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Quality of life in patients with thyroid cancer

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Quality of life in patients with thyroid cancer

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Stockholm 2017

To my family

ABSTRACT

Background: The prevalence of differentiated thyroid cancer (DTC) is increasing as a consequence of rising incidence, young age at diagnosis and excellent survival. The established treatment is surgery, followed by radioiodine as well as levothyroxine substitution. Because of the longevity of DTC patients, health-related quality of life (HRQoL) has become important. Previous studies have shown decreased HRQoL in DTC, nevertheless, changes of HRQoL over time and factors affecting HRQoL are scarcely described. The aims of this thesis were to investigate long-term HRQoL, how HRQoL changes over time and how anxiety and fear of recurrence affect patients with thyroid cancer.

Patients, methods and results: In Studies I-III, SF-36 and a study-specific questionnaire were used. In Studies I-II, long-term HRQoL was measured by including patients 14-17 years after diagnosis. HRQoL was shown to be lower in DTC patients compared with the Swedish general population. Half of the patients had fear of recurrence, and those with fear had significantly lower HRQoL. Thyroid-related symptoms, such as fatigue, sleeping problems, irritability and sweating were measured, and the majority (88%) had at least one of these symptoms. Those with major or moderate symptom intensity had significantly lower HRQoL in eight and four SF-36 domains, respectively. These differences remained after adjustment for age, sex, comorbidities and education.

In study III, DTC patients were included at diagnosis and followed-up. After one year, HRQoL was higher compared with baseline in six of eight SF-36 domains. As the majority of the patients were treated with levothyroxine in TSH suppressive doses, this might have affected HRQoL. Surprisingly, those on moderate TSH suppression had lower HRQoL compared with those on complete suppression. In addition, more than half of the patients had a fear of recurrence, with significantly lower HRQoL. Predictive factors of HRQoL at follow-up were studied and in bivariate models, e.g. comorbidities and HRQoL at diagnosis were associated with lower HRQoL at one year. In regression models, poor HRQoL at diagnosis was the only predictive factor for poor HRQoL at one-year of follow-up, after adjustment for comorbidities, age, sex, stage of disease and fear of recurrence.

To broaden the understanding about anxiety and fear of recurrence, semi-structured interviews were performed with 21 patients in Study IV. Anxiety was present both in patients with and without recurrence and regardless of sociodemographic factors. Fear of recurrence, follow-up routines, distrust in the healthcare system and lack of information were all sources of anxiety. In some patients, hidden anxiety not mentioned in the beginning became apparent later during the interviews. Everyday life and routines were used as protective strategies against frightening thoughts. Avoiding contact with healthcare helped them gather energy to cope with their disease.

Discussion: HRQoL was decreased in DTC patients compared with a general population and was negatively associated with thyroid-related symptoms and fear of recurrence. Interestingly, TSH suppression was not associated to lower HRQoL. The patients' perception of having a “good cancer” might have discouraged them from discussing anxiety with healthcare. As HRQoL at diagnosis was the only independent predictive factor of HRQoL at one year of follow-up, the evaluation of HRQoL early in the disease trajectory is important. Individualised follow-up routines and evaluation of fears and anxiety during consultations might be helpful, and instead of using the term “good cancer”, “low-risk cancer” can be recommended.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I-IV):

I. Hedman C, Djärv T, Strang P, Lundgren CI.
Determinants of long-term quality of life in patients with differentiated thyroid carcinoma - a population-based cohort study in Sweden.
Acta Oncologica. 2016;55(3):365-9.

II. Hedman C, Djärv T, Strang P, Lundgren CI.
Effect of thyroid-related symptoms on long-term quality of life in patients with differentiated thyroid carcinoma: A population-based study in Sweden.
Thyroid. 2017 Aug;27(8):1034-1042.

III. Hedman C, Djärv T, Strang P, Lundgren CI.
Fear of recurrence and view of life affect health-related quality of life in patients with differentiated thyroid carcinoma: A prospective Swedish population-based study.
Manuscript.

IV. Hedman C, Djärv T, Widberg I, Strang P, Lundgren CI.
Anxiety and fear of recurrence despite a good prognosis: An interview study with differentiated thyroid cancer patients.
Thyroid. 2017 Sep 6. doi: 10.1089/thy.2017.0346. [Epub ahead of print]

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CONTENTS

LIST OF ABBREVIATIONS

ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
BP	Bodily pain
CI	Confidence interval
DTC	Differentiated thyroid cancer
EORTC	European organisation for research and treatment of cancer
EORTC QLQ-C30	EORTC quality of life questionnaire
FNAC	Fine needle aspiration cytology
FTC	Follicular thyroid cancer
GBq	Giga Becquerel, radioactivity
GH	General health
HRQoL	Health-related quality of life
^{131}I	Radioactive iodine
MH	Mental health
MID	Minimally important difference
MTC	Medullary thyroid cancer
NIS	Sodium iodine symporter, the Iodine pump
PF	Physical functioning
PRO	Patient-reported outcome
PTC	Papillary thyroid cancer
RAI	Radioiodine
RE	Role emotional
rhTSH	Recombinant human thyroid stimulating hormone
RP	Role physical
SD	Standard deviation
SF	Social functioning
SF-36	Short-Form 36-Item Health Survey
T_3	Triiodothyronine
T_4	Thyroxine
THW	Thyroid hormone withdrawal
TNM	Tumour (lymph) Nodes Metastasis
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone
VT	Vitality
WBS	Whole-body scanning

1 INTRODUCTION

"Lena is a 40-year-old woman. She was diagnosed with a small papillary thyroid cancer four years ago. Initially, she had an operation followed by radioiodine treatment, since then, her levothyroxine dose has been on a therapeutic level and there have been no signs of recurrence. Nonetheless, she has developed an intricate anxiety concerning the healthcare system. Some weeks before her follow-up visit she feels severe anxiety, and experiences sleeping problems and difficulties at work. When it is time for the visit, she can barely make it to the parking area. Several times, she has cancelled the consultation and not taken the recommended laboratory tests."

For healthcare professionals Lena is free of cancer, with an excellent prognosis. So why has she been so affected by the disease? My personal interest in understanding the effect of thyroid cancer on patients' quality of life and how the disease can influence their lives was the starting point for this thesis.

Thyroid cancer is the most common endocrine cancer and the incidence is rapidly increasing worldwide. The disease affects people of all ages, but in contrast to many other cancers, the majority of patients are diagnosed before 50 years of age. The overall survival is regarded as good, but with a risk of recurrence that remains for decades.

As the majority of patients with thyroid cancer will live for many years with the consequences of treatment and follow-up, their long-term quality of life becomes of great importance. Most patients will receive long-term treatment with thyroid hormones, both in high doses to decrease the risk of recurrence and to replace the hormone production of the thyroid gland after surgery. As thyroid hormones affect the metabolism of all human cells, the understanding of hormonal production and regulation is essential to understand. Therefore, side-effects from thyroid hormones might affect health-related quality of life (HRQoL) and, in addition, surgery and radioiodine treatments might give symptoms affecting HRQoL.

Receiving a cancer diagnosis is, moreover, life changing, and can be even more overwhelming when it is received at a young age. Because of the life-long thyroid hormone treatment and recurrence risk, some form of follow-up is paramount for the rest of the patients' lives. To be reminded of the cancer diagnosis both daily when taking medication, and regularly during medical follow-up, also insures that the disease cannot be forgotten. Thus, HRQoL might be negatively affected in thyroid cancer patients due to several reasons. Indeed, little is known about long-term HRQoL in thyroid cancer, which factors might affect it and how it changes over time.

This thesis aimed to study HRQoL in thyroid cancer, both prospectively after the primary treatment, and after many years of follow-up, using both a validated general questionnaire and a disease-specific questionnaire. The study-specific questionnaire was developed, because no disease-specific questionnaire was available in Swedish. In addition, semi-structured qualitative interviews were used, to find unknown factors important for HRQoL in thyroid cancer.

2 BACKGROUND

2.1 THYROID ANATOMY

The thyroid gland is the largest single organ specialised for endocrine hormone production and is located on the anterolateral aspect of the cricothyroid and the trachea [1]. The name thyroid is derived from ancient Greek, which means shield-like, which is related to its relationship to the laryngeal thyroid cartilage, shaped like a shield [2]. The main function is to produce the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) [3]. Anatomically, the thyroid gland consists of two lobes, connected by a thinner tissue band called the isthmus, and is surrounded by a capsule. The normal weight of the thyroid gland ranges from 15-25 g in adults, depending on iodine supply, sex and body weight [1]. It has a rich blood supply from the superior and inferior thyroid arteries. The first lymphatic drainage is mainly to the central compartment followed by the lateral neck compartments. The recurrent laryngeal nerves run in close relationship to the thyroid gland and the parathyroid glands are located on its dorsal surface [1,4,5].

