulic, Charles Mayo, George W. Crile, Rank Lahey, Thomas P. Dunhill, F.A. Coller, and

A.M. Boydena for their contributions in minimising complications during and after thyroid surgery[5].

Since the end of the 19th century, contributions such as a better understanding of the anatomy and function of the thyroid and parathyroid glands along with the efforts to preserve parathyroid glands and the integrity of the recurrent laryngeal nerve have been made[3]. The superior laryngeal nerve was revealed and described in 1935 when the world-famous opera singer Amelita Galli-Curci underwent thyroid surgery and unfortunately lost her soprano voice, which adversely impacted on her singing career[10]. Scientific reports about this complication were published at the end of the century and preserving the superior laryngeal nerve was advocated[11]. Since the middle of the 20th century, many studies worldwide have been performed to recognise and better understand the risk factors to avoid complications during and after thyroid surgery. These efforts have certainly resulted in a further reduction of per- and postoperative complications[12].

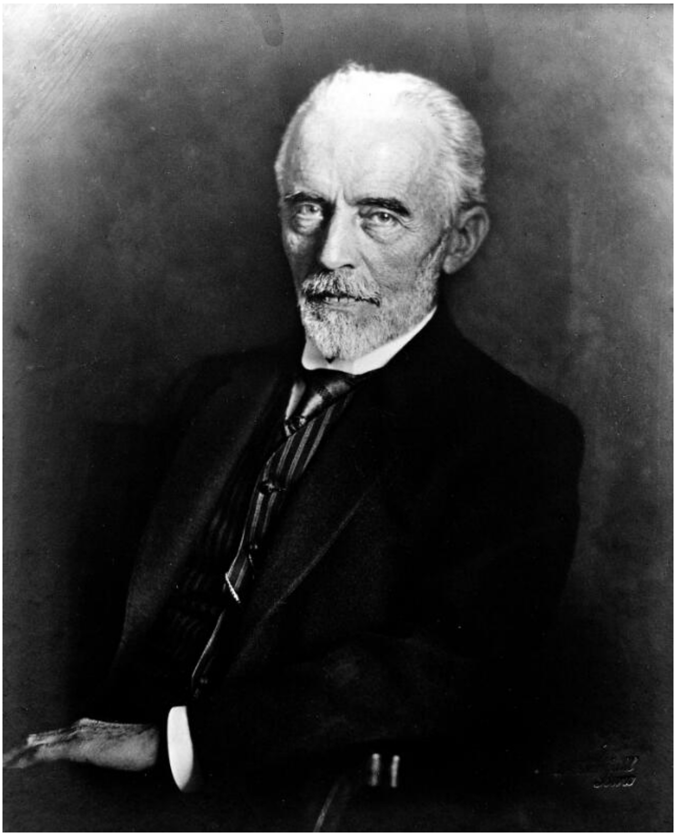

Figure 1. "Theodor Kocher" by L. Zumbühl is licensed under CC BY 4.0.

Embryology of the thyroid gland

The thyroid gland develops between the third and eleventh gestation weeks. It originates from two sources: the primitive pharynx and the neural crest. The primitive pharynx migrating downwards from the base of the tongue along the midline builds the main medial thyroid *anlage*. In 55-76% of people, it also forms the pyramidal lobe, which is a remnant of the thyroglossal tract. The neural crest builds the lateral *anlages*, which fuse laterally with the developing medial body and form up to 30 percent of the gland mass called the Zuckerkandl tubercles. Patho-anatomical variations occur, such as a thyroglossal duct cyst, which is the result of incomplete involution of the thyroglossal duct. This occurs in approximately 7% of people worldwide. Ectopic thyroid tissue can also be formed due to the failure of proper migration of the thyroid gland, mostly occurring at the base of the tongue. Extensive migration can also lead to ectopic thyroid tissue in the superior mediastinum and/or pericardially[13,14]. See figure 2.

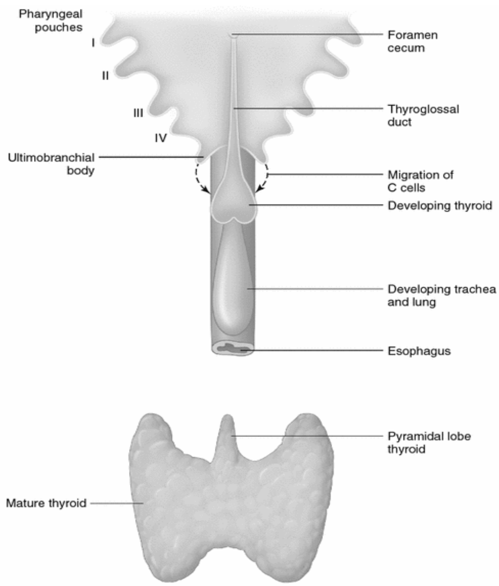

Figure 2. Thyroid gland Embryology. Reprinted with permission from the copyright holder Springer.

Anatomy of the thyroid gland

The word ‘thyroid’ is Greek, which means shield, and is used for the gland due to its shape and position in the neck[15]. The thyroid is a butterfly-shaped gland with two lateral lobes that are connected by the thyroid isthmus. The gland is located anteriorly in the centre of the neck, between the left and right strap muscles (mm.

sternothyroid, sternohyoid, thyrohyoid, and omohyoid), and in front of the trachea[16]. It is a highly vascularised gland with four main arteries and six main veins (Figures 3). The two superior thyroid arteries on each side originate from the ipsilateral external carotid arteries, and the two inferior thyroid arteries originate from the ipsilateral thyrocervical trunk (a branch of the subclavian artery). The two superior thyroid veins and two middle thyroid veins drain into the internal jugular vein on the ipsilateral side. The inferior thyroid veins from both sides drain into the left brachiocephalic vein. There are also several small vessels entering the thyroid gland from the area of Berry's ligament, that attaches the thyroid gland to the trachea[17]. The adjacent organs to the thyroid gland are the strap neck muscles anteriorly, the larynx, trachea, pharynx, oesophagus, the external branch of the superior laryngeal nerve, recurrent laryngeal nerve, and parathyroid glands posteromedially, and the carotid sheet including the internal jugular vein, common carotid artery, and vagus nerve posterolaterally. The lymphatic vessels consist of two sets. An upper set accompany the superior thyroid veins and drain into the upper deep nodes of the cervical chain. A lower set drain to the lower nodes of the cervical plexus, supraclavicular, paratracheal, and parapharyngeal nodes. The lymphatic nodes in the neck are classified in different regions to assess in evaluating the spread of primary head and neck tumors[18]. (Figure 4). The central lymph nodes are classified as region VI and the lateral lymph nodes are classified as regions I-IV. Region VII denotes lymph nodes in the upper mediastinum.

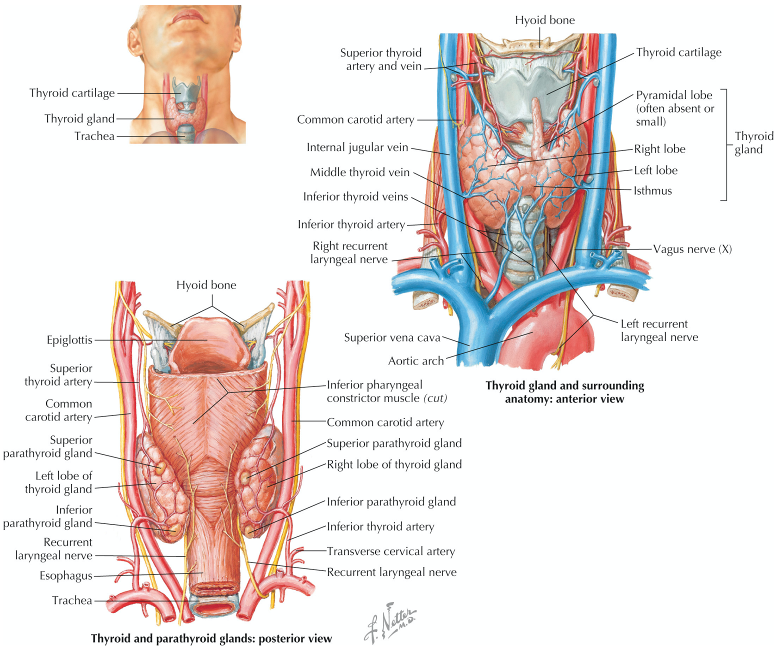

Figure 3. Thyroid Anatomy, anterior and posterior view. Reprinted with permission from the copyright holder Elsevier.

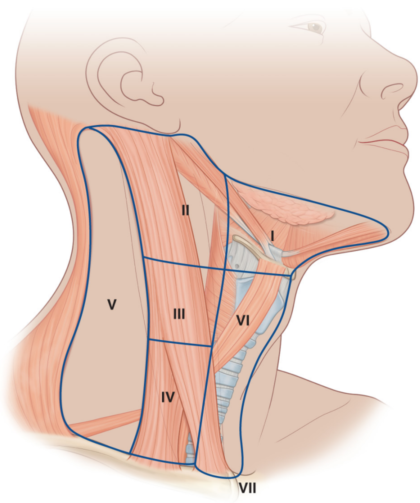

Figure 4. Neck regions used clinically to evaluate lymph nodes. Reprinted with permission from the copyright holder Elsevier

The upper parathyroid glands are usually located dorsal to the recurrent laryngeal nerve in the level where the inferior thyroid artery enters the gland. The lower parathyroid glands, on the other hand, are usually located ventral to the recurrent laryngeal nerve, just below or attached to the lower thyroid lobe[19,20]. Knowledge about the variations and the course of the recurrent laryngeal nerve, the different anatomical positions of the parathyroid glands, and the layout of the lymphatic compartments is necessary for all thyroid surgeons managing patients with thyroid disorders.

Physiology of the thyroid gland

The main function of the thyroid gland is to secrete hormones that regulate metabolism in the human body. The two main bioactive thyroid hormones are thyroxine (T4) and triiodothyronine (T3). These hormones are synthesised in the follicles of the gland and secreted through the attached capillaries into the blood system. The peripheral conversion from T4 to T3 increases the binding affinity of thyroid hormone for the nuclear thyroid receptor protein at least 10-fold. The synthesis of these hormones is regulated by the pituitary gland, which secretes the thyroid-stimulating hormone (TSH). Iodine is an essential substance in the synthesis of the active form of the thyroid hormone. Ultimately, the physiological actions of the thyroid hormones T3 and T4 relate to growth, calorigenesis, and TSH suppression[21,22]. The thyroid gland also secretes calcitonin from the parafollicular cells or C-cells. Exogenous calcitonin decreases blood calcium levels and maintains calcium homeostasis. However, the precise role of endogenous calcitonin in humans remains elusive[23].

Thyroid disorders demanding surgery

1: Thyroid cancer

The incidence of thyroid cancer is increasing worldwide[24,25]. In the United States, 2% of all new malignant tumours are related to the thyroid gland, which makes it the most common endocrine malignancy[26]. In Sweden, the yearly incidence of thyroid cancer is 4.5 – 6 /100,000[27]. The main treatment of thyroid cancer is surgery[28]. There are four main types of thyroid cancer: papillary, follicular, medullary, and anaplastic thyroid cancer. Papillary and follicular thyroid cancers originate from follicular thyroid cells, whereas medullary thyroid cancer originates from the C-cells. Anaplastic thyroid cancer is a highly aggressive, poorly differentiated cancer, characterised by the uncontrolled growth of cells that no longer resemble original thyroid cells. Total thyroidectomy (TT) with or without central lymph node dissection (CLND) is the standard primary treatment in the surgical management of papillary, follicular, and medullary thyroid cancers. In patients with small size papillary or follicular thyroid cancer (less than four centimetres and without vascular invasion) a lobectomy or hemithyroidectomy is a possible procedure[29,30], although the Swedish national guidelines recommend a total thyroidectomy[31]. In anaplastic thyroid cancer, different treatments such as surgery, radiotherapy, and chemotherapy are practised to control the tumour burden due to its highly aggressive character[29]. A rapid diagnostic approach and careful decision making in a multi-disciplinary team conference to decide upon the most appropriate multimodal treatment is necessary and may provide benefit for the patient[32,33].

2: Benign thyroid diseases

Surgery is one of the treatment possibilities for some benign thyroid disorders e.g., goitre causing compression symptoms, Graves´ disease, and toxic adenomas causing hyperthyroidism[34]. Goitre with compression symptoms is most often treated with thyroidectomy. The enlarged gland can displace adjacent organs, making surgery challenging. Total thyroidectomy, lobectomy, or isthmus resection are standard procedures for managing goitre with compression symptoms[35].

Graves´ disease, an autoimmune thyroiditis, is the most common cause of hyperthyroidism. Total thyroidectomy is the treatment of choice when medical therapy by thyrostatic drugs fails to control the disease and radio-iodine therapy is contraindicated. In some patients, for instance, those with severe Graves´

ophthalmopathy, patients with Graves´ disease expecting pregnancy, and drug-induced thyrotoxicosis, surgery is the first-choice therapy[36].

Surgical approaches in thyroid surgery

1: The conventional method

The conventional thyroid operation is with an open technique through a horizontal incision in the front of the neck, known as Kocher´s incision. The dissection starts with one of the thyroid gland lobes and is performed as close to the thyroid capsule as possible. During the dissection, the parathyroid glands, the external branch of the superior laryngeal nerves, and the recurrent laryngeal nerves are identified and preserved[37]. For identification and monitoring of the nerves of the vocal cords, the Nerve Integrity Monitor (NIM) can be used[38] (Figure 5). The function of the nerves is checked before and after the dissection. The parathyroid glands are preserved with their vessels (pedicles) and observed visually by the surgeon after dissection for signs of ischaemia. If ischaemia is suspected, the parathyroid glands can be re-implanted in muscle, such as the mm. sternocleidomastoideus in the neck[39], or alternatively in the subcutaneous fat tissue[40]. Recently, an imaging method using fluorescence has been introduced to assist surgeons with the function monitoring of the parathyroid glands. However, although promising, this method is not yet routinely used in clinical practice[41]. Among other instruments, thyroid surgeons use magnifying glasses called loupe glasses (Figure 6), to distinguish the margins of the tiny adjacent organs, such as normal parathyroid glands. The studies in this thesis are done on operations performed with the conventional open method.

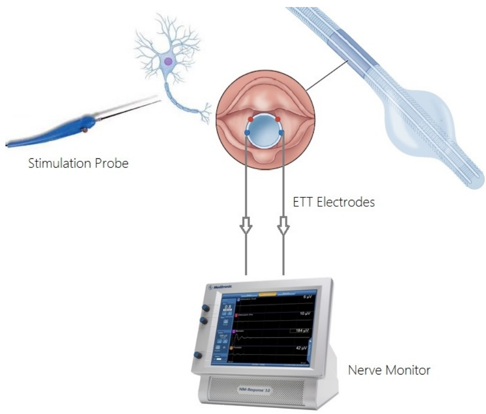

Figure 5 The Medtronic (NIM) by Usman Ghani is licensed under CC BY 3.0

Figure 6. Loupe glasses

2: Minimally invasive thyroid surgery

Over the past 20 years, robotic thyroidectomy has been introduced to avoid neck scarring and minimise surgical morbidity. Different approaches e.g., axillary, anterior chest, breast, postauricular, and transoral have been practised and developed[42,43]. Overall, these methods have not yet been able to improve the per/postoperative outcomes compared to the conventional method, except for the absence of neck scarring[44]. Furthermore, only highly selected patients are suitable for these minimally invasive methods[44].

Surgical morbidity

Major complications after thyroid surgery are neck haematoma, postoperative hypocalcaemia caused by hypoparathyroidism, postoperative vocal cord paresis/paralysis due to injury to the recurrent laryngeal nerves, and postoperative surgical site infection[45]. The severity of these complications varies among patients. In some patients, they are life-threatening with an immediate need for intervention, for example, acute airway obstruction caused by postoperative neck haematoma or bilateral vocal cord paralysis. In other patients, they are of moderate severity but still need intensive care, e.g. severe hypocalcaemia due to hypoparathyroidism or abscess in the neck caused by unintentional injury to the aero-digestive tracts during surgery[46,47].

1: Postoperative neck haematoma due to bleeding

The incidence of postoperative neck haematoma is between 0.6-2%[48-51]. Most re-bleedings occur during the first postoperative hours when the patient is being observed in the postoperative care unit. Almost 90% of the patients who suffer from this complication bleed within 24 hours of the operation[52,53]. Most of the patients need re-exploration due to the risk of airway obstruction but some will have superficial bleeding without obstruction symptoms. One study[54] investigated whether deep or superficial bleeding could be distinguished using clinical manifestations. The study found some differences, such as a smaller extent of skin ecchymosis and discoloration in deep bleedings compared with superficial bleedings, and no signs of respiratory distress symptoms could be observed in patients with superficial bleeding. However, in daily practice, making this distinction is very difficult.

Risk factors for postoperative neck haematoma have been studied thoroughly since the last century[55-58]. There has been a decrease in the frequency of this complication, but still up to two percent of patients suffer from this potentially life-threatening complication. In recent years, outpatient thyroid surgery has become a trend, and it is more commonly used worldwide[59]. Study I in this thesis (Evaluating Risk Factors for Re-exploration due to Postoperative Neck Haematoma after Thyroid Surgery: a Nested Case-Control Study) was performed to investigate risk factors and the time pattern for re-bleeding after thyroid surgery. The study also investigated whether patients with a lower risk of postoperative neck haematoma could be identified preoperatively to assist in selecting patients for outpatient surgery.

2: Postoperative vocal cord palsy/paresis

Postoperative vocal cord palsy occurs due to injury to the recurrent laryngeal nerve. The condition can be unilateral or bilateral, permanent, or transient. The incidence of permanent unilateral vocal cord palsy is 3-5 percent whereas the incidence of bilateral permanent vocal cord palsy is 0.01-0.02 percent[60]. The recurrent laryngeal nerves course adjacent to the dorsal side of the thyroid gland when entering the vocal muscles on both sides[61] (Figure 3). This makes the nerves vulnerable to injuries during surgery. Injury to the recurrent laryngeal nerve may occur due to direct trauma such as cutting, burning, or compressing, or indirectly through forces like stretching, pulling, or pushing the thyroid gland. In recent years, the device of NIM has been introduced in thyroid surgery. This device is a tool to identify the nerves in the early stage of the operation and to monitor the function of the nerves during the surgery. It has been shown that using NIM reduces the risk of permanent vocal cord palsy and almost eliminates the risk of bilateral vocal cord palsy [60,62].

3: Postoperative surgical site infection

Postoperative surgical site infection after thyroid surgery has a low incidence of 0.5-2.0 percent[49,63]. When it occurs, clinically evaluating the severity of the infection is important to decide whether the patient can be treated in outpatient care or should be re-admitted to the hospital. In the most severe forms, a re-intervention is needed to reveal a possible injury to the aero-digestive tract[64]. The infection leads to prolonged recovery after thyroid surgery and also to worsened cosmesis, as well as to increased healthcare costs[65]. Risk factors and the role of prophylactic antibiotics in thyroid surgery have been assessed in several studies, in which antibiotic prophylaxis has been discouraged due to the low incidence of surgical site infection[66-68]. However, there may be patients with a higher risk of surgical site infection after thyroid surgery and with a need for prophylactic antibiotics. Study II in this thesis (A Nested Case-Control Study on the Risk of Surgical Site Infection after Thyroid Surgery) investigated risk factors for surgical site infection after thyroid surgery.

4: Postoperative hypocalcaemia due to hypoparathyroidism

Postoperative hypocalcaemia is a consequence of postoperative hypoparathyroidism. Parathyroid glands are closely attached to the thyroid gland (Figure 3). Hypoparathyroidism occurs when parathyroid glands are removed or injured during surgery. Hypoparathyroidism may be transient or permanent. The incidence of transient and permanent postoperative hypoparathyroidism is estimated in large cohort studies to be between 7.6 -12.5 percent[69,70]. Permanent hypoparathyroidism is associated with an increased risk of morbidity[71] and mortality[72]. In patients with thyroid cancer, extended surgery, e.g., lymph node dissection might be needed. Often a concomitant central lymph node dissection is performed, either prophylactic or therapeutic. Study III in this thesis (Central Lymph Node Dissection and Permanent Hypoparathyroidism after Total Thyroidectomy for Papillary Thyroid Cancer: Population-based Study) investigated the risk of permanent hypoparathyroidism in patients who were operated for papillary thyroid cancer with thyroidectomy with and without central lymph node dissection.

5: Mortality after thyroid surgery

The mortality rate after thyroid surgery decreased notably at the end of the 19th century[1]. A study from 1978 on mortality after thyroid surgery showed a low mortality rate of 0.02 percent in patients younger than 50 years operated for non-toxic goitres. However, the same study found that the mortality rate was 33 times higher, i.e. 0.66 percent for patients >70 years and fivefold higher, 0.10 percent, in patients with toxic goitre, regardless of age[73]. Mortality after thyroidectomy for thyroid cancer was recently studied in a meta-analysis that concluded that patients older than 60 years have reduced overall survival compared to young patients[74]. Other studies[75-77] have shown that thyroid surgery is safe in older patients. However, patients older than 80 years with benign thyroid disorder, e.g., goitre, most often extending behind the sternum with or without compression symptoms, are at a high risk of severe complications of the disease[78], for instance acute airway obstruction with a possible deadly outcome. Therefore, even with the absence of compression symptoms, it is usually beneficial to plan elective surgery in elderly patients when an intrathoracic goitre is diagnosed[79,80]. It is not unusual that the diagnosis is made as an incidental finding on a CT scan performed for other reasons.

Thus, a better understanding of the risk of mortality after benign thyroid surgery in patients aged 80 years or older is important, and this was investigated in study IV in this thesis (Mortality after Benign Thyroid Surgery in Patients Aged 80 and Older).

Measuring the surgical quality

To improve the quality of surgical care, relevant data on preoperative factors and outcomes should be recorded in a standardised and reproducible way. This allows an overall quality measure over time, a comparison of surgical quality among different centres and different therapies. In 2004, the Scandinavian Quality Register for Thyroid, Parathyroid, and Adrenal Surgery (SQRTPA) was initiated in Sweden and Denmark. The register has evolved and now covers more than 90 percent of all thyroid operations performed in Sweden[27]. The Swedish Association of Endocrine Surgeons and the Swedish Association of Otorhinolaryngology and Head and Neck Surgery endorse the register. It is an online register with annual reports. Data from SQRTPA was used for research purposes in all four studies in this thesis.

"Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future".

-T. Billroth, 1862

Aims of the thesis

The three first articles in this thesis aim to evaluate risk factors for complications after thyroid surgery. The fourth article aims to evaluate mortality and survival after thyroid surgery for benign thyroid disease in patients aged 80 years and older.

Paper I

a. To evaluate risk factors for neck haematoma after thyroid surgery.
b. To identify patients with a lower risk of postoperative bleeding, and thus potentially suitable for outpatient surgery.
c. To enhance knowledge on the time pattern for the bleeding event.

Paper II

a. To investigate risk factors for surgical site infection after thyroid surgery.
b. To evaluate the effect of prophylactic antibiotic treatment in thyroid surgery.

Paper III

a. To investigate whether central lymph node dissection in the surgical management of papillary thyroid cancer is associated with postoperative permanent hypoparathyroidism.

Paper IV

a. To evaluate survival after thyroid surgery due to benign thyroid disorders in patients aged 80 years or older.

Patients and Methods

Overview of the studies

Table 1. An overview of all the studies included in this thesis

Paper	Design	Subjects
Paper I	Nested case-control Observational	346 patients
Paper II	Nested case-control Observational	218 patients
Paper III	Retrospective Observational	722 patients
Paper IV	Retrospective Observational	483 patients

Papers I and II

Patients

The cohort in studies I and II consist of adult patients operated with thyroid surgery from 1st January 2004 to 31st December 2010 in Sweden. The data was extracted from the SQRTPA. The register contains information regarding patient demographics, preoperative, operative, and postoperative details, histopathology, and follow-up at six weeks and six months after surgery. Additional data not included in the SQRTPA were collected through a questionnaire that was sent to the attending surgeons in 27 different operating units participating in the SQRTPA. In the questionnaire, information regarding the patients' medication before the operation, comorbidities, smoking habits, body mass index (BMI), laboratory examinations (activated partial thromboplastin time (APTT), prothrombin time international normalised ratio (PT-INR), thrombocytes, and creatinine) was requested. Additional information was queried regarding the haemostatic technique that was used during surgery, the use of a drain, the use of antibiotic prophylaxis, and information about any postoperative complications that occurred and the consequence of the complications. In the case of postoperative neck haematoma, the estimated onset of bleeding was queried.

Study design

Studies I and II were designed as nested case-control studies. Patients with complications (study I, postoperative reoperation due to bleeding, and study II, postoperative surgical site infection) were matched 1:1 by age and gender to patients without complications from the same cohort (controls).

Statistical analysis for paper I

Two types of analysis were performed to evaluate the risk factors. Patients with postoperative bleeding were compared with the total cohort to assess the impact of age and gender as risk factors. Thereafter, patients with postoperative bleeding were compared to controls to investigate the impact of important risk factors not available in the SQRTPA, with the information acquired through questionnaires. To further identify a group of patients with low risk of re-bleeding, the rate of bleeding incidence was calculated in patients without any risk factor for this complication. Finally, the time pattern for postoperative bleeding was classified into four groups: less than six hours, 6-12 hours, 12-24 hours, and > 24 hours.

For comparison between groups, a Pearson chi-square test was used for categorical variables and a Wilcoxon rank-sum test for continuous variables. Continuous variables were reported with median and interquartile range (IQR) and categorical variables as percentages. The results for comparison within groups were reported as p-values. Risk factors for patients with postoperative bleeding compared to the rest of the cohort and controls were evaluated using univariable and multivariable logistic regression and were presented as odds ratio (OR) and 95% confidence interval (CI). A p-value <0.05 was considered significant. Variables with more than 50% missing values or with too few events to evaluate were excluded from the multivariable logistic regression model.

Statistical analysis for paper II

Continuous variables were reported as median with interquartile range (IQR) and categorical variables as percentages. For continuous variables, the Wilcoxon rank-sum test was used and for categorical variables, the Pearson chi-square test was used. Patients were matched by gender and age to controls. To evaluate the impact of age and gender, a comparison between patients with postoperative surgical site infection and the rest of the cohort was also performed. The results were reported with percentages and p-values. A p-value <0.05 was considered significant. Analysis of outcomes was performed using univariable and multivariable logistic regressions. The results were presented as ORs with 95 percent CIs. Patients with independent risk factors for surgical site infection in the case-control cohort were analysed regarding the use of antibiotic prophylaxis.

Paper III

Patients

Adult patients who underwent total thyroidectomy with or without central lymph node dissection with a histopathologic postoperative diagnosis of papillary thyroid cancer between 1 June 2004 and 31 July 2014 were identified. Data was extracted from SQRTPA. Information on medication for treatment of permanent postoperative hypoparathyroidism[81] (active vitamin D. i.e. dihydrotachysterol (Dygratyl®), Anatomical Therapeutic Chemical Classification System (ATC) A11CC02, alfacalcidol (Etalpha®), ATC A11CC03 or calcitriol (Rocaltrol®), ATC A11CC04, with or without oral calcium, i.e. calcium carbonate (Kalcipos®), ATC A12AA04 or with calcium lactogluconate (Calcium-Sandoz®), ATC A12AA06), was retrieved from the Swedish national drug prescription register. This is a register with a nationwide coverage, which has recorded the prescription and dispensation of drugs since July 1st 2005[82]. Patients using any of these drugs before surgery were excluded from the study. The aim of the study was to investigate risk factors for permanent hypoparathyroidism in patients operated for stages I-III papillary thyroid cancer.

Study design

Study III was designed as a retrospective observational cohort study.

Statistical analysis

Continuous variables were reported as median with IQR and categorical variables as percentages. Variables were compared between groups using the Pearson chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Comparisons between groups are reported as numbers, percent, and p-values. A p-value < 0.05 was considered significant.

The risk of permanent hypoparathyroidism was analysed by comparing patients operated with TT versus patients operated with TT+CLND, and then separately in patients who underwent CLND, using uni- and multivariable logistic regression. The results are presented as ORs with 95 percent CIs.

Missing values were included and treated as a separate category apart from preoperative ionised calcium levels in which missing values were imputed with mean values of the cohort.

Paper IV

Patients and data

Data on patients who underwent thyroidectomy between 1st January 2004 and 31st December 2017 were extracted from the SQRTPA. The end date for the study was 30th June 2019. Patients under the age of 18 years, those with histopathological diagnosis of malignancy, malignancy as a cause of death, reoperation for thyroid surgery, concomitant parathyroid surgery, and those with data entry errors were excluded from analysis. Date of death was retrieved from the National Board of Health and Welfare. Data on the mortality rate in the general population was obtained from the Swedish Central Bureau of Statistics.

Study Design

Study IV was designed as a retrospective observational study.

Statistical analysis

Patients were categorised into two groups: those aged 18 – 79 years and those aged 80 years and older. The groups were compared using the Pearson chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Summaries of continuous variables were reported as median with IQR and categorical variables as numbers and percentages. Patients aged 80 years and older were analysed for risk factors for death using univariable and multivariable Cox regression analysis. The standardised mortality ratio (SMR) was calculated in patients aged 80 years and older. The mortality rate was calculated in the study cohort and then compared with the mortality rate of the general Swedish population of the same age and sex, using publicly available mortality rates from the National Board of Health and Welfare[83].

For statistical analysis in all studies, STATA/IC versions 12.1 and 16.1 (StataCorp LP, College Station, TX, USA) were used.

Ethical aspect

The regional ethical committee at Lund University approved the studies in this thesis with the reference number (Dnr 2011/740) on 9th February 2012.

Data sources

Original data for all studies in this thesis were collected from the SQRTPA[84]. The register, which is well recognised in the field, was initiated in 2004 and as of now more than 40000 operations have been recorded. It has a coverage of well over 90 percent in Sweden. The Swedish Association of Endocrine Surgeons and the Swedish Association of Otorhinolaryngology and Head and Neck Surgery endorse this register. The attending surgeons register data prospectively. The register is audited regularly to make sure that data are correctly registered. Since 2017, data from the SQRTPA have also been available in the EUROCRINE® which is a pan European online database with data on endocrine surgical procedures from centres across Europe dating from 2015.

For study III, additional data were collected from the Swedish national drug prescription register which has an almost 100 percent coverage of the drug prescription and dispensation records since 2005. For study IV, additional data on death were retrieved from the Swedish National Board of Health and Welfare[83] and Statistics Sweden[85].