The thyroid gland is composed histologically of two main parenchymal cell types; thyroid follicular and parafollicular, or C cells. The thyroid follicular cells, or thyroid cells, form follicles, spherical structures, which are the functional units of the thyroid. The thyroid cells and the follicles are responsible for concentrating iodine, and the production, storage and secretion of thyroid hormones [3-5]. The parafollicular cells are the source of calcitonin, a hormone that is regulating calcium homeostasis, but with no apparent physiological role in humans [6].

2.2 THYROID PHYSIOLOGY

The thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) are synthesised by the follicular cells of the thyroid gland and iodine is required for the synthesis. Thyroid hormone activity is regulated by the hypothalamic-pituitary-thyroid-peripheral tissue axis. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to release the thyroid-stimulating hormone (TSH) and TSH stimulates the synthesis of thyroid hormones. A negative feedback system is regulating hormone production, where T_3 and T_4 decrease the release of TRH and TSH [3]. Clinically, TSH is the single most useful measurement in the evaluation of thyroid function [4] while TSH stimulates thyroid cell growth, the biosynthesis of thyroid hormones, increases iodine uptake and stimulates the secretion of thyroid hormones [3].

Iodine, an essential nutrient received from the diet, is the corner-stone of thyroid hormone production. At the basolateral membrane of the follicular cells iodine is actively transported into the thyroid cells by the sodium-iodine symporter (NIS). At the apical membrane-colloid interface of the thyroid cells, iodine becomes a substrate for thyroid hormonogenesis. In addition, follicular cells produce a glycoprotein called Thyroglobulin (Tg), which serves as a matrix for the synthesis of the thyroid hormones. The thyroid hormones are stored in the follicular lumen attached to the Tg. Under TSH stimulation, Tg is transported back into the thyroid cells and T_4 and T_3 are secreted into the bloodstream. The released iodine is recycled for hormone synthesis. Smaller amounts of Tg is released from the thyroid and circulates in blood [4,5]. In thyroid cancer derived from the epithelial cells, Tg is excreted in larger amounts and can thus be used as a sensitive tumour marker during follow-up [3].

The main hormone secreted to the blood stream is T_4, and T_3 is mainly produced by extra thyroidal deiodination of T_4, particularly in the liver and kidneys. The thyroid hormones are important for nearly all cells in the human body, and are fundamental for central nervous system development, body growth, thermoregulation, weight, lipid metabolism, regulation of heart rate and myocardial contraction and relaxation. Additionally, they affect gastrointestinal motility and renal water clearance [4].

2.3 DIFFERENTIATED THYROID CANCER

Thyroid nodules are very common, about 4-7% of adults have a palpable thyroid nodule and approximately 5-30% of those will be malignant. Thyroid follicular cells give rise to differentiated thyroid cancer (DTC), i.e. papillary (PTC) and follicular (FTC) thyroid cancer and, in addition, anaplastic thyroid cancer (ATC). Poorly differentiated thyroid carcinoma is a rare epithelial-derived tumour which lacks the characteristics of PTC [7].

DTC represents the most common type of thyroid carcinoma, accounting for more than 90% of all thyroid cancers [6]. ATC is regarded as the most aggressive solid tumour, with a median survival of only five months [8]. The prognosis for poorly differentiated thyroid carcinoma is between PTC and ATC [9]. Medullary thyroid cancer (MTC), rising from the parafollicular cells, accounts for 3-5% of thyroid carcinomas and has a genetic predisposition in about 20% of cases [6]. Although they are rare, metastases from other cancers and lymphomas occur in the thyroid and should be considered during the diagnosis of thyroid nodules [7].

2.3.1 Papillary thyroid cancer

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy and accounts for more than 80% of all thyroid carcinomas [10]. Fine needle aspiration cytology (FNAC) is conclusive in the majority of patients [11]. Lymph node metastases occur in about 20-80% of all PTCs at diagnosis and can be the presenting symptom of PTC [6]. The tumours are often multifocal and, in addition, have extrathyroidal extension [12]. Tumours less than 1 cm in diameter are defined as micro-carcinomas. Although the prognosis is good, distant metastases occur, and lungs and bone are the most common localisations [6].

2.3.2 Follicular thyroid cancer

Follicular thyroid carcinoma (FTC) comprises 5-15% of all thyroid carcinomas. It is a malignant epithelial tumour but lacks the diagnostic features of PTC [7]. The diagnosis is not possible by FNAC and a histological sample is required for diagnosis [11]. FTC is separated histologically into two main groups: minimally invasive and widely invasive. The minimally invasive FTC has minimal capsular and vascular invasion while widely invasive FTC has apparent vascular and/or capsular invasion. Lymph node metastases seldom occur and distant metastases are predominately found in the lungs, bone and brain. The prognosis is clearly worse for widely invasive tumours. Oncocytic carcinomas, or Hürthle cell carcinomas, are a variant of FTC and more common in older patients. These tumours more often metastasise to lymph nodes and also to bone and lungs. Higher rates of follicular carcinomas have been seen in areas with iodine deficiency, with an incidence of 20-40% of all thyroid carcinomas [7].

2.3.3 Epidemiology of thyroid cancer

In Sweden, thyroid cancer accounts for approximately 1% of all cancer diagnoses and more than 600 new cases were diagnosed in 2015 [13]. It is the most common endocrine cancer and its incidence is rising both in Sweden and worldwide [14,15]. More than half of the patients are diagnosed before the age of 50 and thyroid cancer is two to three times more common in women [13]. The incidence in Sweden was 7/100,000 in 2015 compared with 3.4/100,000 10 years earlier [14], and the incidence has been rising since 1970 with a more pronounced increase over the last decade [16]. In the United States, thyroid cancer is now the fifth leading cause of cancer in women, accounting for 5% [17]. It is also suggested that it will be the third most common cancer in women of all ages, and the second most common cancer in women younger than 45 years of age, in the United States by 2019 [18]. This is mainly related to the growing incidence of small PTCs, and the rising incidence has been suspected to be related to better diagnostic procedures and screening [19]. However, a recent study showed an increase in advanced-stage papillary thyroid cancers and a simultaneous increase in mortality in the United States. Thus, this indicates a true increase in thyroid cancer [15].

Radiation exposure during childhood is the only established risk factor for thyroid cancer [20]. After the nuclear power accident in Chernobyl a large number of childhood thyroid carcinomas were reported [21]. Inhalation of radioactive iodine and the consumption of contaminated milk cause DNA damage [22], which leads to an increased risk of thyroid cancer [21]. Moreover, treatment with external radiation under the age of 20 increases the risk of thyroid cancer [23,24]. Radiation-induced PTCs are unique, as most tumours have RET/PTC chromosomal rearrangements. BRAF point mutations, found in sporadic PTC, occur rarely in radiation induced PTC [25].

In iodine-deficient areas there may be more follicular carcinomas and fewer PTCs, but the total amount of thyroid carcinomas does not seem to be affected by iodine intake [26]. There are no other conclusive risk factors although, for example, weight gain [27], obesity, oestrogen and diabetes have been suggested as causes increasing the risk of thyroid cancer [28].

2.3.4 Symptoms and diagnosis

The most common presenting symptom is a lump in the neck, either from the thyroid tumour or from lymph node metastases. More seldom, hoarseness, difficulties swallowing or symptoms from distant metastases are the first symptoms [1]. Ultrasound is the most appropriate radiological method when investigating the thyroid and loco-regional lymph nodes. Computerised tomography might be used, but contrast media with iodine should be avoided when radioiodine treatment might be needed during treatment. Magnetic resonance imaging is of importance if local growth into surrounding organs is suspected [7].

Fine needle aspiration cytology (FNAC) is conclusive in the majority of PTCs. Diagnosis of FTC needs a histological specimen, while growth into vessels or capsule cannot be seen in FNAC and surgery is warranted in follicular tumours [29].

2.3.5 Staging and prognosis

Thyroid cancer is classified according to the TNM classification [30]: tumour size and invasiveness (T), lymph node metastases (N) and presence of distant metastases (M) and a new TNM classification has recently been introduced [31]. Based on the TNM classification, thyroid cancer is divided into risk groups according to recurrence risk: very low, low or high risk, with smaller differences between the American Thyroid Association (ATA) [32] and European Thyroid Association (ETA) [33,34]. The Swedish national recommendations [35] have adjusted treatment recommendations according to the international guidelines. In addition, based on the outcome of the initial treatment, patients are re-classified into four response categories (i.e., excellent, intermediate, biochemical incomplete, and structural incomplete), on the basis of the findings during follow-up [32].

The prognosis of DTC is good, with a 10-year survival of more than 90% [36]. High survival rates are seen especially in patients with small PTCs, while older patients, those with larger tumours and widely invasive FTC have lower survival rates [6,31]. Although survival is high, 25-30 % of patients develop loco-regional recurrence, which can occur as long as 30 years after diagnosis [37,38]. The rising incidence in combination with young age at diagnosis and the excellent prognosis is resulting in a high prevalence in thyroid cancer survivors and about 8000 patients live with thyroid cancer in Sweden [39].