Results

Paper I

Postoperative bleeding was reported in 174 (1.8 %) of 9,494 patients included in the study. All patients with bleeding were matched to controls, except for one who could not be matched because of high age (92 years). The response rate for the questionnaire was 96 % (332 answers out of 346 sent questionnaires).

Patients with postoperative bleeding compared with the total cohort

Patients with bleeding were older than the rest of the cohort, with a median (IQR) age of 58 (46-69) vs. 49 (37-62) years, P = <0.01. In the univariable logistic regression analysis, older age, male patients, gland weight between 200-500 grams and patients with substernal goitre, were factors associated with an increased risk of re-bleeding (Table 1a). In the multiple logistic regression analysis (adjusted for age, gender, indication of surgery, type of operation, operation time, gland weight, substernal gland, sternotomy, lymph node dissection, thymectomy, and previous thyroid surgery), age over 50 years and male gender remained independent risk factors. Age 50-70 years had an OR of 2.58 (1.33-5.00), vs. the reference group; patients >70 years had an OR of 3.62 (1.76-7.43) vs. the reference group; and men had an OR of 1.92 (1.38-2.67) vs. women patients (Table 1a).

Patients with postoperative bleeding compared with controls without postoperative bleeding

In the univariable logistic regression analysis, the use of a drain was associated with postoperative bleeding, OR of 1.64 (1.05-2.57). Patients with distant metastasis of thyroid cancer, and elevated PT-INR were at increased risk of re-bleeding. In the multivariable logistic regression analysis, only the use of a drain remained significant with an OR of 1.71 (1.07-2.74) (Tables 1b and 1c).

Some 97 of 152 patients with postoperative bleeding (64%) bled within six hours, and 121 of 152 patients (80%) bled within 12 hours. Fifteen patients (10%) had bleeding with reoperation after 24 hours. Information about time patterns was missing for 21 (12%) patients and they were excluded from this analysis.

The frequency of postoperative bleeding was 1% if patients with risk factors (male gender and age ≥ 50 years) were removed from the cohort. The frequency for postoperative bleeding remained at 1%, even if patients with the risk factors in the univariable analysis (substernal gland, gland weight 200-500 grams, and elevated PT-INR) were removed.

Analysis of other postoperative complications showed no differences between patients with bleeding and controls (Table 1d).

In patients with bleeding, 35 (20%) suffered from complications after re-exploration. These complications were reported as tracheal and teeth injuries, uni- and bilateral vocal cord palsies, surgical site infection, hypoparathyroidism, dysphagia, pulmonary oedema, atrial fibrillation, pulmonary embolism, and a combination of vocal cord palsy and hypoparathyroidism. One patient was re-reoperated due to a second postoperative bleeding.

Table 1a. Characteristics, uni- and multivariate logistic regression of patients operated for thyroid disease 2004-2010 in the SQRTPA compared with patients who had a postoperative bleeding in the same cohort

Characteristics	**Cases** n=174(%)	**Cohort** n=9320(%)	**Univariate** OR (CI)	**Multivariate** OR (CI)
Age (years)				
<30	11 (6)	1156 (12)	1.00	1.00
30-50	43 (25)	3531 (38)	1.27 (0.65 - 2.48)	1.38 (0.70 – 2.71)
50-70	81 (47)	3463 (37)	2.45 (1.30 – 4.63)	2.58 (1.33 – 5.00)
>70	39 (22)	1170 (13)	3.50 (1.78 – 6.87)	3.62 (1.76 – 7.43)
Sex				
Women	115 (66)	7546 (81)	1.00	1.00
Men	59 (34)	1774 (199)	2.18 (1.58 -2.99)	1.92 (1.38 – 2.67)
Indication for surgery				
Compression symptoms	69 (40)	3605 (39)	1.00	1.00
Malignancy	27 (16)	1133 (12)	1.24 (0.79 – 1.95)	1.59 (0.84 – 3.03)
Suspected malignancy	41 (24)	2269 (24)	0.94 (0.63 – 1.39)	1.05 (0.68 – 1.62)
Thyrotoxicosis	37 (21)	2200 (24)	0.87 (0.58 – 1.31)	1.30 (0.77 – 2.17)
Missing	0	113 (1)	0	0
Type of operation				
Lobectomy	83 (48)	4471 (48)	1.00	1.00
Thyroidectomy	77 (44)	3910 (42)	1.06 (0.77 – 1.43)	0.95 (0.62 – 1.43)
Thyroid resection	11 (6)	636 (7)	0.93 (0.49 - 1.75)	0.87 (0.46 – 1.66)
Other operations *	3 (2)	303 (3)	0.53 (0.16 – 1.69)	0.41 (0.11 – 1.42)
Operation time (minutes)				
<60	5 (3)	488 (5)	1.00	
60-120	50 (29)	3055 (33)	1.59 (0.63 - 4.02)	1.45 (0.57 – 3.71)
>120	57 (33)	2919 (31)	1.90 (0.76 – 4.77)	1.58 (0.60 – 4.13)
Missing	62 (35)	2858 (31)	2.1 (0.84 – 5.29)	1.86 (0.72 – 4.74)

Gland weight (grams)				
<50	66 (38)	4149(45.5)	1.00	1.00
50 – 200	41 (24)	2230 (24)	1.15 (0.78 – 1.71)	0.92 (0.59 – 1.42)
200 – 500	14 (8)	378 (4)	2.34 (1.30 – 4.20)	1.46 (0.75 – 2.84)
>500	2 (1)	37 (0.5)	3.39 (0.80 – 14.39)	2.34 (0.53 – 10.39)
Missing	51 (29)	2528(27)	1.26 (0.87 – 1.83)	1.13 (0.76 – 1.67)
Substernal gland				
No	150 (86)	8532 (92)	1.00	
Yes	24 (14)	788 (8)	1.73 (1.11 – 2.68)	1.17 (0.71 – 1.95)
Sternotomy				
No	172(99)	9275(99.5)	1.00	
Yes	2 (1)	45 (0.5)	2.39 (0.57 – 9.95)	1.22 (0.27 -5.51)
Lymph node dissection				
No	147 (84)	7854 (84)	1.00	
Yes	27 (16)	1466 (84)	0.98 (0.65 – 1.48)	0.77 (0.44 – 1.33)
Thymus operation				
No	173 (99.5)	9276 (99.5)	1.00	
Yes	1 (0.5)	44(0.5)	1.22 (0.16 – 8.89)	1.30 (0.17 – 9.85)
Previous thyroid operation				
No	157 (90)	8271 (89)	1.00	
Yes	17 (10)	1049 (11)	0.85 (0.51 – 1.41)	0.78 (0.44 – 1.39)

SQRTPA= Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery. OR=Odds Ratio. CI=Confidence Interval. * Missing values and those registered for any other type of operation related to thyroid disease are included in *other operations*.

Table 1b. Clinical characteristics and univariate logistic regression of the patients with postoperative bleeding and controls using data from the SQRTPA

Characteristics	**Cases** N=173 (%)	**Controls** N=173 (%)	**Odds ratio** (Confidence interval)
Indication for surgery			
Compression symptoms	68 (39)	60 (35)	1.00
Malignancy	27 (16)	32 (19)	0.74 (0.40 – 1.38)
Suspected malignancy	40 (23)	42 (24)	0.84 (0.48 – 1.46)
Thyrotoxicosis	38 (22)	35 (20)	0.95 (0.53 – 1.70)
Other	0	4 (2)	
Type of operation			
Lobectomy	82 (47)	87 (50)	1.00
Thyroidectomy	77 (45)	65 (38)	1.25 (0.80 – 1.96)
Any type of thyroid resection	11 (6)	14 (8)	0.83 (0.35 – 1.94)
Other operations	3 (2)	7 (4)	0.45 (0.11 – 1.27)
Operation time (minutes)			
<60	5 (3)	11 (6)	1.00
60-120	50 (29)	60 (35)	1.8 (0.59 – 5.62)
>120	58 (33)	44 (25)	2.9 (0.93 – 8.95)
Missing	60 (35)	58 (34)	2.2 (0.70 – 6.95)
Gland weight (grams)			
<50	75 (43)	83 (48)	1.00
50 - 200	46 (27)	53 (30.5)	0.96 (0.58 – 1.58)
200 - 500	14 (8)	10 (6)	1.54 (0.64 – 3.69)
>500	2 (1)	1 (0.5)	2.21 (0.19 – 24.9)
Missing	36 (21)	26 (15)	1.53 (0.84 – 2.77)
Substernal gland			
No	149 (86)	157 (91)	1.00
Yes	24 (14)	16 (9)	1.58 (0.80 – 3.09)
Sternotomy			
No	171 (99)	173 (100)	1.00
Yes	2 (1)	0	Omitted
Lymph node dissection			
No	146 (84)	143 (83)	
yes	27 (16)	30 (17)	0.88 (0.49 – 1.55)
Thymus operation			
No	172 (99.5)	172 (99.5)	1.00
Yes	1 (0.5)	1 (0.5)	1.00 (0.06 -16.11)

Reoperation			
No	156 (90)	148 (86)	
Yes	17 (10)	25 (14)	0.64 (0.33 – 1.24)
Tumour classification (TNM)	60(100)	62(100)	
pT0	4 (7)	3 (5)	1
pT1	5 (8)	4 (6)	0.93 (0.12 – 6.87)
pT2	6 (10)	16 (26)	0.28 (0.04 – 1.64)
pT3	14 (23)	13 (21)	0.80 (0.15 – 4.32)
pT4	22 (37)	17 (27)	0.97 (0.19 – 4.93)
pTx	9 (15)	9 (15)	0.75 (0.12 – 4.35)
N0	16 (27)	20 (32)	1
N1	30 (50)	27 (44)	1.38 (0.60 – 3.21)
Nx	14 (23)	15 (24)	1.16 (0.43 – 3.11)
M0	22 (37)	34 (55)	1
M1	15 (25)	7 (11)	3.31 (1.16 – 9.41)
Mx	23 (38)	21 (34)	1.69 (0.38 – 1.10)

SQRTPA= Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery

Table 1c. Univariate and multivariate logistic regression of the patients with postoperative bleeding and controls using data retrieved from questionnaires

Characteristics	**Cases** N=173 (%)	**Controls** N=173 (%)	**Univariate analysis** OR (CI)	**Multivariate analysis** OR(CI)
Body Mass Index				
Normal (18.5–24.9)	49 (28)	52 (30)	1.00	
Overweight (≥25)	58 (33)	62 (36)	0.99 (0.58 – 1.68)	2.70 (0.39 -18.4)
Underweight (≤18.4)	4 (2)	2 (1)	2.12 (0.37 – 12.1)	0.93 (0.53 -1.61)
Missing	62 (36)	57 (33)	1.15 (0.67 – 1.96)	0.93 (0.48- 1.80)
Medication				
Anticoagulants/Anti-platelets				
No	123 (71)	123 (71)	1.00	
Yes	28 (16)	29 (17)	0.96 (0.54 – 1.71)	0.95 (0.48-1.86)
Missing	22 (13)	21 (12)	1.04 (0.54 – 2.00)	0
NSAID				
No	143 (83)	149 (86)	1.00	
Yes	7 (4)	4 (2)	1.82 (0.52 – 6.36)	2.46 (0.60-10.1)
Missing	23 (13)	20 (12)	1.19 (0.63 – 2.27)	0
SSRI				
No	148 (86)	148 (86)	1.00	
Yes	2 (1)	4 (2)	0.50 (0.09 – 2.77)	0.47 (0.08-2.73)
Missing	23 (13)	21 (12)	1.09 (0.58 – 2.06)	0
Cytostatic				
No	149 (86)	150 (87)	1.00	
Yes	0	2 (1)	Omitted	0
Missing	24 (14)	21 (12)	1.15 (0.61 – 2.15)	0

Comorbidities				
Bleeding disorder				
No	156 (90)	149 (86)	1.00	
Yes	2 (1)	0	Empty	0
Missing	15 (9)	24 (14)	0.59 (0.30 – 1.18)	0
Renal failure				
No	155 (90)	158 (91)	1.00	
Yes	1 (0.5)	4 (2)	0.25 (0.02 – 2.30)	0.19 (0.01-2.09)
Missing	17 (10)	11 (7)	1.5 (0.71 – 1.22)	0
Liver dysfunction				
No	155(89.5)	162 (94)	1.00	
Yes	1(0.5)	0	Empty	0
Missing	17(10)	11 (6)	1.61 (0.73 – 3.55)	0
Cardiovascular disease				
No	142(82)	150(87)	1.00	
Yes	14(8)	12(7)	1.23 (0.55 – 2.75)	1.17 (0.44-3.10)
Missing	17(10)	11(6)	1.63 (0.74 – 3.60)	0
Smoking habits				
Non-smoker	66(38)	72(42)	1.00	
Smoker	19(11)	18(10)	1.15 (0.55 – 2.38)	1.16 (0.54-2.49)
X-smoker	14(8)	14(8)	1.09 (0.48 – 2.45)	1.06 (0.45-2.51)
Missing	74(42)	69(40)	1.16 (0.73 – 1.86)	0
Laboratory Examination*				
Elevated PT-INR	7 (4)	1(0.5)	9.56 (1.13 – 80.74)	0
Missing	124(72)	116(67)	1.46 (0.90 – 2.34)	
Elevated APTT	3 (2)	2(26)	1.87 (0.29 – 11.83)	0
Missing	134 (77)	126(73)	1.32 (0.80 – 2.19)	
Thrombocytopenia	5(3)	5 (3)	1.07 (0.30 – 3.82)	0.84 (0.20-3.37)
Missing	72(42)	65(38)	1.18 (0.77 – 1.83)	0
Haemostatic technique				
Ligature	116(67)	113(65)	1.00	
Electric instrument	31(18)	34(20)	0.88 (0.51 – 1.54)	0.90 (0.50-1.61)
Ligature and electric instrument	11(6)	14(8)	0.76 (0.33 – 1.75)	0.66 (0.26-1.66)
Missing	15(9)	12(7)	1.21 (0.54 - 2.71)	0
Drain				
No	74(43)	96(56)	1.00	
Yes	80(46)	63(36)	1.64(1.05 – 2.57)	1.71 (1.07-2.74)
Missing	19(11)	14(8)	1.76(0.82 – 3.74)	0

OR=Odds Ratio. CI=Confidence Interval. NSAID=Non-Steroidal Anti-Inflammatory Drugs. SSRI= Selective Serotonin Reuptake Inhibitors. PT-INR=Prothrombin Time- International Normalised Ratio. APTT= Actived Partial Thromboplastin Time. * A value within the reference zone is the reference for logistic regression. Missing values are not filled in the multivariate analysis due to no use.

Table 1d. Information regarding other complications in patients with postoperative bleeding and controls

Postoperative complication	Cases N=173 (%)	Controls N=173 (%)	P-value
Permanent vocal cord palsy			
None	47 (27)	46 (27)	0.13
Unilateral	3 (2)	10 (6)	
Bilateral	1 (0.5)	0	
Missing	122 (70.5)	117 (68)	
Hypoparathyroidism			
No	155 (89)	154 (89)	0.16
Temporary	18 (11)	19 (11)	
Permanent	4 (2)	7 (4)	
Surgical site infection			
Yes	7 (4)	3 (2)	0.19
No	165 (96)	170 (98)	
Missing	1	0	

Paper II

Surgical site infection was reported in 109 (1.2%) patients. All 109 patients with SSI were matched with control patients without SSI. The response rate for the questionnaire was 96% (210 answers out of 218 sent questionnaires).