2.3.6 Treatment of differentiated thyroid cancer

The treatment of DTC is not considered as aggressive as the treatment for many other cancers. The main treatment is surgery, followed by radioiodine and levothyroxine treatment. In selected cases, external radiotherapy might be indicated and tyrosine kinase inhibitors are an option in metastatic disease [32].

Surgical treatment

The preferred surgical treatment of DTC is thyroidectomy in combination with lymph node dissection when appropriate. If PTC is diagnosed pre-operatively, total thyroidectomy is preferred in all cases except for those with a tumour <1cm, then hemithyroidectomy can be recommended. In follicular tumours, hemithyroidectomy is preferred, to enable a correct diagnosis based on histopathology [32] followed by a completion of the other side if invasiveness is observed. Prophylactic central lymph node dissection is debated. The risk of complications might be higher than the benefit, when it comes to reducing recurrences [40]. According to the international guidelines the aims of surgical treatment are;

I) to remove the primary tumour and involved lymph nodes, in order to decrease recurrence and metastatic spread
II) to facilitate postoperative treatment with radioactive iodine
III) to permit accurate long-term surveillance with whole-body scanning (WBS) and Tg measurement

Adequate surgery is the most important treatment influencing prognosis, while radioactive iodine, TSH suppression, and external beam radiation play an adjunctive role [32]. Possible complications from surgery are recurrent laryngeal nerve injury with vocal cord palsy or dysphonia, hypoparathyroidism or bleeding. Post-operative hypoparathyroidism is often reversible, but is life-long in 0.9-1.6% of patients and requires vitamin D and/or calcium supplementation [41]. Dysphonia is reversible in more than 90% of the patients but can give life-long hoarseness [42].

Radioiodine treatment

Radioiodine (RAI) treatment with ^{131}I is indicated both post-operatively and in metastatic disease. The initial ^{131}I treatment of DTC patients after total thyroidectomy is divided into ablation, adjuvant therapy, and the therapy of persistent disease. The aim of post-operative ablation is to eradicate persistent normal thyroid tissue to enable adequate follow-up. Adjuvant therapy, in addition to ablation, is intended to destroy possible, but not proven, residual disease to decrease the risk of recurrence. RAI therapy is intended to increase survival by treating persistent disease. The RAI treatment enables proper follow-up with WBS and measurement of the tumour marker Tg, while the normal thyroid tissue to a lesser extent is visible on WBS and the measured Tg reflects tumour activity instead of normal thyroid tissue. RAI treatment is avoided in low-risk patients, in which the benefit for recurrence and survival has not been proven [32]. A more selective use with both lower doses and an increase in the number of patients not recommended RAI has been seen over the last few years, in order to decrease the risk of side-effects [43].

The effect of RAI is based on the ability of iodine uptake of the thyroid cells by the sodium-iodine symporter (NIS), with the same mechanism as dietary iodine. Stimulation by TSH is needed to promote iodine uptake by thyroid cells, while the NIS have lesser activity in thyroid cancer cells compared with normal thyroid cells. The TSH stimulation is achieved either through thyroid hormone withdrawal (THW) for three to five weeks, or the administration of recombinant human TSH (rhTSH) [32]. When TSH is high, the expression of NIS rises which increases iodine uptake and makes radioiodine treatment more efficient [44]. Similar efficacy between THW and rhTSH has been demonstrated for post-operative thyroid ablation [45,46], with lesser side-effects for rhTSH. The drawback of rhTSH is the high costs, and the cost effectiveness of its administration has not been proven [47]. Treatment activity depends on the aim of the treatment, with lower activities (1.1 GBq) in ablation and higher activities (3.7-7.4 GBq) in adjuvant and therapy indication. Even higher activities might be delivered with the use of dosimetry [48].

Side-effects from RAI treatment include symptoms from salivary glands with both acute sialoadenitis [49] and persisting xerostomia [50-52]. Transient gonadal function disturbances are described both in men and women [53]. The most worrying side-effect is the risk of secondary malignancies, which increases with higher cumulative doses of ^{131}I [43,53,54].

Levothyroxine treatment

Patients with thyroid cancer operated with total thyroidectomy are dependent on life-long levothyroxine treatment. According to international recommendations, levothyroxine is given in doses both to replace the absent production of thyroid hormones and to suppress TSH [32,33]. DTC cells express TSH-receptors and TSH is considered to be a growth factor in DTC [55,56]. Suppression of TSH is associated with a decreased tumour recurrence, but the effect of suppression is seen only in patients with a higher risk of recurrence [37,57,58]. On the other hand, subclinical hyperthyroidism is associated with side-effects. The most harmful complications are the increased risk of atrial fibrillation [59] and cardiovascular death [60]. Diminished bone density in women over 50 years of age is another negative consequence of TSH suppressive therapy [61,62]. In low-risk patients, TSH suppression is maintained for a shorter period, but in patients with loco-regional recurrence or metastatic disease the suppressive treatment can be life-long [32]. As in the use of RAI, the benefit of TSH-suppression has been discussed over the last few years, and a more selective use in low-risk patients is advocated [32,63]. The level of TSH-suppression is divided into three groups: moderate or complete suppression is defined as TSH <0.1 mU/L; mild suppression as TSH 0.1-<0.5 mU/L (0.5 represents the lower limit of the reference range for TSH, which can be 0.3-0.5 depending of method); and no suppression as TSH ≥0.5 mU/L [32]. In our studies, the lower limit is defined as 0.4 mU/L, according to the most wildly used method.

2.3.7 Follow-up and treatment of recurrence

DTC has a good prognosis with a 10-year overall survival of >90 % [36]. Still, the recurrence risk is considerable which makes long-term follow-up necessary [38]. The follow-up depends on recurrence risk and includes ultrasonography [64], evaluation of the levothyroxine dose, Tg measurement and WBS [32]. WBS requires elevation of TSH levels either with THW or rhTSH. Measurement of Tg during the elevation of TSH makes the measurement more reliable [32].

In loco-regional recurrent disease, surgery is the recommended treatment [1]. In metastatic disease, radioiodine is the preferred first-line treatment, and can be repeated as long as the tumours are radioiodine avid [32,65-67]. In radioiodine-avid disease, survival is significantly longer than in non-avid [68]. External radiotherapy should be considered in gross residual cervical disease and in painful bone metastases [6]. In progressive disease TSH suppression is of great importance for survival [69,70]. Over the last few years, two tyrosine kinase inhibitors have been approved for locally advanced or metastatic DTC. Sorafenib [71] and lenvatinib [72] have both showed improved progression-free survival and these drugs have substantially changed the treatment for patients with metastatic disease [73].

2.4 HEALTH-RELATED QUALITY OF LIFE

Quality of life (QoL) is a broad multidimensional concept that includes individuals' subjective perceptions of their position in life and evaluation of both the positive and negative aspects of life [74]. Thus, it includes physical, functional, emotional and social well-being [75]. Health, in itself, is one important domain in the overall quality of life [74]. Subjectivity refers to the fact that QoL can be understood only from the patients themselves, and can be only assessed by them [75]. To understand what health is, the constitution of the World Health Organization defined health in 1948 as follows: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [76]. To distinguish QoL in a more general sense from aspects important for clinical medicine and clinical trials, health-related quality of life (HRQoL) is used. HRQoL encompasses those aspects of QoL that are affected by disease or treatment of disease [77], symptoms and functions affected by the disease, and also the side-effects of treatment. The definition of HRQoL is not well defined, but it is generally agreed that "HRQOL is the functional effect of a medical condition and/or its consequent therapy up on the patient" [78]. Thus it is subjective and multi-dimensional covering dimensions such as physical, psychological, occupational and social functioning" [77].

Patient-reported outcomes

The assessment of HRQOL does not usually include aspects such as needs assessment or satisfaction with care. A more inclusive term, patient-reported outcomes (PROs), includes any information about the status of a patient's health condition [79], reported directly by the patient, without a proxy such as healthcare professionals or family members. A PRO can be measured by self-report or by interview, as long as only the patient's views are documented [80,81]. Thus, HRQoL is one type of PRO [82]. The use of electronic PROs is on the rise in today's clinical trials. The process of obtaining PRO data is sometimes referred to as PRO measurement (PROM), and is increasingly used synonymous with PRO. PROs are gradually more used in clinical trials, and are mandatory in trials investigating new treatments in oncology. The use of PROM could help transform healthcare, while it not only helps patients and clinicians to make better decisions, it can also facilitate comparisons between healthcare providers and, in the end, stimulate improvements in healthcare [83].

2.4.1 HRQoL as a conceptual model

To better understand the concept of HRQoL and its determinants, Wilson and Cleary constructed a conceptual model that integrates the biological and psychological aspects of health and how they affect HRQoL [84]. This model is the most frequently used to characterise HRQoL conceptually and was later revised by Ferrans and colleagues [85]. The model of Ferrans has been assessed to be the most useful one, while the addition of the relationship between the individual characteristics and biological function was added [86]. The model links traditional clinical variables with HRQoL and emphasises that HRQoL is more than just physical health. Additionally, it integrates both the biological and psychological aspects of health outcomes. The model focuses on five different levels of patient outcomes. The first level is the biological function, which includes cellular and whole organ functions. The next level, symptoms, includes emotional, cognitive and physical symptoms. The functional status in this model focuses on the optimisation of the patient's function that remains, and includes physical, social, physiological and cognitive functioning. The general health perception is a subjective evaluation that integrates all the components that come earlier in the model, thus this is a synthesis of all the different aspects of health. Overall quality of life, the last component of this model, is subjective well-being, and includes how happy or satisfied a patient is with his or her whole life. Although the simplified model has shortcomings, as individual perception of QoL is a complex phenomenon, the model still highlights important components [85].

2.4.2 Why HRQoL is important to measure

The ultimate goal of healthcare is not only to increase survival, but also to prevent further morbidity and to make patients feel better [78,87]. Thus the rationale for measuring HRQoL is to clarify to which degree the medical condition, or its treatment, impacts the patients' lives. HRQoL is an important measure along with other clinical measurements such as survival or tumour response to understand how patients experience a disease or its treatments. The measurements can then be used to study HRQoL changes over time or to compare HRQoL in patients with different diseases. Data from PROs, including HRQoL data from randomised clinical trials (RCT), can be used in clinical decision making, approval of new drugs, health policy, and also in reimbursement decisions [88]. Evaluation of PRO data is now regarded as standard in clinical trials [89].

Measuring HRQoL can benefit both patients and clinicians in two ways. Firstly, the use of HRQoL instruments in clinical trials can provide important evidence for how different treatments affect the patients, both which side-effects can occur and how the treatment affects HRQoL. This information is equally important for both patients and clinicians, and can help them to decide which treatment is the most suitable. Secondly, patients completing HRQoL questionnaires during treatment or follow-up provide information to the clinicians about their function, symptoms of the disease and possible side-effects from treatment. Thus, clinicians are informed about side-effects or other problems which are possible to treat and, in the end, this might improve the patients' outcomes [87]. In oncology, survival was the crucial end-point at the beginning, but with the introduction of more treatment options, HRQoL has risen to be an important part in the treatment decision making process [90]. This seems to be even more important in an elderly cancer population, where older patients, compared with younger ones, tend to regard HRQoL as more important than longer survival [91].

Measuring HRQoL in cancer patients is important, where patients have many symptoms and the loss of different functions. Many of the symptoms and functions are not possible to measure with laboratory tests or imaging and it is important to rely on the patients' descriptions. Moreover, several studies have found associations between HRQoL and survival [92-94], and HRQoL can even be a better prognostic marker than functional status [95]. In palliative care, the intent of treatments is mostly to improve HRQoL, not to prolong life, and thus measuring HRQoL is crucial [96].

2.4.3 Response shift

When measuring HRQoL over time, it might be difficult to know what the data should be compared to, and how the results should be interpreted. Patients experiencing a serious illness or deterioration of their functional status adapt themselves to their new condition and define new internal standards and values for their health after a period of time. Such subjective changes in the patients' perceptions and self-evaluation of HRQoL are regarded as a response shift [97]. Thus, patients might give different answers to HRQoL measurements over time, not only because their health or HRQoL has changed, but also because they have changed their own meaning of what health or HRQoL is to them. The patients may get used to various symptoms and a decrease of functions and, therefore, report diminishing levels over time. A change in HRQoL might reflect a response shift, an effect of the given treatment or a combination of both, which makes interpretation of HRQoL data challenging [98].

2.4.4 Instruments for measuring HRQoL

HRQoL can be measured through interviews, focus groups or questionnaires. Instruments used to measure HRQoL are either general, disease-specific, or detailed to measure a specific aspect of HRQoL and should preferably be completed by the patients themselves [77].

- **Generic instruments** are intended for general use, irrespective of the illness or condition of the patients. They may often be applicable to healthy people. Examples are the Short-Form 36-Item Health Survey (SF-36) and Sickness Impact Profile (SIP). Advantages of generic instruments are that scores from patients with various diseases can be compared against each other and against the general population. On the other hand, they fail to capture particular concerns or symptoms in patients with disease and lack the sensitivity to detect differences important to measure in clinical trials comparing different treatments.
- **Disease-specific instruments** focus on disease-specific issues and examples are the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and Functional Assessment of Cancer Therapy - General (FACT-G). These instruments measure functions and symptoms important in a specific disease but lack the possibility to explore particular issues in greater depth, and can therefore be combined with aspect-specific instruments.
- **Aspect-specific instruments** are used to explore particular issues in greater depth. Examples are the Hospital Anxiety and Depression Scale (HADS) [99] and Multidimensional Fatigue Inventory (MFI). These instruments evaluate specific aspects of HRQoL and should normally be used together with a more general questionnaire.

2.4.5 Choosing an instrument

When choosing a HRQoL instrument, it is important to take the aim of the trial into account. Disease-specific questionnaires have better sensitivity and/or specificity than generic ones regarding disease- and treatment-related issues. On the other hand, if the intention is to compare HRQoL in different diseases or to make health-economic assessments, generic questionnaires are preferred. If a disease-specific instrument does not have a generic question, it can be combined with a generic questionnaire. The same is applicable for instruments for specific aspects of HRQoL [77]. In addition, other aspects to take into account are the timing, to use a wording understandable for all the included patients [100], to take into account missing values and to choose well-validated instruments. In clinical trials at least three time points are recommended, with the first one before the beginning of treatment.

Instruments used to measure HRQoL should be well documented, the development needs to be described and the instrument should be validated and have good psychometric properties. Also, validated questionnaires can be troublesome when instruments tested in one context might not be valid in another, thus, the questionnaire should be suitable to the target population. In addition, the wording of the instrument is important and the scoring procedure needs to be defined. If the instrument does not cover all the issues important in the study, supplementary questions could be added at the end of the validated questionnaire. Psychometric properties have four important independent basic fundaments, which are interrelated [77]:

- **Validity** – does the instrument measure what it is intended to and is it useful for the intended purpose? In HRQoL assessment, does the instrument really measure HRQoL? Content validity relates to the adequacy of the content of an instrument in terms of the number and scope of the individual questions, are all aspects covered and are the included questions relevant? Criterion validity involves assessing the instrument against the true value, or against another accepted standard, and by comparing it against other established instruments. Construct validity evaluates whether an instrument measures the construct it was designed for. Thus, all the items of a subscale should relate to a single latent variable and items from one subscale should not correlate with other latent variables.
- **Reliability** – determines that the instrument produce reproducible and consistent results when circumstances remain the same. Reliability is used for both internal reliability and repeatability. **Internal reliability** assesses the homogenity of multi-item scales, that is, all items on a domain should measure the same thing. Thus, it is a form of validity. **Repeatability** is another measure of reliability, that is, the stability of measurements. If the instrument is used several times on the same patient, and the patients's condition has not changed, then the result should be the same.
- **Sensitivity** – is the ability of the instrument to detect differences between groups, e.g. patients with mild disease from those with more severe disease or between two

treatment groups. The more sensitive the instrument is the smaller sample size is needed. This can be assessed in cross-sectional studies.

- **Responsiveness** – is the ability of the instrument to detect changes within patients, if the patient's health status changes over time. This can be assessed longitudinally in patients in whom change is expected to occur.

Sensitivity and responsiveness can be reduced if floor or ceiling effects are present, which is if a high proportion of the patients grade themselves as having the minimum or maximum scores, respectively [77].

2.4.6 Short-Form 36-item Health Survey

The Short-Form 36-Item Health Survey (SF-36) is a HRQoL instrument developed by Ware et al. to evaluate general health status and to fill a gap between lengthy questionnaires used in research and coarse single-item questionnaires. It is designed to assess general health, and is not specific to any age, disease or treatment group. The SF-36 was mainly developed based on various earlier instruments measuring limitations in physical, social and role functioning, mental health and general health perceptions, and two additional concepts supported by empirical studies, bodily pain and vitality [101]. It has become the most widely used of the general health status measures [102,103].

SF-36 is a multidimensional instrument with 36 questions measuring eight health profiles: physical functioning (PF, ten items), physical role functioning (RP, four items), emotional role functioning (RE, three items), social functioning (SF, two items), bodily pain (BP, two items), mental health (MH, five items), vitality (VT, four items) and general health (GH, five items). In addition, there is a general health transition question: “Compared to one year ago, how would you rate your general health now?”. This question, however, is not included in the final score [101]. The health profiles can be combined into two summary measures; the physical component summary (PCS) and the mental component summary (MCS). The physical component summary is most correlated with PF, RP and BP whereas MH, RE and SF contributes most to the mental component summary. Three of the scales; VT, GH and SF have noteworthy correlations with both components [104].