Patients with surgical site infection compared with the cohort

Patients with SSI were older with a median (IQR) age of 53 (41-65) vs. 49 (37-62) years compared with patients without SSI, p=0.01, and more often subjected to lymph node dissection, 40/109 (36.7%) vs. 1453/9494 (15.3%), p<0.01, and had a higher incidence of postoperative bleeding, 7/109 (6.5%) vs. 167/9494 (1.8%), p<0.01. (Table 2a). In the multivariable logistic regression analysis, lymph node dissection, OR 4.10 (95% CI 1.88-8.91), p<0.01, was an independent risk factor for SSI (Table 2b).

Patients with surgical site infection compared with controls

After matching for gender and age, patients with SSI were more often operated for malignancy, and more often underwent concomitant lymph node dissection. Patients with SSI were also more often treated with per/postoperative drain 68/109 (62.4%) vs. 46/109 (42.2%) patients, p=0.01 (Table 2c).

In the multivariable logistic regression analysis of risk factors for SSI in the matched case-control cohort, lymph node dissection, OR 3.22 (95 % CI 1.32-7.82) and the use of a drain, OR 1.82 (95% CI 1.04 – 3.18) were independent risk factors for SSI (Table 2d).

Diagnosis and treatment of the surgical site infection

The attending surgeon reported that 30 (27%) patients with SSI were diagnosed before discharge from the hospital whereas 53 (49%) patients were diagnosed after the date of discharge. Data were missing for 26 (24%) patients. Among patients with SSI, 78 (72%) patients were treated with antibiotics, three (2%) did not receive antibiotics and data was missing for 28 (26%) patients. Re-admission to the hospital due to SSI was reported for 36 (33%) patients.

Data from the case-control cohort showed that among the 34 patients with independent risk factors for SSI (i.e., lymph node dissection and postoperative drain), 26 (76%) had SSI. Only two (8%) out of these 26 patients were treated with antibiotics prophylactically, whereas 16 (62%) patients did not receive prophylactic antibiotics. Data regarding antibiotic prophylaxis was missing for eight (31%) patients, p = 0.12.

Table 2a. Clinical characteristics of patients registered in the SQRTPA, with and without postoperative surgical site infection

Characteristics	**No SSI** n=9385 (%)	**SSI** n=109 (%)	**P – value**
Age			0.01
Median / IQR	*49 / 37-62*	*53 / 41-65*	
Sex			0.05
Men	1804 (19.2)	29 (26.6)	
Women	7581 (80.8)	80 (73.4)	
Indication for operation			0.01
Compression symptom	3627 (38.6)	47 (43.1)	
Malignancy	1137 (12.1)	23 (21.1)	
Excluding malignancy	2290 (24.4)	20 (18.3)	
Thyrotoxicosis	2220 (23.7)	17 (15.6)	
Other(*)	111 (1.2)	2 (1.8)	
Type of operation			0.70
Total thyroidectomy	3944 (42.0)	43 (39.5)	
Hemi thyroidectomy	4500 (48.0)	54 (49.5)	
Other(**)	711 (7.6)	6 (5.5)	
Missing value	230 (2.4)	6 (5.5)	
Lymph node dissection			<0.01
Yes	1453 (15.3)	40 (36.7)	
No	7932 (83.5)	69 (63.3)	
Reoperation due to postoperative bleeding			<0.01
Yes	167 (1.8)	7 (6.5)	
No	9218 (98.2)	102 (93.5)	
Operation time (minutes)			<0.01
< 60	492(5.2)	1(0.9)	
61-120	3085(32.9)	20(18.4)	
>120	2945(31.4)	40(36.7)	
Missing value	2863 (30.5)	48 (44.0)	
Previous thyroid surgery			0.82
Yes	1053 (11.2)	13 (11.9)	
No	8332 (88.8)	96 (88.0)	
Specimen weight (gram)			0.02
Median / IQR	*37 / 20-82*	*65 / 24-125*	
Missing value	2522 (26.9)	42 (38.5)	
Substernal gland			0.10
Yes	798 (8.5)	14 (12.8)	
No	8587 (91.5)	95 (87.2)	

(*****) Unknown indication registered. (******) Includes unilateral and bilateral resections of the thyroid gland. *Median/IQR is presented in italic style.* Data are reported in percentages for categorical variables, and medians (interquartile range) for quantitative ones. SQRTPA= Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery. SSI; surgical site infection. IQR; interquartile range

Table 2b. Multivariable analysis of risk factors for SSI in patients registered in the SQRTPA

Variables	**Odds ratio**	**Confidence interval**	**p-value**
Age (year)	1.01	1.00-1.03	0.05
Sex			
Women	1.00		
Men	1.12	0.63-2.01	0.68
Indication for operation			
Compression symptoms	1.00		
Malignancy	0.47	0.18-1.22	0.12
Excluding malignancy	0.39	0.17-0.88	0.02
Thyrotoxicosis	0.94	0.49-1.79	0.85
Lymph node dissection			
No	1.00		
Yes	4.10	1.88-8.91	<0.01
Postoperative bleeding			
No	1.00		
Yes	2.24	0.68-7.32	0.18
Operation time (minutes)			
<60	1.00		
61-120	1.88	0.23-13.87	0.56
>120	3.34	0.44-25.16	0.24
Missing	3.19	0.04-24.21	0.26
Specimen weight (gram)	1.00	0.99-1.00	0.61

SSI= Surgical Site Infection. SQRTPA= Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery

Table 2c. Clinical characteristics of the patients with SSI and controls using data from the SQRTPA and survey data from participating departments

Characteristics	**SSI** n=109 (%)	**Controls** n=109 (%)	**p-value**
Age			1.00
Median / IQR	*53 / 41-65*	*53 / 41-65*	
Sex			1.00
Men	29 (26.6)	29 (26.6)	
Women	80 (73.4)	80 (73.4)	
Indication for surgery			0.03
Compression symptoms	47 (43.1)	53 (48.6)	
Malignancy	23 (21.1)	8 (7.3)	
Excluding malignancy	20 (18.3)	19 (17.4)	
Thyrotoxicosis	17 (15.6)	28 (25.7)	
Other	2 (1.8)	1 (0.9)	
Type of operation			0.30
Total thyroidectomy	43 (39.5)	46 (42.2)	
Hemi thyroidectomy	54 (49.5)	56 (51.3)	
Other	6 (5.5)	4 (3.7)	
Missing value	6 (5.5)	3 (2.8)	
Lymph node dissection			<0.01
Yes	40 (36.7)	14 (13.0)	
No	69 (63.3)	95 (87.0)	
Previous thyroid surgery			1.00
Yes	13 (12.0)	13 (12.0)	
No	96 (88.0)	96 (88.0)	
Operation time (minutes)			0.03
<60	1(0.9)	5(4.6)	
61-120	20(18.4)	34(31.2)	
>120	40(36.7)	36(33.0)	
Missing value	48 (44.0)	34 (31.2)	
Specimen weight (gram)	*65 / 24-125*	*54.5 / 26-123*	0.93
Missing value	42 (38.5)	26 (29.0)	
Substernal goitre			0.84
Yes	14 (12.8)	15 (13.6)	
No	95 (87.2)	94 (86.4)	
Reoperation due to postoperative bleeding			0.09
Yes	7 (6.4)	2 (1.8)	
No	102 (93.6)	107 (98.2)	
Long term cortisone medication			0.12
Yes	4 (3.6)	6 (5.4)	
No	99 (91.0)	89 (81.6)	
Missing value	6 (5.4)	14 (13.0)	

Prophylactic antibiotics			0.50
Yes	3 (2.8)	6 (5.5)	
No	75 (69.0)	94 (86.2)	
Missing value	31 (28.2)	9 (8.3)	
Diabetes			0.06
Yes	9 (8.3)	2 (1.8)	
No	95 (87.0)	98 (89.9)	
Missing value	5 (4.7)	9 (8.2)	
Drainage			0.01
Yes	68 (62.4)	46 (42.2)	
No	34 (31.2)	56 (51.4)	
Missing	7 (6.4)	7 (6.4)	
BMI	*27 / 23-29*	*26 / 23-29*	0.88
Missing value	79 (72.4)	46 (42.2)	
Smoker or Ex-smoker			0.02
Yes	10(9.1)	14(12.8)	
No	18(16.5)	33(30.2)	
Missing value	81(74.4)	62(57.0)	

Data are reported in percentages for categorical variables and medians (interquartile range) for quantitative ones. *Median/IQR is presented in italic style.* SQRTPA= Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery. SSI; surgical site infection. BMI; body mass index. IQR; interquartile range

Table 2d. Multivariable analysis for the risk of surgical site infection, comparing cases and controls using data from the SQRTPA and questionnaire data from participating departments

Variables	**Odds ratio**	**Confidence interval**
Thyroidectomy	1.00	
Lymph node dissection with or without thyroidectomy	3.22	1.32-7.82
Benign histology	1.00	
Malignancy	1.25	0.40-3.91
Postoperative drain		
No	1.00	
Yes	1.82	1.04-3.18
Diabetes		
No	1.00	
Yes	0.55	0.29-1.04
Operation time (minutes)		
< 60	1.0	
61-120	2.22	0.23-21.24
>120	3.76	0.40-34.82
Missing value	4.63	0.50-42.78
Postoperative bleeding		
No	1.00	
Yes	3.34	0.59-18.83

Paper III

There were 722 patients, 568 (79%) women, and 154 (21%) men, operated with TT with or without CLND for papillary thyroid cancer stage pT1-3 during the study period 1st July 2004 -30th June 2014. The median (IQR) age was 47 (36-60) years. A total of 265/722 (37%) patients underwent TT only, and 457/722 (63%) patients underwent TT+ CLND.

There were no significant differences in the distribution in age categories (18-39 years, 40-59 years, 60 and older) between the groups. The frequency of parathyroid gland re-implantation was high; 333 of 722 (46.1%) patients. It was higher in patients who underwent TT+ CLND 260/457 (56.9%) vs. patients who underwent TT 73/265 (27.6%), p <0.001. The rate of permanent hypoparathyroidism in these patients was 20/333 (6%). In patients who underwent CLND, 197/457 (43.1%) patients had no lymph node metastasis (N0), 233/457 (51%) patients had lymph nodes metastasis (N1) and 27/722 (5.9%) patients had a lymph node status of NX (not assessable), most likely due to few lymph nodes being yielded in the specimen (Table 3a).

Six months after surgery, 78/457 (17.1%) patients operated with TT+CLND were prescribed oral calcium vs. 15/265 (5.7%) patients operated with TT, p<0.001. Active vitamin D was prescribed six months after surgery to 38/457 (8.3%) patients operated with TT+CLND vs. 10/265 (3.8%) patients operated with TT, p=0.018. Combined therapy with both oral calcium and oral vitamin D was more often prescribed to patients operated with TT+CLND 30/457 (6.6%) vs. 6/265 (2.3%) patients operated with TT only, p=0.011.

In the multivariable logistic regression analysis, CLND was significantly associated with the use of oral vitamin D, calcium, or both drugs within and for more than six months after thyroidectomy with an OR (95% CI) of 2.56 (1.19 to 5.52), 3.31 (1.80 to 6.09) and 3.74 (1.46 to 9.59), respectively. See table 3b.

In a subgroup of patients operated with TT and CLND, node-negativity was associated with permanent hypoparathyroidism six months after surgery, OR (95% CI) 3.08 (1.31 to 7.25). See table 3c.

Table 3a. Patient demographics and clinical characteristics using data from the SQRTPA

Variable	All n. 722 (%)	Thyroidectomy n. 265 (%)	TT + CLND* n. 457 (%)	P-value
Age				
Median (i.q.r.)	*47 (36-60)*	*47 (35-60)*	*47 (36-61)*	0.871 †
Age categories				
18 – 39 years	230 (31.9)	88 (33.2)	142 (31.1)	0.794
40 – 59 years	301 (41.7)	110 (41.5)	191 (41.8)	
60 years and older	191 (26.4)	67 (25.3)	124 (27.1)	
Sex				
Men	154 (21.3)	35 (13.2)	119 (26.0)	< 0.001
Women	568 (78.7)	230 (86.6)	338 (74.0)	
Indication for surgery				
Cancer	435 (60.3)	36 (13.6)	399 (87.3)	< 0.001
Excluding cancer	80 (11.1)	36 (13.6)	44 (9.6)	
Thyrotoxicosis	141 (19.5)	133 (50.2)	8 (1.8)	
Compression symptom	66 (9.1)	60 (22.6)	6 (1.3)	
Operation time				
Median (i.q.r)	*146 (113-180)*	*120 (95-162)*	*151 (123-185)*	< 0.001 †
<2 hours	202 (28.0)	110 (41.5)	92 (20.1)	< 0.001
>2 hours	417 (57.7)	107 (40.4)	310 (67.8)	
Missing	103 (14.3)	48 (18.1)	55 (12.1)	
Operating units**				
High-volume	512 (70.9)	174 (65.7)	338 (74.0)	0.018
Low-volume	210 (29.1)	91 (34.3)	119 (26.0)	
Number of parathyroid glands visually identified				
Two or less	170 (23.5)	64 (24.2)	106 (23.2)	0.770
More than two	552 (76.5)	201 (75.8)	351 (76.8)	
Re-implantation of the parathyroid gland				
Yes	333 (46.1)	73 (27.6)	260 (56.9)	<0.001
No	389 (53.9)	192 (72.4)	197 (43.1)	
Tumour Classification (T)				
T0	3 (0.4)	0	3 (0.7)	<0.001
T1	432 (59.8)	227 (85.7)	205 (44.9)	
T2	147(20.4)	23 (8.7)	124 (27.1)	
T3	140 (19.4)	15 (5.6)	125 (27.3)	
Nodal Status (N)				
Nx			27 (5.9)	
N0			197 (43.1)	
N1			233 (51.0)	
Distant metastasis (M)				
Mx	416 (57.7)	156 (59.1)	260 (56.9)	0.260
M0	296 (41.0)	107 (40.3)	189 (41.4)	
M1	9 (1.2)	1 (0.3)	8 (1.7)	
Missing	1 (0.1)	1 (0.3)	0	
Tumour size				
Median (i.q.r) in millimetres	*15 (7-25)*	*6 (3-12)*	*20 (14-30)*	*<0.001†*
Missing values in a number	154 (21.3)	64 (24.1)	90 (19.7)	

Variable	All n. 722 (%)	Thyroidectomy n. 265 (%)	TT + CLND* n. 457 (%)	P-value
Calcium levels before surgery				
Normal	688 (95.3)	253 (95.5)	435(95.2)	0.641
Mild hypocalcaemia***	19 (2.6)	8 (3.0)	11 (2.4)	
Hypercalcaemia	15 (2.1)	4 (1.5)	11 (2.4)	
Calcium level 6 weeks after surgery				
Normal	573 (79.4)	209 (78.9)	364 (79.6)	0.058
Hypocalcaemia	87 (12.0)	25 (9.5)	62 (13.6)	
Hypercalcaemia	3 (0.4)	2 (0.7)	1 (0.2)	
Missing	59 (8.2)	29 (10.9)	30 (6.6)	

Median values and Interquartile ranges (i.q.r.) are presented in italics. ***** Total/near-total thyroidectomy and central lymph node dissection. **High-volume units = Over a hundred TTs / year. Low-volume units= Less than a hundred TTs/year. ******Ionised calcium levels 1.0 -1.14 mmol/L. **†** Wilcoxon rank-sum test. SQRTPA= Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery

Table 3b. Multivariable analysis for the calculation of risk factors for permanent hypoparathyroidism including all patients in the cohort.