The International Quality of Life Assessment (IQOLA) Project was established in 1991 to translate the SF-36 into a range of languages and to validate, norm, and document the translations. SF-36 has been translated into Swedish, and it has been psychometrically tested and validated in a Swedish normative population [105-108]. A Swedish manual and interpretation guide is available, with data from the Swedish general population collected 1991-1992 [109]. Data from a Swedish general population is also available from 2002 [110].

2.4.7 Psychometric properties of SF-36

Several studies have investigated the psychometric properties of SF-36. SF-36 was developed using items from previous questionnaires and many of the items have been widely used and tested in earlier studies, thus the content validity is assessed as good. Additionally, when SF-

36 has been compared to other widely used generic health instruments, the criterion validity has been evaluated as good [104]. Construct validity measured with convergent and discriminant validity has been tested and shown to be good for all items. Reliability has been evaluated using internal consistency and test-retest. Internal reliability, measured with Cronbach α, has been shown to exceed the recommendations on a group level [111]. Sensitivity in SF-36 has been shown to discriminate between diseases of different severity, and also to distinguish psychiatric disease from medical conditions in a Swedish population [106]. In addition, SF-36 has been shown to be sensitive measuring HRQoL in thyroid cancer [45,47,112]. Responsiveness has been shown as change in health status over time in four common clinical conditions; low back pain, menorrhagia, suspect peptic ulcer and varicose veins and also in the postoperative period after colorectal surgery [113,114]. SF-36, version 2, is thought to have better responsiveness due to changes in the response formats of the role functioning scales because of improved precision, reliability and validity [108].

2.4.8 Interpreting results from SF-36

The SF-36 items and scales are constructed for scoring using the Likert method of summated ratings [115]. The scores from each domain are transformed into a scale ranging from 0 to100 where 100 indicate the best possible health. Statistical significance is not the only criterion used to compare data in HRQoL, because it can be reached although there is no clinical relevance for the patients. Statistical significance is important to assure that the results are not explained by chance fluctuations alone, but significance can be found in a large sample without having any clinical meaning for the patients [77]. To evaluate if differences between groups or between different measurement points in one patient are relevant, the differences should also be clinically significant. The smallest difference that is significant for patients is often called minimally important difference (MID). The MID is defined as the smallest difference in score which patients perceive as beneficial or negative [116,117]. Different methods to evaluate MID exist. In anchor-based methods, HRQoL changes are compared with clinical changes or results. Osoba suggested that a difference of 5-10 points between groups on a 100-point scale is interpreted as a clinically small relevant MID, 10-20 points is interpreted as a moderate difference and over 20 points is a large difference [118]. In distribution-based approaches, comparisons are based on a statistical distribution of results. As presented by Cohen, a standard deviation (SD) between groups of at least 0.2 is interpreted as a small difference, 0.5 as a moderate, and 0.8 as a large difference [119]. A more conservative estimate is that the effect size of a 0.5 SD is likely to be clinically meaningful [120].

2.4.9 The rationale for choosing instruments

At the beginning of this thesis there were no validated disease-specific questionnaires regarding thyroid cancer in Swedish. As the treatment of thyroid cancer does not include the major cancer treatments, such as chemotherapy and external radiotherapy, the cancer-specific questionnaires like as EORTC-QLQ C30 or FACT-G were not regarded as suitable for this patient population. Thus, a generic questionnaire was regarded as appropriate. SF-36 is the most widely used generic instrument, there is a validated Swedish translation and data from

Swedish general populations are available for comparisons. In addition, is has been regarded as sensitive in thyroid cancer. As a complement, a study-specific questionnaire was developed to capture symptoms important to patients with thyroid cancer (see Appendix).

2.4.10 The study-specific questionnaire

The study-specific questionnaire includes important sociodemographic questions about level of education, work, civil status, smoking, weight changes, and menopause status. In addition, comorbidities, thyroid cancer treatment and recurrences are asked for. To study thyroid cancer related symptoms and side-effects from treatment these issues are extensively asked for. The last questions include aspects about change in view of life, fear of recurrence and, in addition, open-ended questions about the same aspects, as open-ended questions have been shown to reveal additional information [121].

The study-specific questionnaire was developed by the research group, which included knowledge about both the surgical and oncological treatment of thyroid cancer and, in addition, expertise in measuring HRQoL. The questions regarding symptoms and side-effects from thyroid cancer were based on literature review and clinical experience. The questionnaire was pilot-tested in five patients with thyroid cancer and no changes were made. The patients regarded the questions to be easy to understand and answer, and also not offensive.

2.5 FEAR OF RECURRENCE AND ANXIETY

Anxiety and fear of recurrence are both well-known factors affecting quality of life in cancer patients. The number of cancer survivors is increasing worldwide [13,17], and this emphasises the importance of exploring factors affecting their quality of life.

2.5.1 Fear of recurrence

Fear of recurrence affects 39-97% of all cancer patients and 22-87% reported moderate to high levels [122,123]. In the majority of the studies, fear of recurrence is stable over time [122]. It is one of the most commonly reported issues bothering cancer patients and one of the most distressing consequences [124]. With an increasing number of long-term cancer survivors this fear becomes an important factor affecting their lives. This very term is defined as fear of recurrence of the disease, disease progression, or dissemination of the disease [122,125]. Recently, a novel definition has been introduced: “Fear, worry, or concern relating to the possibility that cancer will come back or progress” [126]. Fear of recurrence should be differentiated from the psychiatric concept of anxiety, as cancer patients have a real threat and their reactions should be considered as a normal and a rational response to the life threatening disease [125]. If the fear of recurrence develops to a dysfunctional state, i.e. affecting quality of life and social functioning, treatment should be offered. Thus, it is important to identify patients at a greater risk of developing a fear of recurrence and offer them interventions.

Determinants of fear of recurrence

A demographic factor associated with fear of recurrence is age, as young age in general, and young age at diagnosis is an important predictor of fear of recurrence [127,128]. Sex, education and marital status do not have a clear correlation with fear of recurrence [125,127], whereas having children seems to be related to higher levels of fear [129]. Among disease- and treatment-related factors, time from diagnosis shows no association with fear of recurrence [125] and progression of the disease shows conflicting results [122,130].

Several psychological factors are associated with an increased fear of recurrence such as neuroticism [131], anxiety, depression [125] and lower optimism [132]. Coping strategies play a role in decreasing the fear of recurrence. Physical symptoms such as fatigue and pain are associated with fear of recurrence whereas comorbidities show no associations. Strong evidence emerged for negative associations between QoL and fear of recurrence. Cancer survivors with a fear of recurrence express lower QoL both on physical and mental domains [122,133]. A surprising finding is that levels of fear of recurrence seem to be comparable between different cancer diagnoses [134]. As a conclusion, patient-related characteristics seem to be more important predicting fear of recurrence than treatment- and tumour-related factors [135].

Measuring fear of recurrence

Fear of recurrence has been investigated in numerous studies, and the assessment has been carried out with longer (>10 items) and shorter (2-10 items) questionnaires. In addition, subscales within quality of life questionnaires and single items have been used. The most used questionnaires are the Fear of Progression Questionnaire and the Cancer-Related Health Worries Scale [122,123]. As there is no consensus about which levels of fear of recurrence are clinically important, the interpretation of results is challenging [122]. Both group interventions and face-to-face interventions have an effect on fear of recurrence in cancer patients [136,137].

2.5.2 Anxiety

To receive a cancer diagnosis is traumatic and can be perceived as a threat to patients’ lives. According to Cullberg, a crisis reaction can be divided into four different stages; shock, reaction, process/adaptation, and reorientation. The first two stages represent the acute crisis while the two latter ones constitute the adaptation process. When the crisis reaction progresses according to the four stages, it will lead to better recovery. However, several factors can disrupt the process and impair recovery [138].

Coping mechanisms play a major role in handling difficult life events, primarily to avoid anxiety. The process of coping is initiated only if important values are threatened or lost and the meaning and intent of coping is to handle demanding situations. The coping process consists both of understanding the situation and of what can be done or how someone can protect themselves [139]. If the crisis after a cancer diagnosis is not processed and coping mechanisms fail, anxiety is a possible outcome.

Anxiety is known to be common in cancer survivors and is the most prevalent of mental disorders [140]. Anxiety has a prevalence of 18% in one meta-analysis [141] and 11.6% in patients with various cancer diagnoses and disease stages [140]. It seems to be more common in patients with breast, head and neck cancer and melanoma [140], and high levels of anxiety are seen in both cured patients and in those with progressive disease [141-143]. Variations of anxiety are seen over time [144] and the highest prevalence is shown soon after diagnosis [145]. Moreover, the risk of anxiety during follow-up seems to be increased in patients with pre-existing anxiety and in those with high levels of anxiety around diagnosis [146]. It is also correlated to a fear of recurrence [122,147].

2.6 QUALITATIVE RESEARCH METHODS

When using quantitative questionnaires, reliability and sensibility are usually good due to the psychometric testing of the questionnaires. In addition, validity might be strong but a draw-back is that the respondents are only allowed to answer predefined questions. Important questions not covered by the questionnaire might be of high relevance, and therefore missed. To explore new, and partly unknown, knowledge of phenomena connected to the human experience, such as expectations, thoughts and attitudes, a qualitative study method is suitable [148]. Moreover, questionnaires do not allow for personalised follow-up questions. For this reason, qualitative methods constitute an important complement to quantitative measurements in order to explore a phenomenon in depth [149]. Qualitative data can be gathered by different kinds of collection methods; e.g. interviews or focus groups, observational studies or written documents [148].

2.6.1 Qualitative interviews

Interviews are the most used qualitative techniques in healthcare, and both semi-structured and in-depth interviews are useful in gathering data. In semi-structured interviews an interview guide with open-ended questions can be used [150] to encourage spontaneous comments. To validate and deepen the information, follow-up questions are important [148,150,151]. In-depth interviews are less structured, and may cover only a few issues, but in greater detail. When conducting interviews, it is important to explore what patients are saying in as much detail as possible, and try to find new unknown areas of information [152]. Good interview questions should be open-ended, neutral, sensitive, and easy to understand for the interviewee [148]. The audio-recording of interviews instead of taking notes is regarded as a suitable method, in order not to miss any details or to interfere with the process of interviewing. It is followed by a verbatim transcription of the recordings [152].

2.6.2 Sampling

Sampling in qualitative research differs from quantitative research. In contrast to large random samples allowing for the calculation of probabilities in quantitative research, purposeful sampling is the preferred method in qualitative studies [153]. Purposeful sampling covers various sampling methods and all have in common the intent to select information-rich cases for in-depth studies. Examples of purposeful sampling are single significant cases sampling (to gather deep understanding of the subject), comparison focused sampling (where cases are selected to compare and contrast them), and group characteristic sampling (selecting cases to create an information-rich group). One important example of group characteristic sampling is the maximum variation sampling, in which cases are picked purposefully with a wide range of characteristics to document diversity and to identify important common patterns [148]. In contrast to quantitative research, the number of patients is significantly lower and not always predefined. Saturation is the term (initially defined in Grounded theory) used when no new information is provided from, for example, interviews, and the data gathering process can be terminated [154,155].

2.6.3 Analysing qualitative data

When analysing qualitative data, different methods can be used. Qualitative content analysis is a method used to interpret meaning from the content of text data by systematically classifying data with different codes and, thus, identifying common themes [150]. Several steps are required in the analyses differing between the methods, and usually include the following steps: reading of the text to get a picture of the data, preliminary coding of meaning bearing units (sentences containing aspects related to the research question) in the text and comparison of codes and gathering codes into categories (a group of contents that has something in common). Developing themes is the last part of the analysis, meaning a thread of an underlying meaning that can be found between condensed meaning units, codes and categories [150,156,157]. Inductive analysis is defined as discovering patterns, themes and categories from the research data. On the other hand, in deductive or abductive analysis, data are analysed in agreement with a pre-existing framework [148]. In addition, the terms latent and manifest are important when analysing qualitative data. Latent refers to analysis of the interpretation of the underlying meaning of the data, whereas a manifest analysis refers to what the text says and the obvious components of the data [156].

2.6.4 Trustworthiness

The concepts of describing trustworthiness differ between qualitative and quantitative research. Trustworthiness can be defined in several ways and useful concepts are credibility, dependability, and transferability according to Graneheim et al [156,158]. **Credibility** refers to the confidence in how well findings and the data analysis suit the focus of the study. The sampling method is crucial in achieving credibility and, as discussed earlier, purposeful sampling is preferred. To gather enough data for the purpose of the study the number of participants is not fixed, which is in contrast to quantitative research. Instead, saturation is paramount, as the amount and quality of the data depends on the aims of the study, that is how broad or limited the predefined phenomenon we intend to study is. In addition, it is important to demonstrate differences and similarities between categories, and showing representative quotations is one approach. **Dependability**, another aspect of trustworthiness, refers to the creation of categories. To decide which codes should be included in which categories is a matter of dependability and to include several researches in the analysis is one way of addressing it. **Transferability** refers to the degree of which results can be transferred to other contexts. By giving a clear description of the context, selection of participants, data gathering and analysis, transferability can easier be judged by the reader [156,158].

2.7 HEALTH-RELATED QUALITY OF LIFE IN THYROID CANCER

Due to the good prognosis of thyroid cancer long-term survival is excellent. Despite the longevity of the disease, the risk of recurrence remains considerable for decades and long-term follow-up is needed. Thus, survival is not, alone, sufficient as an outcome measure and HRQoL has risen to be an important factor in DTC.

According to a review, HRQoL in DTC has been investigated in a number of studies with results showing both lower and similar HRQoL compared with a general population [159]. HRQoL can be affected at different time points during the disease trajectory, from diagnosis, surgery, radioiodine treatment to follow-up and possible recurrence. The effects of surgery, levothyroxine withdrawal and, to a lesser extent, follow-up have been studied according to HRQoL. On the other hand, HRQoL has been scarcely studied at the time of diagnosis, in prospective studies, or in patients with recurrent disease.

2.7.1 HRQoL related to surgery and radioiodine treatment

Surgery

Several studies focus on HRQoL related to surgery. HRQoL is studied pre-operatively and followed up at three, six and twelve months in patients having thyroid surgery for either benign or malignant thyroid diseases. HRQoL is lower compared with the general population during the first six months with a trend of recovery during follow-up. No difference is seen between hemithyroidectomy and total thyroidectomy, and no difference is seen between patients with benign or malignant thyroid disease [160]. In thyroid cancer with tracheal invasion, tracheal resection gives considerable per-operative symptoms. One year after surgery these patients have even better HRQoL than the patients treated with surgery for oropharyngeal cancers. All these patients would have chosen the same treatment modality again [161]. Patients treated with modified radical neck-dissection are shown to have worse chewing function and more shoulder problems compared with patients treated with thyroidectomy with or without central lymph node dissection [162]. Different surgical methods are compared, and robotic thyroidectomy seems to give less sensory changes and better cosmetic outcome, whereas the other QOL measurements seem equal [163,164].

Radioiodine treatment

The THW used for radioiodine treatment, WBS and Tg measurement has a clearly demonstrated negative effect on HRQoL. In several randomised trials, THW is compared with rhTSH during post-operative radioiodine treatment. In all studies, patients in the THW group have a significantly lower HRQoL compared with the rhTSH group [45-47,165-167], but no remaining differences are seen after six months [47]. In addition, similar impairments of HRQoL are shown when comparing THW and rhTSH during follow-up investigations with

WBS, and HRQoL during THW is even worse than in patients with congestive heart failure, depression and migraine [112]. Of those patients having both THW and rhTSH on separate occasions, 127 of 128 patients would have chosen rhTSH in the future [168]. The symptoms patients mostly mention during THW are fatigue, intolerance to cold, sleep changes and weight gain [169].

Radioiodine doses higher than 5.5 GBq are associated with significantly worse pain, swallowing, chewing, taste, and anxiety scores [162], and in addition, sialoadenitis is more frequent [170].

2.7.2 HRQoL in thyroid cancer survivors

Several studies focus on HRQoL in thyroid cancer survivors during follow-up. The majority of the studies demonstrate lower HRQoL in thyroid cancer survivors compared with a general population [171-174], although two studies show no significant differences [175,176]. Examples of domains with lower scores compared with the general population are physical, role, emotional, cognitive and social functioning [173]. HRQoL in thyroid cancer is also compared with HRQoL in patients with breast cancer, colon cancer, gynaecological cancer and glioma. Although survival is significantly lower in those cancer diseases, HRQoL is at the same level [177].

A few studies assess HRQoL longitudinally. Although HRQoL increases over time, it does not reach the same levels as a general population [171]. During the first years of follow-up, HRQoL seems to fluctuate and starts increasing after five years [178]. In one study, HRQoL is measured both preoperatively and during two years of follow-up. Although HRQoL increases during follow-up, it does not reach the same level as the general population [179]. In another study HRQoL is measured pre-operatively and during a one-year follow-up, and according to these results HRQoL return to baseline values [180]. One study demonstrates that HRQoL measured at diagnosis seems to predict HRQoL at follow-up [181].