Characteristics	Oral active vitamin D therapy six months after thyroid surgery	Oral calcium therapy six months after thyroid surgery	Combined therapy six months after thyroid surgery
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age categories			
18 – 39 years	1.00	1.00	1.00
40 – 59 years	0.67 (0.33 – 1.35)	1.03 (0.61 – 1.76)	0.65 (0.29 – 1.47)
60 years and older	0.77 (0.36 – 1.63)	1.12 (0.62 – 2.01)	0.90 (0.39 – 2.08)
Gender			
Female	1.00	1.00	1.00
Male	0.93 (0.45 – 1.90)	0.59 (0.33 – 1.06)	1.03 (0.46 – 2.28)
CLND			
No	1.00	1.00	1.00
Yes	2.56 (1.19 – 5.52)	3.31 (1.80 – 6.09)	3.74 (1.46 – 9.59)
Operating units*			
High-volume	1.00	1.00	1.00
Low-volume	1.55 (0.83 – 2.93)	0.77 (0.46 – 1.32)	1.61 (0.78 – 3.29)
Tumour staging			
T1	1.00	1.00	1.00
T2	0.62 (0.27 – 1.44)	0.98 (0.54 – 1.77)	0.43 (0.15 – 1.19)
T3	1.19 (0.57 - 2.49)	1.41 (0.80 – 2.45)	0.89 (0.38 – 2.05)

OR = Odds ratio, c.i. = confidence interval, CLND = Central lymph node dissection. *High-volume units= Over a hundred TTs/year. Low-volume units = Less than a hundred TTs/year

Table 3c. Multiple regression analysis for the calculation of risk factors for permanent hypoparathyroidism in those patients who had thyroidectomy and concomitant central lymph node dissection

Characteristics	Oral active vitamin D therapy six months after thyroid surgery	Oral calcium therapy six months after thyroid surgery	Combined therapy six months after thyroid surgery.
	OR (95% c.i.)	OR (95% c.i.)	OR (95% c.i.)
Age categories			
18 – 39 years	1.00	1.00	1.00
40 – 59 years	0.70 (0.32 – 1.57)	0.93 (0.51 – 1.70)	0.60 (0.24 – 1.52)
60 years and older	0.79 (0.33 – 1.87)	1.04 (0.53 – 2.02)	0.81 (0.31 – 2.11)
Gender			
Female	1.00	1.00	1.00
Male	1.10 (0.50 – 2.40)	0.69 (0.37 – 1.30)	1.46 (0.62 – 3.43)
Operating units*			
High-volume	1.00	1.00	1.00
Low-volume	1.41 (0.67 – 2.93)	0.78 (0.43 – 1.43)	1.79 (0.80 – 3.98)
Tumour			
T1	1.00	1.00	1.00
T2	0.70 (0.29 – 1.67)	0.94 (0.50 – 1.78)	0.46 (0.16 – 1.32)
T3	1.35 (0.61 - 3.01)	1.77 (0.96 – 3.23)	1.22 (0.50 – 2.98)
Nodal status			
Node-positive	1.00	1.00	1.00
Node-negative **	1.88 (0.92 – 3.87)	2.17 (1.26 – 3.71)	3.08 (1.31 – 7.25)

OR = Odds Ratio, c.i. = confidence interval. *High-volume = Over a hundred TTs/year, Low-volume = less than a hundred TTs /year. ** Node-negative = N0 and NX

Paper IV

There were 17,969 patients undergoing thyroid surgery for benign thyroid disease during the study period; 483(2.7%) patients aged 80 years or older, 397 (82.2%) women, and 86 (17.8%) men.

Unilateral procedures were more common in patients aged 80 years or older 312/483 (64.6%) versus 9,305/17,486 (53.2%), p<0.001. Patients aged 80 years or older more often had a substernal growth of the thyroid gland, 154/483 (31.9%) versus 1,472/17,486 (8.4%) in patients aged 18-79 years, p<0.001. Histopathological diagnosis of patients aged 80 years or older was more often nodular goitre 375/483 (77.6%) versus 9,639/17,486 (55.1%) in patients aged 18-79 years, p<0.001. The mortality rate at 30, 31-90 and 91-365 days after surgery for patients aged 80 years or older was 0.41%, 0.20 % and 2.5 %, respectively and for patients aged 18-79 years, 0.03%, 0.04%, 0.2%, respectively, p<0.001; (See table 4a).

The median (IQR) follow-up time in patients aged 80 years or older was 4.5 (2.9-7.2) and the median (IQR) survival time for these patients was 8.0 (4.1– 12.5) years. Apart from age, there were no significant risk factors for death in the Cox regression analysis (Table 4b).

Patients aged 80 years or older had increased survival compared to the general Swedish population, with an SMR of 0.67 (0.49-0.91) for men and 0.76 (0.65-0.89) for women.

Table 4a. Characteristics of patients operated with thyroidectomy for benign thyroid disorder between 2004 and 2017. A comparison between patients 18-79 and patients aged 80 years or older.

Characteristics	**Total Cohort** nr. 17,969 (100%)	**(80 -)** nr. 483 (2,7%)	**18 - 79 years** nr.17,486 (97,3%)	**p-value**
Sex				
Women	14,898 (82.9)	397 (82.2)	14,501 (82.9)	0.67 †
Men	3,071 (17.1)	86 (17.8)	2,985 (17.1)	
Main indication for surgery				
Compression symptoms	8,393 (46.7)	302 (62.5)	8,091 (46.3)	<0.01 †
Excluding malignancy	3,869 (21.5)	139 (28.8)	3,730 (21.3)	
Thyrotoxicosis	5,530 (30.8)	37 (7.7)	5, 493 (31.4)	
Other indications	177 (1.0)	5 (1.0)	172 (1.0)	
Type of thyroid operation				
Bilateral procedure*	7,969 (44.3)	156 (32.3)	7,813 (44.7)	<0.01 †
Unilateral procedure**	9,617 (53.5)	312 (64.6)	9,305 (53.2)	
Isthmus resection	316 (1.8)	11 (2.3)	305 (1.7)	
Missing data	67 (0.4)	4 (0.8)	63 (0.4)	
Operation time in minutes median (IQR)				
Bilateral procedure	*120 (95–153)*	*109 (87 – 150)*	*120 (95 – 153)*	0.07 ††
Unilateral procedure	*80 (60–106)*	*80 (60 – 105)*	*80 (60 – 106)*	0.83 ††
Missing data	3,207 (17.8)	78 (16.1)	3,129(17.9)	
Substernal gland				
Yes	1,626 (9.0)	154 (31.9)	1,472 (8.4)	<0.01 †
No	14,081 (78.4)	267 (55.3)	13,814 (79.0)	
Missing	2,262 (12.6)	62 (12.8)	2,200 (12.6)	
Sternotomy				
Yes	66 (0.4)	4 (0.8)	62 (0.4)	0.09 †
No	17,903 (99.6)	479 (99.2)	17,424 (99.6)	
Gland weight in grams Median (IQR)	*38 (20.4–83.7)*	*100 (30–171)*	*37.5 (20–81)*	<0.01 ††
Missing	4,314 (24.1)	114 (23.4)	4,200 (24.1)	
Histopathological diagnosis				
Nodular goitre	10,014 (55.7)	375 (77.6)	9,639 (55.1)	<0.01 †
Autoimmune inflammatory thyroid disease	4,275 (23.8)	19 (4.0)	4,256 (24.3)	
Benign tumour	2,128 (11.9)	63 (13.0)	2,065 (11.8)	
Other ***	492 (2.7)	3 (0.6)	489 (2.8)	
Normal gland	98 (0.5)	2 (0.4)	96 (0.6)	
Missing data	962 (5.4)	21 (4.4)	941 (5.4)	

Postoperative complications:				
Bleeding requiring reoperation				
Yes	282 (1.6)	15 (3.1)	267 (1.5)	0.02†
No	17,602(97.9)	467(96.7)	17,135(98)	
Missing data	85 (0.5)	1 (0.2)	84 (0.5)	
Permanent vocal cord palsy				
Yes	120 (0.7)	7 (1.5)	113 (0.6)	0.10†
No	13,782 (76.7)	369 (76.4)	13,413 (76.7)	
Missing data	4,067 (22.6))	107 (22.1)	3,960 (22.7)	
Permanent Hypoparathyroidism				
Yes	197 (1.1)	5 (1)	192 (1.1)	0.97†
No	13,737 (76.4)	371 (76.8)	13,366 (76.4)	
Missing data	4,035 (22.5)	107 (22.1)	3,928 (22.5)	
Surgical site infection				
Yes	174 (1)	8 (1.6)	166 (1)	0.11†
No	17,601 (98)	473 (98)	17,128 (98)	
Missing data	194 (1)	2(0.4)	192(1)	
Mortality				
Within 30 days after thyroid surgery	8 (0.04)	2 (0.41)	6 (0.03)	<0.01 †
Within 31- 90 days after thyroid surgery	9 (0.05)	1 (0.20)	8 (0.04)	
Within 91-365.25 days after thyroid surgery	50 (0.27)	12 (2.5)	38 (0.2)	

Continuous variables are shown in italics. †† The Wilcoxon rank-sum test. † The Chi-square/X^2 test. *Total/near-total thyroidectomy and bilateral thyroid gland resections. ** Hemithyroidectomy and unilateral thyroid gland resections. *** Cysts and other thyroiditis than those caused by autoimmune disease.

Table 4b. Cox regression analysis of predictors for death after thyroidectomy for benign thyroid disease in patients aged 80 years and older

Characteristics	**Hazard ratio**	
	Univariable	Multivariable
Age (years)		
80 - 85	1	
86 - 90	1.44 (1.01 – 2.04)	1.44 (1.00 – 2.07)
>90	3.50 (2.13 – 5.74)	3.20 (1.92 – 5.32)
Sex		
Women	1	
Men	1.18 (0.83 – 1.67)	1.16 (0.81 – 1.67)
Indication for surgery		
Goitre with compression symptoms	1	
Excluding malignancy	0.91 (0.66 – 1.24)	1.03 (0.71 – 1.49)
Inflammatory thyroid disease	0.94 (0.54 – 1.63)	1.04 (0.58 – 1.85)
Other indication	0.82 (0.20 – 3.34)	0.91 (0.21 – 3.83)
Substernal goitre		
No	1	
Yes	1.26 (0.94 – 1.68)	1.23 (0.87 – 1.74)
Missing	0.60 (0.26 – 1.39)	0.63 (0.27 – 1.47)
Operation time		
Less than 2 hours	1	
Over two hours	1.01 (0.72 – 1.42)	1.04 (0.72 – 1.49)
Missing	1.12 (0.78 – 1.60)	1.21 (0.83 – 1.75)
Gland weight		
Less than 200 grams	1	
200 – 499 grams	0.84 (0.55 – 1.27)	0.90 (0.58 – 1.38)
500 grams and more	1.37 (0.43 – 4.34)	1.23 (0.37 – 4.09)
Missing	0.85 (0.60 – 1.20)	0.77 (0.54 – 1.10)
Postoperative bleeding requiring reoperation		
No	1	
Yes	1.04 (0.51-2.12)	0.93 (0.45 -1.92)
Missing	5.43 (0.75–39.12)	6.41 (0.82–49.86)

"The knowledge of anything since all things have causes, is not acquired or complete unless it is known by its causes."

Abu-Ali Ibn Sina (Avicenna) 980-1037

Discussion

Since modern thyroid surgery was introduced by Theodor Kocher[86], many efforts have been made[1,2,5,12] to identify risk factors for complications and to minimise them[86]. The results of these efforts are observed in better outcomes for patients, such as shorter in-hospital stay and fewer postoperative complications[87]. These changes were possible because the contemporary thyroid surgeons have greater knowledge in this field, use a better surgical technique and have improved tools e.g., NIM, haemostatic devices and fluorescence. However, there are still patients who suffer from postoperative complications. Thus, this thesis aimed to further enhance the knowledge of complications occurring after thyroid surgery.

Paper I

This population-based study found that the incidence of re-exploration for postoperative bleeding after surgery for thyroid disease was 1.8%. Age over 50 years, male gender, and use of a drain were independent risk factors. Two-third of the patients with postoperative bleeding requiring re-exploration bled within six hours after the end of the primary surgery.

Previously performed studies on complications after thyroid surgery have also shown that high age and male gender were independent risk factors for postoperative bleeding[46,48,49,88]. The reason why high age and male gender are risk factors is unknown and remains to be investigated. The present study also identified the use of a drain as an independent risk factor. Whether a drain causes the bleeding or is a confounding factor due to the selection bias could not be evaluated in the study: use of a drain in surgery could be a marker for an operation prone to bleeding. However, the finding regarding the use of a drain as a risk factor for bleeding was similar to the results of a multi-institutional international study performed by Campbell et al[89].

Postoperative neck haematoma is not prevented by using a drain in neck surgeries other than thyroid surgery[90]. Furthermore, the use of a drain has been associated with postoperative pain after thyroid surgery in a single-centre randomised clinical trial[91].

The time pattern for postoperative bleeding is of great interest due to the increasing trend for outpatient thyroid surgery[92,93]. Several other studies have recently been performed to evaluate the safety of day thyroid surgery[59,94-97]. A meta-analysis and systematic review on 34 studies concluded that discharging selected patients the same day after thyroid surgery is safe[98].

Of the patients with postoperative bleeding in study I in this thesis, 64% were identified within six hours and 80% within 12 hours after the end of the primary surgery. Except for the morning procedures, it is difficult to extend observation over six hours in most settings of day surgery. One-third (36%) of the patients with postoperative bleeding needed re-intervention after six hours of postoperative care. One-tenth of postoperative haemorrhages were not apparent until more than 24 hours after surgery.

Even though the individual risk of late postoperative bleeding is low, some patients will need re-intervention after the end of postoperative observation. Facilities for easy and quick access to professional care for these patients are needed in the case of day surgery.

Elevated PT-INR, large substernal goitre, and distant metastasis in patients with thyroid malignancy were significant risk factors for bleeding in the univariable analysis. It is well known from other studies that elevated PT-INR is associated with a higher risk of bleeding due to its effect on the coagulation system[99,100]. Additionally, studies[48,89,101] also show that the use of other anticoagulants such as direct oral anticoagulants (DOACs), active antiplatelet, warfarin, and low molecular weight heparin is associated with a higher risk of postoperative bleeding. Outpatient surgery in patients with elevated PT-INR, patients taking other anticoagulants, large substernal goitre, and thyroid malignancy with distant metastasis is not recommended.

Considering the results of this study, women under the age of 50, with a PT-INR equal to or under 1.2 before surgery, without a substernal goitre, a gland weight >200 grams, and a drain had the lowest risk of postoperative bleeding and could potentially be selected for outpatient thyroid surgery. However, the risk of postoperative bleeding is only decreased by 47% in this group, which means that even in such selected group of patients, one out of a hundred patients might still need an intervention for postoperative bleeding.

Paper II

The main finding was that concomitant lymph node dissection and the use of a drain were independent risk factors for surgical site infection (SSI) after thyroid surgery. The incidence rate for SSI after thyroid surgery was 1.2%.

A previous study on the complications after thyroid surgery using data from SQRTPA showed that patients who underwent lymph node dissection and patients that were re-operated due to bleeding had an increased risk of SSI[49]. The present study included data from three times more patients, and additional information from the attending surgeons, which enabled a nested case-control analysis. In the present study, lymph node dissection was verified as an independent risk factor for SSI. Additionally, the use of a drain proved to be an independent risk factor. However, reoperation for postoperative bleeding was not a risk factor.