Thyroid-stimulating hormone

TSH suppressive therapy is thought to affect HRQoL negatively [182], but the results are not consistent. Two studies shows no effect of high TSH levels and HRQoL during follow-up [183,184], and one additional study investigates several thyroid function tests without finding any associations with HRQoL [185]. On the other hand, in another paper, DTC patients with subclinical hyperthyroidism are compared with euthyroid, non-cancer patients. HRQoL is lower in DTC patients measured with SF-36, fatigue is higher and muscle function in the upper limbs is reduced [186]. In the same cohort, patients are randomised to an exercise programme or a control group. After three months, patients in the exercise group show an increased HRQoL on five of eight SF-36 domains [187].

Fatigue is one of the most commonly perceived symptoms reported by thyroid cancer patients, and negatively affects HRQoL [173]. Compared with a general population, thyroid cancer patients have significantly higher levels of fatigue [188] and they have similar levels of fatigue compared with other cancer patients [189]. Those patients that are more physically active are shown to have lower levels of fatigue [190], and exercise contributes to better HRQoL in thyroid cancer patients [191]. Other frequent symptoms negatively affecting HRQoL are sleeping problems [192], irritability, and nervousness [172,173,193], which all negatively affect HRQoL.

Few patient characteristics seem to be associated with HRQoL in thyroid cancer. Lower age shows conflicting results, and is both associated with lower [178,194] and higher HRQoL [162,174]. Lower HRQoL in women could be expected, but this is scarcely shown [178]. In addition, lower education is associated with lower HRQoL [174,178].

2.7.3 Fear of recurrence and anxiety in thyroid cancer

Fear of recurrence is frequently present in thyroid cancer. Surprisingly, it is as common in thyroid cancer as in other cancer diagnoses with a worse prognosis [134]. About 35% of thyroid cancer patients have some kind of fear of recurrence [195] and, additionally, one in seven experiences a lot of fear [196]. Fear of cancer recurrence is also the most often mentioned worry in a phase I study developing an EORTC module for measuring HRQoL in thyroid cancer [197].

Anxiety varies among different cancer diagnoses, but is surprisingly high in thyroid cancer patients compared with patients with more aggressive tumours [144]. Anxiety seems to be one important determinant of HRQoL [198], and between 17-25% of thyroid cancer patients have significant anxiety [193,196,199]. Psychological and behavioural interventions during the first year after RAI treatment show declining levels of anxiety and depression [200].

2.7.4 HRQoL evaluated with qualitative methods

HRQoL in DTC patients is described in a few qualitative studies. The most prominent finding is the “good cancer” definition. The experience of having a “good cancer” is a paradox. On one hand, patients are glad to have a disease with a good prognosis. On the other hand, the optimism invalidates their fears of having a cancer and they feel dismissed by the healthcare system by not being offered psychosocial support [201-203]. In addition, they feel isolated from other cancer patients, as the physical signs and symptoms differ from the others [204].

The impact of DTC is described on both emotional and cognitive functions across all treatment phases. Patients with recurrent or metastatic disease are most affected according to daily activities, mobility, and energy levels [204]. Patients with loco-regional recurrence have significant psychological distress and worry about further recurrence, however, they also appreciate life more and evaluate family relationships higher [205].

In addition, receiving a cancer diagnosis is life-changing, resulting in uncertainty for the future and a fear of recurrence. Several participants express the need for long-term support during follow-up [203], and the need for adequate information about treatment and follow-up routines is evident [206]. Follow-up of patients with thyroid cancer is crucial both due to the life-long levothyroxine treatment and the remaining recurrence risk decades after the diagnosis. Follow-up options are studied with open ended questions, and the important factor for patients is the reassurance that the method of follow-up, whether it is primary care or specialised care, provides adequate care [207].

3 AIMS

The overall aim of this thesis was to study aspects of quality of life in patients with DTC, and to identify factors affecting quality of life from diagnosis and during follow-up.

The specific aims of Studies I-IV were:

I) To study long-term health-related quality of life in patients with DTC compared with the general population in Sweden, more than 10 years after treatment for DTC.

II) To study treatment related side-effects and their impact on health-related quality of life in patients with DTC, more than 10 years after treatment for DTC.

III) To prospectively compare short-term health-related quality of life in DTC patients, between diagnosis and one-year of follow-up.

IV) To broaden the understanding about anxiety and fear of recurrence in thyroid cancer patients through semi-structured interviews.

4 MATERIAL AND METHODS

4.1 OVERVIEW

An overview of the material and methods used in Studies I-IV included in this thesis is provided in Table 1.

Table 1. Overview of material and methods in Studies I-IV

	Study I	**Study II**	**Study III**	**Study IV**
Design	Cross-sectional Population-based	Cross-sectional Population-based	Prospective Population-based	Qualitative interview study
Data source	DTC diagnosis 1995-1998 Sweden	DTC diagnosis 1995-1998 Sweden	DTC diagnosis 2012-2017 Sweden	DTC patients Stockholm
Study time	14-17 years after diagnosis	14-17 years after diagnosis	At diagnosis and at 1-year of follow-up	3 months-18 years after diagnosis
Outcome	Long-term HRQoL Anxiety Fear of recurrence	Long-term HRQoL Comorbidities Thyroid symptoms	Short-term HRQoL TSH Anxiety Fear of recurrence	Patients' experiences of DTC
Quality of life measurements	SF-36 and study-specific questionnaire	SF-36 and study-specific questionnaire	SF-36 and study-specific questionnaire	Semi-structured interviews
Methods of analyses	Mann-Whitney U-test, Kruskal Wallis, one-sample t-test	Mann-Whitney U-test, Kruskal Wallis, Multivariate logistic regression	Mann-Whitney U-test, Kruskal Wallis, Wilcoxon signed-rank test, Multivariate logistic regression	Qualitative content analysis

4.2 STUDY DESIGN

Four studies are included in this thesis. Studies I and II are cross-sectional population-based studies evaluating HRQoL, fear of recurrence, and thyroid-related symptoms. Study III is a prospective population-based study assessing HRQoL, TSH-values, anxiety and fear of recurrence during follow-up. Study IV is an interview study using qualitative content analysis addressing anxiety and fear of recurrence.

4.3 DATA SOURCES

4.3.1 The Swedish Cancer Registry

The Swedish Cancer Registry was established in 1958 and is held by the National Board of Health and Welfare. The registry is nationwide and population-based and is generally considered to be of good quality with a national coverage of 96.3% in 1998 of all diagnosed cancers in Sweden [208]. The purpose of the cancer registry is to monitor cancer incidence and its temporal trends in Sweden, and it aims to provide statistics both to the public and for research purposes.

4.4 STUDY POPULATION

4.4.1 Studies I and II

For the purpose of Studies I and II, all DTC patients aged 35-64 years diagnosed between the years 1995-1998 in Sweden were identified from the Swedish Cancer Registry. The aim was to study long-term HRQoL 14-17 years after diagnosis. By choosing the age group of 35-64 year-olds at inclusion in 2012, the patients were 18-50 years old at diagnosis. Younger patients would have been children at the time of diagnosis and older patients might have had heterogeneous confounding factors [209]. Inclusion criteria were a diagnosis of DTC and having a permanent address in Sweden.

4.4.2 Study III

For the purpose of Study III, newly diagnosed DTC patients were included. Patients were prospectively included from January 2012 to March 2017. All hospitals in Sweden (n=13) treating DTC patients with radioactive iodine were invited to participate. All hospitals participated and, thus, the inclusion was population-based. Inclusion started at various time points in the different hospitals; therefore the inclusion was not evenly distributed geographically. Inclusion criteria were: age ≥18 years at diagnosis, Swedish speaking, a primary diagnosis of DTC, scheduled for a total thyroidectomy with or without lymph node dissection and planned for RAI treatment. Exclusion criteria were: small DTC (T1a), no planned RAI treatment, ongoing treatment for other malignancies, ATC or MTC and a recurrence of DTC. Patients were identified during the post-operative multi-disciplinary conference and included after surgery, but before RAI treatment. Patients were followed-up after one year.

4.4.3 Study IV

For the purpose of Study IV, patients with DTC followed-up at the Department of Oncology at Karolinska University Hospital in Stockholm, Sweden, were invited to participate in an interview study. Karolinska University Hospital serves the entire county of Stockholm (2.2 million inhabitants) with specialised care for thyroid cancer patients. Study participants were eligible if they were over 18 years of age and were fluent in Swedish, had a diagnosis of DTC, and were previously treated with minimum total thyroidectomy and RAI.

The patients were selected through purposeful maximum variation sampling [148] regarding age, sex, stage of disease, education, and time since diagnosis. The number was determined based on "saturation", that is when the collection of data ceases to provide substantial new information and when patterns in the data become evident. The patients were contacted by telephone, and were given the opportunity to reflect upon whether they would wish to participate when contacted again. During the telephone call, information about the study's aims and procedures was provided. When the patient agreed to participate, an interview was booked at a time and place chosen by the interviewee. Interviews were conducted in patients' homes, at the Karolinska University Hospital, in a patient's office or at a café. During the interviews, saturation was achieved after 15 interviews. To accomplish saturation, inclusion was continued with six further patients to ensure that no new aspects would emerge, which was not the case. None of the patients declined to participate. Verbal informed consent was obtained both before and after the interviews.