The issue of prophylactic antibiotics in thyroid surgery has been studied previously[102-105]. The results from a national multicentre retrospective observational study[106] and a randomised controlled trial[107] showed that antibiotic prophylaxis did not protect the patient from SSI in thyroid surgery. However, in the latter study[107] it was not reported if the patients had concomitant lymph node dissection or not. Surgical site infection after modified radical neck dissection is estimated to occur in 13-20% of patients[103]. The reason for this is not clear but could be due to prolonged operation time or the lymph node dissection *per se*. It might be considered that lymph node dissection may cause disruption to the immune system and reduce the local barrier for infection. In a previous investigation, the duration of operation was an independent risk factor for SSI in thyroid surgery[66]. The duration of operation was, however, not significant in the multivariable analysis in the present investigation. It is therefore likely that the duration of operation is a confounder due to the time required for lymph node dissection.

A recent meta-analysis has shown that the use of a drain in thyroid surgery is associated with a high rate of SSI, prolonged hospital stay, and a high pain score[108]. The use of drains in other surgeries with a low risk of postoperative infection, such as breast surgery, has also been associated with a higher risk of SSI[109]. Therefore, the use of a drain in routine thyroid surgery should be discouraged. However, in patients scheduled for more extensive surgery, such as a concomitant lateral lymph node dissection with risk of postoperative lymphatic leakage, a drain might be necessary. Prophylactic antibiotics may reduce the risk of SSI in these patients.

Due to the low incidence of SSI in thyroid surgery, it might be helpful to evaluate the effect of antibiotic prophylaxis in subgroups with independent risk factors rather than evaluating this effect in the whole cohort. Subgroups of patients with independent risk factors might benefit from prophylactic antibiotics in thyroid surgery.

Paper III

The main finding of this population-based nationwide study was that concomitant CLND with TT for stage pT1-3 papillary thyroid carcinoma (PTC) is a risk factor for postoperative permanent hypoparathyroidism as compared to TT without CLND. Furthermore, when analysing patients undergoing TT and CLND, patients without metastasis to lymph nodes (node-negative (N0/Nx)) had a higher risk of permanent hypoparathyroidism than patients with positive lymph nodes (N1). There was a high rate of parathyroid gland re-implantation, but re-implantation was not associated with lower rates of permanent hypoparathyroidism.

Thus, TT+CLND is a strong risk factor for permanent hyperparathyroidism, which is in agreement with a prospective randomised controlled trial performed on 181 patients[110] that showed an increased frequency of permanent hypoparathyroidism after TT+CLND compared to TT alone. An earlier meta-analysis published in 2009 on five single-institutional retrospective observational studies showed that CLND was a risk factor for transient but not permanent hypoparathyroidism[111]. However, a more recent meta-analysis published in 2017 which evaluated 22 retrospective studies found that CLND in cN0 patients was a risk factor for permanent hypoparathyroidism[112].

The most likely cause for the increased rate of permanent hypoparathyroidism after CLND is unintentional removal of or damage to the parathyroid glands. Compared with the upper parathyroid glands, the lower parathyroid glands are at a higher risk of being removed or damaged unintentionally while performing CLND due to their anatomical location[113,114]. However, this risk might be lower in the hands of experienced surgeons[115-117].

Node-negativity (N0/NX), compared to node positivity, in the central compartment after TT with CLND was associated with an increased risk of permanent hypoparathyroidism in the present study. This finding is surprising. A potential explanation could be that normal lymph nodes might be more similar in appearance to the parathyroid glands than metastatic lymph nodes, and therefore the lower parathyroid glands might be at increased risk of unintentional removal in node-negative patients. Another explanation is that surgeons might be more extensive in dissection of lymph nodes while performing a prophylactic and/or diagnostic CLND than when there are clinically enlarged pathological lymph nodes to remove, since the surgeon might be aiming to remove a minimum number of lymph nodes to comply with diagnostic requirements[118].

The observation that re-implantation of the parathyroid gland/glands did not protect patients from permanent hypoparathyroidism is disappointing but in line with a previously performed study in our center[119], and studies by Lorente-Poch L et al[120] and Annebäck et al[69].

Microscopic lymph node metastasis in low-grade papillary thyroid cancer does not seem to have an impact on survival or recurrence according to retrospective studies[121-125]. In contrast, permanent hypoparathyroidism is associated with an increased risk of serious morbidity[81,126-128] and mortality[72].

The finding in the present study, namely that CLND in node-negative patients is a risk factor for postoperative permanent hypoparathyroidism, supports recent American Thyroid Association (ATA) guidelines that advocate against prophylactic CLND in pT1-2 papillary thyroid cancer[29].

In the present study, T3 tumours were included since during the study period the tumours were classified according to the 7th edition of the American Joint Committee on Cancer/Tumour-Node-Metastasis (AJCC /TNM) classification of thyroid cancer. The tumours studied were thus limited to the thyroid or had a minimal invasion into the infrahyoid muscles[129].

During the time span of the present study, national guidelines recommended TT and prophylactic CLND in preoperatively or intraoperatively suspected papillary thyroid cancer (PTC) larger than 10 mm in Sweden. In 2017 guidelines changed, and now recommend CLND only when there is pre- or intraoperative suspicion of lymph node metastasis, in line with the ATA guidelines[31].

Paper IV

In this nationwide, population-based study, short-term mortality after surgery for benign thyroid disease in patients aged 80 years or older was very low, and overall survival high.

Compared with other types of surgeries with greater risk of surgical comorbidities in patients aged 80 years or older[130] thyroid surgery is considered safe[76]. However, preoperative comorbidities of these patients may play a crucial role in postoperative outcomes. Therefore, an individual risk-benefit analysis, and careful preoperative preparation is the key to guaranteeing a successful postoperative outcome[131].

The low SMR in this study indicates that patients aged 80 years or older are highly selected for benign thyroid surgery. However, in some situations, e.g., acute airway obstruction due to large goitre and/or acute thyrotoxicosis due to treatment with the antiarrhythmic drug amiodarone (Cordarone)[132], thyroid surgery has to be performed on vital indication, i.e. to save life. In this situation, patients might have multiple comorbidities, increasing the risk of early mortality.

Strengths and Limitations

Paper I and paper II

Both papers reported retrospective nested case-control studies, however, on pre-defined data fields. Additional data retrieved by questionnaire from the attending surgeons investigated additional variables. An advantage of the nested case-control design is that it is a valid and efficient method for diagnostic and etiologic studies[133]. Both studies were based on a national register with high coverage, which also is a strength.

A limitation of studies I and II is that more than one control group could be matched, but the data collection for additional control groups would take more time. In addition, there would be a risk of losing more cases if there were a mismatch.

Paper III

The strengths of the present investigation include the use of data from nationwide, population-based registers such as the Swedish Prescribed Drug Register, with reliable information about prescriptions and dispensation of oral calcium or active vitamin D after thyroid surgery[82].

Information on levels of the parathyroid hormone (PTH) would have been valuable but was available in neither the SQRTPA nor in any national databases. However, treatment with oral calcium and active D-vitamin within and six months after thyroid surgery is a potential definition of postoperative permanent hypoparathyroidism[134]. The information about the laterality of the CLND is missing in the register; this information would have been useful to verify if all CLNDs in this study were performed bilaterally. Institution volume does not equal surgeon volume; the latter might be equally or more important for outcomes. Unfortunately, the SQRTPA for the period studied did not contain information on individual surgeon volume. Adherence to registration in the SQRTPA is high in Sweden, but even though coverage is very high, it is not complete. Patients not registered in SQRTPA might differ from those not registered[69].

Paper IV

The strength of the study is the use of nationwide databases with a coverage of over 90 percent for thyroid surgery[84] and almost 100 percent for population mortality[83,85]. The limitations of the study include a lack of detailed data on comorbidities of the patients, as well as smoking habit, and other potential risk factors, which would have provided insights into patient selection.

Conclusions

Paper I

Age over 50 years, male gender, and the use of a drain are independent risk factors for postoperative neck haematoma after thyroid surgery. Thyroid malignancy with distant metastasis, large goitre, and preoperative elevated PT-INR are associated with this complication. Slightly less than two-thirds of the patients bleed within six hours postoperatively, whereas 36% of patients suffer from bleeding after the six-hour observation period.

Paper II

The use of drains and concomitant lymph node dissection are independently associated with SSI in surgery for thyroid disease. Patients with these two risk factors constitute a subgroup in which prophylactic antibiotics might be considered, although this was not specifically investigated in the present study. The use of drains in routine non-malignant thyroid surgery should be discouraged.

Paper III

CLND in the surgical management of stages pT1–3 PTC is an independent risk factor for permanent hypoparathyroidism. The increased risk of permanent hypoparathyroidism after CLND must be weighed against the potential benefits of the procedure. Node-negativity is associated with a higher risk of permanent hypoparathyroidism, suggesting an increased risk of permanent hypoparathyroidism in patients who undergo prophylactic CLND. This is in line with the present guidelines advocating against prophylactic CLND in low-stage PTC.

Paper IV

Mortality after surgery for benign thyroid disease in patients 80 years or older is lower than in the general population. Therefore, age (80 years or older), should not be a contraindication *per se*. Surgery can be safely performed in properly selected patients aged 80 years or older, with low short-term mortality and high overall survival.

Future Perspectives

Thyroid surgery has evolved enormously during the last 150 years through great efforts by individual surgeons, although technical development has had an impact as well[12]. As an example, recent studies show that using intraoperative nerve monitoring (IONM) during thyroid surgery decreases the risk of unilateral permanent vocal cord and almost eliminates the risk of bilateral vocal cord palsy[60,62]. The incidence of thyroid cancer is increasing worldwide[135], which is leading to a corresponding increase in thyroid surgery. Therefore, efforts to further minimise the burden of surgical morbidity are needed.

The risk of postoperative bleeding after thyroid surgery is estimated at around two percent, which means seven to ten patients suffer from a life-threatening state in a high-volume centre that performs five hundred thyroidectomies yearly. The reason why high age and male gender are associated with this potential complication is not known and needs to be investigated.

The use of antibiotic prophylaxis is not recommended in thyroid surgery. However, some patients might benefit from it because it might avoid the burden of surgical site infection with its subsequent complications. The use of antibiotic prophylaxis should be further investigated in selected patients with risk factors (lymph node dissection and the use of a drain) for this complication.

Postoperative permanent hypoparathyroidism has in recent studies been shown to be associated with both morbidity and mortality[72,127]. The frequency of this complication is higher than what was previously believed[69]. Avoiding or minimising the burden of this complication is a challenge faced by all thyroid surgeons. A concomitant CLND benefits patients with thyroid cancer by giving better information about disease staging, Additionally, metastatic lymph nodes in the central compartment are not always innocuous[136]. However, in low stage thyroid cancer, the harm after this procedure i.e., permanent hypoparathyroidism, weighs more than the benefits. New techniques for detection and preserving the parathyroid glands e.g., fluorescence with or without indocyanine green angiography are promising but the impact of such novel inventions should be investigated in randomised clinical trials.

As the number of aged people is increasing worldwide[137] the need for surgical care among them is increasing simultaneously[138]. Paper IV showed a low mortality in patients undergoing thyroid surgery for benign thyroid disease. In contrast, mortality after thyroid surgery in aged patients with thyroid cancer has increased[74].

This could be because patients with malignant thyroid disease undergoing surgery are usually not as selected as those with benign disease. Additionally, thyroid cancer might be more hazardous in aged patients compared with young patients, which could have a negative impact on survival in these patients.

There is a need to further investigate the possible risk factors for the increased mortality in aged patients.

Populärvetenskaplig sammanfattning

I Sverige opereras ca 3000 patienter för sköldkörtelsjukdom. Dessa sjukdomar kan vara både godartade och elakartade. Sköldkörtelkirurgi, i vana händer är säker. Ändå drabbas ett antal individer av komplikationer som i extrema fall kan vara livshotande eller ge patienten bestående men i form av röstpåverkan och permanent kalkbrist som kräver livslång medicinering.

Blödning efter sköldkörteloperation är en livshotande komplikation på grund av direkt hot mot luftvägen. Om blödning inträffar, behövs den oftast åtgärdas omedelbart med reoperation och utrymning av koagel i livräddande syfte. Dagkirurgiska sköldkörteloperationer har påbörjats i Sverige och därför är det viktigt att välja lämpliga patienter för denna verksamhet. Delarbete I i denna avhandling handlar om att kunna identifiera patienter som har låg eller ingen risk att drabbas av blödning efter operation. Resultat från studien visar att hög ålder >50 år, män och användandet av drän är oberoende riskfaktorer för blödning i halsen efter sköldkörtelkirurgi. Hos patienter utan dessa riskfaktorer, drabbas ändå 1 % av blödning som kräver reoperation. Tre fjärdedelar av patienterna blöder inom 6 timmar efter skölkörteloperationen och 80% inom 12 timmar. Studiens konklusion är att extrem noggrannhet behövs för att välja lämpliga patienter till dagkirurgi och en observationstid på minst 12 timmar bör eftersträvas. Kirurgerna bör vara medvetna om att det ändå finns ett fåtal patienter som kan blöda även efter observationstiden. Dagkirurgiska patienter bör därför vistas i närheten av sjukhuset och ha möjlighet till att snabbt få vård.

Sårinfektion förekommer hos cirka 1–2 % av patienter efter ett sköldkörtelingrepp och kan leda till återinläggning på sjukhus med ibland reoperation, dränage eller intravenös antibiotikabehandling. Med tanke på antalet patienter som opereras varje år så drabbas 30 till 60 patienter av denna typ av komplikation. Att identifiera riskfaktorer för sårinfektion och förebygga dessa är viktig. Om man kan förebygga den postoperativa infektionen skulle dessa patienter slippa den besvärliga komplikationen och inte minst sjukvårdsresurser skulle kunna sparas. Delarbete II i denna avhandling studerade riskfaktorer för postoperativ sårinfektion efter sköldkörtelkirurgi och behov av antibiotikabehandling i förebyggande syfte. Resultat från studien visar att risken för sårinfektion är högre om patienten genomgår lymfkörtelutrymning i samband med sköldkörtelkirurgi och om kirurgen anser att drän behövs i operationssåret i slutet på operationen. Det är möjligt att antibiotika i förebyggande syfte minskar risken för infektion just vid lymfkörtelutrymning eller dräninläggning.

Vid sköldkörtelcancer utförs förutom sköldkörteloperation, även operation på intilliggande lymfkörtlar (central lymfkörtelutrymning) för att kunna identifiera cancerstadium och minska risken för återfall. Problemet med borttagande av de intilliggande lymfkörtlarna är att ingreppet är förknippat med komplikationer främst i form av bisköldkörtelhormonbrist (hypoparatyreoidism) som leder till kalkbrist (hypokalcemi) efter sköldkörteloperation. Anledning till detta är att man i samband med ingreppet kan råka att oavsiktligt ta bort de nedre bisköldkörtlarna som är lokaliserade på samma ställe som de centrala lymfkörtlarna och dessa kan vara svåra att skilja från de drabbade lymfkörtlarna. Senaste studier har visat att patienter med permanent kalkbrist trots sina läkemedelsbehandling har ökad risk för sjuklighet i hjärtkärlsjukdomar och även död. Merparten av sköldkörtelcancer är så kallad papillär sköldkörtelcancer och har god prognos, med minimal återfallsrisk och risk för död. Att utföra förebyggande lymfkörtelutrymning hos patienter med papillär sköldkörtelcancer kan därför vara mer skadligt än nyttigt. Delarbete III i denna avhandling studerade denna komplikation i en svensk population. Studien visar att individer som genomgår lymfkörtelutrymning vid sköldkörtelkirurgi av papillär sköldkörtelcancer oftare drabbas av permanent postoperativ kalkbrist på grund av bisköldkörtelhormonbrist. Riktlinjer idag säger att man skall avstå förebyggande lymfkörtelutrymning vid papillär sköldkörtelcancer av låg cancerstudium.

Medianåldern för sköldkörtelkirurgi i Sverige är 49 år. Emellertid ökar antalet ingrepp också hos äldre patienter och för närvarande utgör gruppen över 80 år 2,5 % procent av samtliga sköldkörtelopererade patienter. Andelen äldre i befolkningen ökar snabbt. En rapport från FN uppskattar att antalet människor som är 80 år och äldre kommer att öka till det tredubbla år 2050. Detta innebär att kirurgi hos äldre kommer också att öka. Operativ behandling av äldre på grund av godartade sköldkörtelsjukdomar har varit omdiskuterat. En del studier genomförda med stort antal patienter har konkluderat att äldre har ökad risk för postoperativa komplikationer och därmed också ökad risk för död. En del andra studier har kommit fram till att om man väljer rätt patienter d.v.s. patienter som inte är allt för sjuka, så är risken liten för äldre patienter. Samtliga dessa studier har studerat cancerpatienter och patienter med godartade sköldkörtelsjukdomar. Delarbete IV i denna avhandling studerade risk för död hos patienter som är 80 år och äldre och som har genomgått sköldkörteloperation p.g.a. godartad sköldkörtelsjukdom. Resultatet från studien visar att äldre patienter som genomgår sköldkörtelkirurgi för godartade sköldkörtelsjukdomar har mycket låg dödlighet och en lång förväntad överlevnad vilket gör sköldkörteloperation rimlig inte minst då den förbättrar patientens livskvalitet.

Sammanfattningsvis är komplikationer till sköldkörtelkirurgi relativt ovanliga, men dessvärre kan komplikationerna vara potentiellt livshotande när de uppträder och ge upphov till livslångt handikapp.

Errata

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References

1. Zizic M. *History of Thyroid and Parathyroid Surgery.* 2003.
2. Radu Mihai APR, Gregory W. Randolph. *The History and Evolution of Techniques for Thyroid Surgery.* 2009.
3. Sarkar S, Banerjee S, Sarkar R, Sikder B. A Review on the History of 'Thyroid Surgery'. *Indian J Surg.* 2016;78(1):32-36.
4. DuBose J, Barnett R, Ragsdale T. Honest and sensible surgeons: the history of thyroid surgery. *Curr Surg.* 2004;61(2):213-219.
5. Hannan SA. The magnificent seven: a history of modern thyroid surgery. *International journal of surgery (London, England).* 2006;4(3):187-191.
6. Terris DJ. Incision in Thyroid and Parathyroid Surgery. In: GW R, ed. *Surgery of the Thyroid and Parathyroid Glands.* 2nd ed. Philadelphia: Elsevier/Saunders; 2013:403-406.
7. Vieni S, Latteri S, Lo Dico R. [Short account of the history of thyroid surgery]. *Annali italiani di chirurgia.* 2005;76(1):5-7.
8. Ignjatovic M. [Overview of the history of thyroid surgery]. *Acta chirurgica Iugoslavica.* 2003;50(3):9-36.
9. Becker WF. Presidential address: Pioneers in thyroid surgery. *Annals of surgery.* 1977;185(5):493-504.
10. Marchese-Ragona R, Restivo DA, Mylonakis I, et al. The superior laryngeal nerve injury of a famous soprano, Amelita Galli-Curci. *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale.* 2013;33(1):67-71.
11. Kark AE, Kissin MW, Auerbach R, Meikle M. Voice changes after thyroidectomy: role of the external laryngeal nerve. *British medical journal (Clinical research ed).* 1984;289(6456):1412-1415.
12. Sakorafas GH. Historical evolution of thyroid surgery: from the ancient times to the dawn of the 21st century. *World journal of surgery.* 2010;34(8):1793-1804.
13. Rosen RD, Sapra A. Embryology, Thyroid. In: *StatPearls.* Treasure Island (FL)2020.
14. Nilsson M, Fagman H. Development of the thyroid gland. *Development.* 2017;144(12):2123-2140.
15. Konstantinidou S, Konstantinidou E. The thyroid gland in ancient Greece: a historical perspective. *Hormones (Athens).* 2018;17(2):287-291.
16. Mnatsakanian A, Al Khalili Y. Anatomy, Head and Neck, Thyroid Muscles. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing

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17. White AM, Lasrado S. Anatomy, Head and Neck, Thyroid Arteries. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing

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18. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. *Archives of otolaryngology--head & neck surgery.* 2002;128(7):751-758.
19. Amit Agarwal AKM, Celestino P. Lombardi, Marco Raffaelli. *Applied Embryology of the Thyroid and Parathryoid Glands.* 2003.
20. Allen E, Fingeret A. Anatomy, Head and Neck, Thyroid. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing

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21. L.Lee S. Thyroid Physiology and Thyroid Function Testing. In: Randolph GW, ed. *Surgery of the Thyroid and Parathyroid Glands.* Philadelphia, Pa.: W. B. Saunders; 2003:25-26.
22. Shahid MA, Ashraf MA, Sharma S. Physiology, Thyroid Hormone. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing

Copyright © 2021, StatPearls Publishing LLC.; 2021.

23. Felsenfeld AJ, Levine BS. Calcitonin, the forgotten hormone: does it deserve to be forgotten? *Clinical kidney journal.* 2015;8(2):180-187.
24. Miranda-Filho A, Lortet-Tieulent J, Bray F, et al. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. *The Lancet Diabetes & Endocrinology.* 2021;9(4):225-234.
25. Olson E, Wintheiser G, Wolfe KM, Droessler J, Silberstein PT. Epidemiology of Thyroid Cancer: A Review of the National Cancer Database, 2000-2013. *Cureus.* 2019;11(2):e4127.
26. Figge JJ. Epidemiology of Thyroid Cancer. In: Wartofsky L, Van Nostrand D, eds. *Thyroid Cancer: A Comprehensive Guide to Clinical Management.* Totowa, NJ: Humana Press; 2006:9-13.
27. *Annual report Thyroid Cancer in Sweden.* Regionalt Cancer Centrum;2019.
28. Callender GG, Carling T, Christison-Lagay E, Udelsman R. Surgery for thyroid cancer. *Endocrinol Metab Clin North Am.* 2014;43(2):443-458.
29. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid : official journal of the American Thyroid Association.* 2016;26(1):1-133.
30. Mitchell AL, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: United Kingdom National Multidisciplinary Guidelines. *The Journal of laryngology and otology.* 2016;130(S2):S150-s160.

31. Swedish National Guidelines for Treatment of Thyroid Cancer. https://www.cancercentrum.se/samverkan/cancerdiagnoser/skoldkortel/vardprogram/gallande-vardprogram/ Web site. Published 2017. Accessed.
32. Limaiem F, Kashyap S, Giwa AO. Cancer, Anaplastic Thyroid. In: *StatPearls.* Treasure Island (FL)2020.
33. Busnardo B, Daniele O, Pelizzo MR, et al. A multimodality therapeutic approach in anaplastic thyroid carcinoma: study on 39 patients. *J Endocrinol Invest.* 2000;23(11):755-761.
34. Hussain YS, Hookham JC, Allahabadia A, Balasubramanian SP. Epidemiology, management and outcomes of Graves' disease-real life data. *Endocrine.* 2017;56(3):568-578.
35. Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS. The Diagnosis and Management of Thyroid Nodules: A Review. *Jama.* 2018;319(9):914-924.
36. Smithson M, Asban A, Miller J, Chen H. Considerations for Thyroidectomy as Treatment for Graves Disease. *Clin Med Insights Endocrinol Diabetes.* 2019;12:1179551419844523.
37. Gregory W. Randolph OHC. *Principles in Thyroid Surgery.* Philadelphia: Elsevier Saunders; 2003.
38. Gregory W. Randolph OHC. *Surgical Anatomy and Monitoring of the Recurrent Laryngeal Nerve.* Philadelphia: Elsevier Saunders; 2003.
39. Lo CY, Tam SC. Parathyroid autotransplantation during thyroidectomy: documentation of graft function. *Archives of surgery (Chicago, Ill : 1960).* 2001;136(12):1381-1385.
40. Cavallaro G, Iorio O, Centanni M, et al. Parathyroid Reimplantation in Forearm Subcutaneous Tissue During Thyroidectomy: A Simple and Effective Way to Avoid Hypoparathyroidism. *World journal of surgery.* 2015;39(8):1936-1942.
41. Spartalis E, Ntokos G, Georgiou K, et al. Intraoperative Indocyanine Green (ICG) Angiography for the Identification of the Parathyroid Glands: Current Evidence and Future Perspectives. *In vivo (Athens, Greece).* 2020;34(1):23-32.
42. Jongekkasit I, Jitpratoom P, Sasanakietkul T, Anuwong A. Transoral Endoscopic Thyroidectomy for Thyroid Cancer. *Endocrinol Metab Clin North Am.* 2019;48(1):165-180.
43. Kandil E, Attia AS, Hadedeya D, Shihabi A, Elnahla A. Robotic Thyroidectomy: Past, Future, and Current Perspectives. *Otolaryngol Clin North Am.* 2020;53(6):1031-1039.
44. Tae K, Ji YB, Song CM, Ryu J. Robotic and Endoscopic Thyroid Surgery: Evolution and Advances. *Clinical and experimental otorhinolaryngology.* 2019;12(1):1-11.
45. Picucci L, Persico Stella L, Alibrandi M, Cardillo L, Trombini R, Morano C. [Postoperative complications after thyroid surgery. Review of the literature and personal experience]. *Minerva Chir.* 1997;52(7-8):901-912.

46. Ted H. Leem EV, David W. . *Non-Neural Complications of Thyroid and Parathyroid Surgery.* Philadelphia, Pa.: W. B. Saunders; 2003.
47. Arturo Ramon Franco J, Akira Miyauchi. *Management of Recurrent Laryngeal Nerve Paralysis.* Philadelphia, Pa.: W. B. Saunders; 2003.
48. Weiss A, Lee KC, Brumund KT, Chang DC, Bouvet M. Risk factors for hematoma after thyroidectomy: Results from the nationwide inpatient sample. *Surgery.* 2014;156(2):399-404.
49. Bergenfelz A, Jansson S, Kristoffersson A, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbeck's archives of surgery.* 2008;393(5):667-673.
50. Rosenbaum MA, Haridas M, McHenry CR. Life-threatening neck hematoma complicating thyroid and parathyroid surgery. *American journal of surgery.* 2008;195(3):339-343; discussion 343.
51. Edafe O, Cochrane E, Balasubramanian SP. Reoperation for Bleeding After Thyroid and Parathyroid Surgery: Incidence, Risk Factors, Prevention, and Management. *World journal of surgery.* 2020;44(4):1156-1162.
52. Farooq MS, Nouraei R, Kaddour H, Saharay M. Patterns, timing and consequences of post-thyroidectomy haemorrhage. *Annals of the Royal College of Surgeons of England.* 2017;99(1):60-62.
53. Xie QP, Xiang C, Wang Y, et al. The patterns and treatment of postoperative hemorrhage and hematoma in total endoscopic thyroidectomy via breast approach: experience of 1932 cases. *Endocrine.* 2019;63(3):422-429.
54. Lee HS, Lee BJ, Kim SW, et al. Patterns of Post-thyroidectomy Hemorrhage. *Clinical and experimental otorhinolaryngology.* 2009;2(2):72-77.
55. Burkey SH, van Heerden JA, Thompson GB, Grant CS, Schleck CD, Farley DR. Reexploration for symptomatic hematomas after cervical exploration. *Surgery.* 2001;130(6):914-920.
56. Materazzi G, Ambrosini CE, Fregoli L, et al. Prevention and management of bleeding in thyroid surgery. *Gland surgery.* 2017;6(5):510-515.
57. Liu J, Sun W, Dong W, et al. Risk factors for post-thyroidectomy haemorrhage: a meta-analysis. *European journal of endocrinology.* 2017;176(5):591-602.
58. Fan C, Zhou X, Su G, et al. Risk factors for neck hematoma requiring surgical re-intervention after thyroidectomy: a systematic review and meta-analysis. *BMC surgery.* 2019;19(1):98.
59. Balentine CJ, Sippel RS. Outpatient Thyroidectomy: Is it Safe? *Surgical oncology clinics of North America.* 2016;25(1):61-75.
60. Bergenfelz A, Salem AF, Jacobsson H, Nordenstrom E, Almquist M. Risk of recurrent laryngeal nerve palsy in patients undergoing thyroidectomy with and without intraoperative nerve monitoring. *The British journal of surgery.* 2016;103(13):1828-1838.

61. Mohebati A, Shaha AR. Anatomy of thyroid and parathyroid glands and neurovascular relations. *Clinical anatomy (New York, NY)*. 2012;25(1):19-31.
62. Abdelhamid A, Aspinall S. Intraoperative nerve monitoring in thyroid surgery: analysis of United Kingdom registry of endocrine and thyroid surgery database. *British Journal of Surgery*. 2021.
63. Bures C, Zielinski V, Klatte T, et al. [Streptococcal mediastinitis after thyroidectomy. A literature review]. *Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen*. 2015;86(12):1145-1150.
64. Leem TH VE, Eisele DW Non-neural complications of thyroid and parathyroid surgery. In: GW R, ed. *Surgery Of The Thyroid And Parathyroid Glands*. Philadelphia: Elsevier Saunders; 2003:446-452.
65. Urban JA. Cost analysis of surgical site infections. *Surgical infections*. 2006;7 Suppl 1:S19-22.
66. Bures C, Klatte T, Gilhofer M, et al. A prospective study on surgical-site infections in thyroid operation. *Surgery*. 2014;155(4):675-681.
67. Lu Q, Xie SQ, Chen SY, Chen LJ, Qin Q. Experience of 1166 thyroidectomy without use of prophylactic antibiotic. *BioMed research international*. 2014;2014:758432.
68. Qin Q, Li H, Wang LB, Li AH, Chen LJ, Lu Q. Thyroid surgery without antibiotic prophylaxis: experiences with 1,030 patients from a teaching hospital in China. *World journal of surgery*. 2014;38(4):878-881.
69. Anneback M, Hedberg J, Almquist M, Stalberg P, Norlen O. Risk of Permanent Hypoparathyroidism After Total Thyroidectomy for Benign Disease: A Nationwide Population-based Cohort Study From Sweden. *Annals of surgery*. 2020.
70. Powers J, Joy K, Ruscio A, Lagast H. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. *J Bone Miner Res*. 2013;28(12):2570-2576.
71. Bergenfelz A, Nordenström E, Almquist M. Morbidity in patients with permanent hypoparathyroidism after total thyroidectomy. *Surgery*. 2020;167(1):124-128.
72. Almquist M, Ivarsson K, Nordenstrom E, Bergenfelz A. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy. *The British journal of surgery*. 2018;105(10):1313-1318.
73. Foster RS, Jr. Morbidity and mortality after thyroidectomy. *Surgery, gynecology & obstetrics*. 1978;146(3):423-429.
74. Joseph KR, Edirimanne S, Eslick GD. Thyroidectomy for thyroid cancer in the elderly: A meta-analysis. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2019;45(3):310-317.
75. Seybt MW, Khichi S, Terris DJ. Geriatric thyroidectomy: safety of thyroid surgery in an aging population. *Archives of otolaryngology--head & neck surgery*. 2009;135(10):1041-1044.

76. Wong EH, Smith M, Fish B, et al. Thyroidectomy in octogenarians is not associated with poorer postoperative outcomes. *Head & neck.* 2019.
77. Canonico S, Pellino G, Pameggiani D, et al. Thyroid surgery in the elderly: a comparative experience of 400 patients from an Italian university hospital. *International surgery.* 2014;99(5):523-527.
78. Ben Nun A, Soudack M, Best LA. Retrosternal thyroid goiter: 15 years experience. *Isr Med Assoc J.* 2006;8(2):106-109.
79. Chen AY, Bernet VJ, Carty SE, et al. American Thyroid Association statement on optimal surgical management of goiter. *Thyroid : official journal of the American Thyroid Association.* 2014;24(2):181-189.
80. Knobel M. An overview of retrosternal goiter. *J Endocrinol Invest.* 2021;44(4):679-691.
81. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. *Nature reviews Disease primers.* 2017;3:17055.
82. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf.* 2007;16(7):726-735.
83. Swedish National Board of Health and Welfare. https://www.socialstyrelsen.se/en/. Accessed.
84. Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal surgery. https://sqrtpa.se. Accessed.
85. Statistics Sweden https://www.scb.se/en/.
86. Fortuny JV, Guigard S, Karenovics W, Triponez F. Surgery of the thyroid: recent developments and perspective. *Swiss Med Wkly.* 2015;145:w14144.
87. Dedivitis RA, Pfuetzenreiter EG, Jr., Castro MA, Denardin OV. Analysis of safety of short-stay thyroid surgery. *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale.* 2009;29(6):326-330.
88. Godballe C, Madsen AR, Pedersen HB, et al. Post-thyroidectomy hemorrhage: a national study of patients treated at the Danish departments of ENT Head and Neck Surgery. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery.* 2009;266(12):1945-1952.
89. Campbell MJ, McCoy KL, Shen WT, et al. A multi-institutional international study of risk factors for hematoma after thyroidectomy. *Surgery.* 2013;154(6):1283-1289; discussion 1289-1291.
90. Basques BA, Bohl DD, Golinvaux NS, Yacob A, Varthi AG, Grauer JN. Factors predictive of increased surgical drain output after anterior cervical discectomy and fusion. *Spine.* 2014;39(9):728-735.
91. Kalemera Ssenyondo E, Fualal J, Jombwe J, Galukande M. To drain or not to drain after thyroid surgery: a randomized controlled trial at a

tertiary Hospital in East Africa. *African health sciences.* 2013;13(3):748-755.
92. Tuggle CT, Roman S, Udelsman R, Sosa JA. Same-day thyroidectomy: a review of practice patterns and outcomes for 1,168 procedures in New York State. *Annals of surgical oncology.* 2011;18(4):1035-1040.
93. Sun GH, DeMonner S, Davis MM. Epidemiological and economic trends in inpatient and outpatient thyroidectomy in the United States, 1996-2006. *Thyroid : official journal of the American Thyroid Association.* 2013;23(6):727-733.
94. Terris DJ, Snyder S, Carneiro-Pla D, et al. American Thyroid Association statement on outpatient thyroidectomy. *Thyroid : official journal of the American Thyroid Association.* 2013;23(10):1193-1202.
95. Lee DJ, Chin CJ, Hong CJ, Perera S, Witterick IJ. Outpatient versus inpatient thyroidectomy: A systematic review and meta-analysis. *Head & neck.* 2018;40(1):192-202.
96. Grubey JS, Raji Y, Duke WS, Terris DJ. Outpatient thyroidectomy is safe in the elderly and super-elderly. *The Laryngoscope.* 2018;128(1):290-294.
97. Doran HE, England J, Palazzo F. Questionable safety of thyroid surgery with same day discharge. *Annals of the Royal College of Surgeons of England.* 2012;94(8):543-547.
98. Khadra H, Mohamed S, Hauch A, Carter J, Hu T, Kandil E. Safety of same-day thyroidectomy: meta-analysis and systematic review. *Gland surgery.* 2017;6(4):292-301.
99. Dargaud Y, Hoffman M, Lefrapper L, et al. Bleeding risk in warfarinized patients with a therapeutic international normalized ratio: the effect of low factor IX levels. *J Thromb Haemost.* 2013;11(6):1043-1052.
100. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Arch Intern Med.* 2007;167(13):1414-1419.
101. Dubois V, Dincq AS, Douxfils J, et al. Perioperative management of patients on direct oral anticoagulants. *Thromb J.* 2017;15:14.
102. Gentile I, Rosato L, Avenia N, et al. Do Italian surgeons use antibiotic prophylaxis in thyroid surgery? Results from a national study (UEC--Italian Endocrine Surgery Units Association). *Annali italiani di chirurgia.* 2014;85(1):33-37.
103. Coskun H, Erisen L, Basut O. Factors affecting wound infection rates in head and neck surgery. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2000;123(3):328-333.
104. Elfenbein DM, Schneider DF, Chen H, Sippel RS. Surgical site infection after thyroidectomy: a rare but significant complication. *Journal of Surgical Research.* 2014;190(1):170-176.
105. Moalem J, Ruan DT, Farkas RL, et al. Patterns of antibiotic prophylaxis use for thyroidectomy and parathyroidectomy: results of an international

survey of endocrine surgeons. *Journal of the American College of Surgeons.* 2010;210(6):949-956.
106. De Palma M, Grillo M, Borgia G, Pezzullo L, Lombardi CP, Gentile I. Antibiotic prophylaxis and risk of infections in thyroid surgery: results from a national study (UEC-Italian Endocrine Surgery Units Association). *Updates in surgery.* 2013;65(3):213-216.
107. Uruno T, Masaki C, Suzuki A, et al. Antimicrobial prophylaxis for the prevention of surgical site infection after thyroid and parathyroid surgery: a prospective randomized trial. *World journal of surgery.* 2015;39(5):1282-1287.
108. Tian J, Li L, Liu P, Wang X. Comparison of drain versus no-drain thyroidectomy: a meta-analysis. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery.* 2016.
109. Teija-Kaisa A, Eija M, Marja S, Outi L. Risk factors for surgical site infection in breast surgery. *Journal of clinical nursing.* 2013;22(7-8):948-957.
110. Viola D, Materazzi G, Valerio L, et al. Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study. *The Journal of clinical endocrinology and metabolism.* 2015;100(4):1316-1324.
111. Chisholm EJ, Kulinskaya E, Tolley NS. Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. *The Laryngoscope.* 2009;119(6):1135-1139.
112. Zhao WJ, Luo H, Zhou YM, Dai WY, Zhu JQ. Evaluating the effectiveness of prophylactic central neck dissection with total thyroidectomy for cN0 papillary thyroid carcinoma: An updated meta-analysis. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2017.
113. Akerstrom G, Malmaeus J, Bergstrom R. Surgical anatomy of human parathyroid glands. *Surgery.* 1984;95(1):14-21.
114. Sadowski SM, Vidal Fortuny J, Triponez F. A reappraisal of vascular anatomy of the parathyroid gland based on fluorescence techniques. *Gland surgery.* 2017;6(Suppl 1):S30-s37.
115. White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. *World journal of surgery.* 2007;31(5):895-904.
116. Jennifer A. Sipos ELM. Papillary Thyroid Cancer. *Surgery of the Thyroid and Parathyroid Glands, GW Randolph.* 2003:183.
117. Wang JB, Wu K, Shi LH, Sun YY, Li FB, Xie L. In situ preservation of the inferior parathyroid gland during central neck dissection for papillary

thyroid carcinoma. *The British journal of surgery.* 2017;104(11):1514-1522.

118. Robinson TJ, Thomas S, Dinan MA, Roman S, Sosa JA, Hyslop T. How Many Lymph Nodes Are Enough? Assessing the Adequacy of Lymph Node Yield for Papillary Thyroid Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2016;34(28):3434-3439.

119. Nordenstrom E, Bergenfelz A, Almquist M. Permanent Hypoparathyroidism After Total Thyroidectomy in Children: Results from a National Registry. *World journal of surgery.* 2018;42(9):2858-2863.

120. Lorente-Poch L, Sancho J, Munoz JL, Gallego-Otaegui L, Martinez-Ruiz C, Sitges-Serra A. Failure of fragmented parathyroid gland autotransplantation to prevent permanent hypoparathyroidism after total thyroidectomy. *Langenbeck's archives of surgery.* 2017;402(2):281-287.

121. Nixon IJ, Ganly I, Patel S, et al. The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. *Surgery.* 2011;150(6):1242-1249.

122. Nixon IJ, Ganly I, Patel SG, et al. Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. *Surgery.* 2013;154(6):1166-1172; discussion 1172-1163.

123. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid : official journal of the American Thyroid Association.* 2012;22(11):1144-1152.

124. Liu J, Xu Z, Li Z, Zhang Z, Tang P, Liu S. Long-term outcomes of observation for clinically negative central compartment lymph nodes in papillary thyroid carcinoma. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery.* 2015;272(12):3801-3804.

125. Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. *Surgery.* 2008;144(6):1070-1077; discussion 1077-1078.

126. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *The Journal of clinical endocrinology and metabolism.* 2012;97(12):4507-4514.

127. Senay Yildiz Celik D. Diffuse Cerebral Calcification due to Iatrogenic Hypoparathyroidism. *Turkish Journal of Neurology.* 2017;23:130-131.

128. Cusano NE, Bilezikian JP. Update on hypoparathyroidism. *Current opinion in rheumatology.* 2019;31(4):381-387.

129. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why?

Thyroid : official journal of the American Thyroid Association. 2017;27(6):751-756.
130. Xu Y, Wang Y, Xi C, Ye N, Xu X. Is it safe to perform gastrectomy in gastric cancer patients aged 80 or older?: A meta-analysis and systematic review. *Medicine (Baltimore).* 2019;98(24):e16092.
131. Passler C, Avanessian R, Kaczirek K, Prager G, Scheuba C, Niederle B. Thyroid surgery in the geriatric patient. *Archives of surgery (Chicago, Ill : 1960).* 2002;137(11):1243-1248.
132. Kotwal A, Clark J, Lyden M, McKenzie T, Thompson G, Stan MN. Thyroidectomy for Amiodarone-Induced Thyrotoxicosis: Mayo Clinic Experience. *J Endocr Soc.* 2018;2(11):1226-1235.
133. Biesheuvel CJ, Vergouwe Y, Oudega R, Hoes AW, Grobbee DE, Moons KG. Advantages of the nested case-control design in diagnostic research. *BMC Med Res Methodol.* 2008;8:48.
134. Harsløf T, Rolighed L, Rejnmark L. Huge variations in definition and reported incidence of postsurgical hypoparathyroidism: a systematic review. *Endocrine.* 2019;64(1):176-183.
135. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol.* 2013;2013:965212.
136. Mazzaferri EL, Doherty GM, Steward DL. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma. *Thyroid : official journal of the American Thyroid Association.* 2009;19(7):683-689.
137. *World Population Ageing 2019.* New York: Department of Economic and Social Affairs, Population Division, The UN. ST/ESA/SER.A/444, p. 6;2019.
138. The American College of Surgeons. Geriatric Surgery Verification Program. https://www.facs.org/Quality-Programs/geriatric-surgery/standards. Accessed.

Supplementary Documents

The questionnaire sent to attending surgeons for studies I and II.

Complications after thyroid surgery

Post- operative bleeding and surgical site infection

Questionnaire

(Part I)

1. Personal identification number. ……………………
2. Operation id. …………………………
3. Weight……….kg   Height……………cm.
4. Patient´s medication before the operation?
(Which medication did the patient have before surgery and what is the policy in your clinic/hospital regarding interruption of medicines affecting surgery? If the time of interruption is not clear, please answer according to the hospital´s policy)

a. Warfarin. ☐Paused……..days before surgery. ☐Was not paused

b. Low Molecular Volume Heparin (LMVH). ☐Paused…….days before surgery. ☐Was not paused

c. Clopidrogel. ☐Paused…….days before surgery. ☐Was not paused

d. Other anticoagulants. ☐Paused……..days before surgery. ☐Was not paused

e. Non Steroid Anti Inflammatory Drugs (NSAID). ☐Paused……..days before surgery. ☐Was not paused

f. Acetylsalicylic acid (ASA). ☐Paused……..days before surgery. ☐Was not paused

g. Cortisone therapy. ☐Paused……..days before surgery. ☐Was not paused

h. Immunosuppressive therapy. ☐Paused……..days before surgery. ☐Was not paused

i. Ongoing chemotherapy. ☐Paused……..days before surgery. ☐Was not paused

j. Selective Serotonin Reuptake Inhibitor (SSRI). ☐Paused……..days before surgery. ☐Was not paused

k. Prophylactic antibiotics for thyroid surgery? ☐Yes ☐No

5. Did the patient have any of the following diseases when thyroid surgery was planned?

a. Bleeding disorder (Von Willebrand disease, Haemophili A or B, Other bleeding disorder)

☐Yes ☐No

b. Kidney failure ☐Yes ☐No

c. Liver failure ☐Yes ☐No

d. Cardiovascular disease ☐Yes ☐No

e. Diabetes Mellitus ☐Yes ☐No

f. Any other malignancy than thyroid cancer ☐Yes ☐No

6. Smoking habits

☐ Smoker

☐ not smoker

☐ ex-smoker

7. Laboratory examination

a. Level of Thrombocytes in the serum ………..10^9/L

b. PT- (INR)………

c. APTT…………..seconds

d. Level of Creatinine in the plasma………µmol/L

8. Haemostatic technic used during the operation

☐ Ligature

☐ Electric instrument for cutting and sealing

9. Drain used? ☐Yes ☐No

10. Specimen weight………………… grams

(Part II) To be answered only if the patient had a postoperative bleeding.

1. When did the bleeding occur?

(Time relationship with end of surgery in hours)

☐<1 hour ☐1-6 hours ☐6-12 hours ☐12-24 hours ☐> 24 hours

2.

Where was the bleeding detected?

☐In the operating room ☐In the postoperative care or ward ☐Outside the hospital

3. What was done for immediate action?

(Information regarding the management of the hematoma. If before intubation at the site where the bleeding was detected due to respiratory affection or in the OR with the patient intubated)

☐ Immediate evacuation of hematoma before intubation.

☐ Hematoma evacuation after intubation.

4. How was the bleeding interpreted ☐Superficial ☐Deep ☐Diffuse

(If the cause of the bleeding has been interpreted in another way, please indicate in the line below the question.)

……

5. How many days, from the day of surgery, was the patient cared in the hospital? ....

6. Was the patient affected by rebleeding or any other complications?

(If the patient has suffered from other complications after postoperative bleeding, e.g. re-bleeding, infection in the operative wound, hypocalcaemia, pneumonia, etc. please indicate in the line below.)

……

Part III. To be answered only if the patient had a postoperative surgical site infection.

1. Which postoperative day was the surgical site infection (SSI) detected? …………………
2. How was the complication (infection) managed?
   - ☐ Surgical incision
   - ☐ Percutaneous drainage
   - ☐ Antibiotics
3. Where was the patient treated?
   - ☐ In the hospital ward
   - ☐ In the outpatient department
   - ☐ Outside the hospital

4. Additional information or comments:

Original Papers