4.5 DATA COLLECTION

4.5.1 Studies I and II

Patients fulfilling the inclusion criteria were invited to participate by mail. By completing and returning HRQoL questionnaires, the patients consented to participate and agreed for their data to be used for research purposes. Up to two reminding letters were sent to non-responders. All data used in the study were gathered from the questionnaires. SF-36 provided data on HRQoL whereas sociodemographic data, as well as comorbidities, thyroid-related symptoms, information about received cancer treatment and possible recurrences, fear of recurrence and view of life were gathered from the study-specific questionnaire.

4.5.2 Study III

In Study III, those patients fulfilling the inclusion criteria were invited by mail or received questionnaires during their first visit after the multi-disciplinary conference. By completing and returning the questionnaires, the patients consented to participate in the study and their data to be used for research purposes. Up to three letters were sent to non-responders. SF-36 provided data on HRQoL and the study-specific questionnaire provided information about sociodemographic data, comorbidities, thyroid-related symptoms, fear of recurrence and view of life. Clinical data such as tumour characteristics, surgical and radioiodine treatment, laboratory data, and information about possible recurrences were gathered manually by the first author through reviewing medical records.

4.5.3 Study IV

Data was gathered by semi-structured interviews that were audio-recorded and transcribed verbatim. The interview guide included questions regarding the experience of living with thyroid cancer. Examples of questions were: “Has something changed after your cancer diagnosis?”, “Has your view on life changed?”, and “How have you experienced your disease from diagnosis until today?”. When needed, follow-up questions were posed. The interviews were carried out by two interviewers, co-author IW conducted eight of the interviews and the first author conducted the others. The interviews lasted for 20-65 minutes.

4.6 HRQOL MEASUREMENTS AND QUALITATIVE INTERVIEWS

In Studies I-III two different HRQoL questionnaires were used: SF-36 and a study-specific questionnaire. In Study IV semi-structured interviews were used to explore the effect of DTC on the lives of the patients.

4.6.1 SF-36

SF-36 is a HRQoL questionnaire developed to measure general health, and can be used in different diseases. SF-36 is described in the Background. As there was

Scoring and presentation

The results from SF-36 were linearly transformed to a score between 0-100 according to the scoring manual [109,210]. A high score represents a higher function or better quality of life. Clinical relevance was assessed on statistical significance but, in addition, a difference in scores >5 points was regarded as clinically relevant according to Osoba [118].

In Study I, mean scores were compared to an age- and sex-matched Swedish general population. Differences in mean scores based on the number of comorbidities, that is “no”, “one” or “two or more” comorbidities, were measured. In addition, differences in mean scores were calculated based on fear of recurrence and recurrence and grouped into “no fear” “fear” and “actual recurrence” and change in view of life grouped into “no or positive” and “negative”.

In Study II, SF-36 mean scores were compared between patients with thyroid-related symptoms grouped into “no” symptoms, “moderate” or “major” symptoms. In addition, different thyroid-related symptoms were grouped as above, and mean SF-36 scores were compared between patients with “no” and “major” symptoms and between “no” and “moderate and major” symptoms.

In Studies II-III, SF-36 responses were dichotomised into ‘‘good’’ versus ‘‘poor’’. The cut-off was based on clinical relevance. Patients answering “no” or “little” symptoms / impact on

HRQoL, for all questions on one domain, were categorised as having good HRQoL. Otherwise, they were categorised as having poor HRQoL.

In Study III, SF-36 mean scores were compared according to levels of TSH suppression: “no”, “mild” and “moderate or complete”. SF-36 mean scores were also compared based on fear of recurrence grouped into “no”, “seldom” and “often” and change in view of life grouped into “no or positive” and “negative”.

4.6.2 Study-specific questionnaire

The study-specific questionnaire (see Appendix) includes questions concerning sociodemographic factors, comorbidities, received treatment, possible recurrences and, symptoms and side-effects possibly related to thyroid cancer. The term ‘‘thyroid-related symptoms’’ was used to cover both symptoms that probably are related to thyroid disease or levothyroxine treatment and side-effects from surgery and/or radioiodine treatment. The specified symptoms related to thyroid disease or levothyroxine treatment were: fatigue, sleeping disorders, irritability, lower stress resistance, muscle weakness, bodily restlessness, sweating, palpitations, and flushes. The following symptoms with a probable relation to thyroid cancer treatment were also registered: xerostomia, hoarseness, dysphagia, numbness in the operation area and, salivary gland problems. In addition, questions about fear of recurrence and change in view of life were included; both of a quantitative character and as open-ended questions.

For analysis, comorbidities were divided into three groups: “no”, “one” and “two or more”. As regards symptoms related to thyroid disease or levothyroxine treatment, the patients completed a questionnaire with five verbal alternatives (Likert scale). The results were divided into three groups for the analysis: “no”, “moderate” (including “a little” and “moderate”), and “major” symptoms (including “quite a bit” and “very much”). Treatment-related symptoms were also divided into “no”, “moderate” and “major” symptoms.

In Studies I and II, treatment-related information was gathered from questionnaires and, in Study III tumour and treatment-related information was gathered from medical records.

Missing data

Missing data according to SF-36 in Studies I and II were evaluated using the half-scale rule in the SF-36 scoring software, according to the manual SF-35 4.0 [211]. Further improvements have been made in the SF-36 software 5.0 [212] concerning missing items, and these were used in Study III. In this version, scores are estimated when the respondent has provided a response to at least one item on a scale. The only exception is the Physical Functioning (PF) scale where item response theory was used to develop a model for estimating a score on PF scale. The PF scale differs from the other scales in having different amounts of physical activity asked for in the different questions, from vigorous activities, such as running, lifting heavy objects, participating in strenuous sports, to bathing or dressing yourself, and thus another method for calculating missing scores is used [212].

Missing data in the study-specific questionnaire were evaluated according to the half-scale rule according to thyroid-related symptoms. If half of the items were answered, the question was included into the analysis. Otherwise the answers were excluded and thus missing.

4.7 DATA ANALYSES

4.7.1 Statistical methods

The statistical methods used in the thesis are listed in Table 1. Patient characteristics were described by standard descriptive statistics.

Comparisons

In Studies I and II, the mean scores of the transformed SF-36 scores were calculated and presented with standard deviation (SD). Statistical significance was tested using the Mann-Whitney U-test in comparisons of two groups and Kruskal-Wallis when three groups were compared. In all calculations, the level of significance was 0.050. In Study I, the results of SF-36 were compared with an age- and sex-stratified Swedish general population and statistical significance was examined with one sample t-test.

In Study III, mean scores were calculated and presented with confidence intervals (CI). Statistical significance was tested using the Mann-Whitney U-test or Kruskal-Wallis test in comparisons between two and three groups, respectively. In all calculations, the level of significance was 0.050. In addition, the Wilcoxon signed-rank test at the 0.050 significance level was used when comparing SF-36 measurements between diagnosis and one-year of follow-up, when the patients in both groups were the same.

In Studies I-III, in all comparisons including SF-36, a difference of 5-10 points (scale 0-100) between groups was interpreted as a clinically relevant, minimally important difference (MID), a difference of 10-20 points as a moderate difference, and >20 points as a considerable difference [118].

Multivariate regression models

In Studies II and III, SF-36 responses were dichotomised into “good and “poor”. Logistic regression models were used to assess associations in the form of odds ratios (OR) with confidence intervals (CI) between “good” and “poor” HRQoL levels. In Study II the aim was to assess a correlation between thyroid-related symptoms and HRQoL. Adjustments were made for age, sex, comorbidities, education, and menopause. In Study III the aim was to identify factors at diagnosis predictive of HRQoL at one year of follow-up. The results of SF-36 domains at one-year follow-up were adjusted for age, sex, education, marital status, comorbidities, view of life, fear of recurrence, tumour stage and the corresponding SF-36 domain at diagnosis.

4.7.2 Qualitative content analysis

A qualitative conventional content analysis, as described by Hsieh et al., was chosen as this type of design is usually appropriate when existing theory or research literature on a phenomenon is limited [150]. The analysis was performed by two of the authors (first author and co-author PS) as follows:

1. The interviews were read through several times to become acquainted with, and get a sense of, the whole content.
2. Secondly, they were re-read systematically to identify meaning units, which are words or text segments, patterns of meaning, and issues of potential interest with reference to the research question. In this study, the focus was on anxiety and protective strategies. The segments were also marked with a preliminary code, thus this is the initial analysis. A preliminary code is close to the text written in the interview.
3. Next, those segments marked with similar codes were brought together and formed meaningful clusters, also called preliminary categories. As far as possible, the actual words expressed by the informants were used.
4. Then, the statements in each preliminary category were scrutinised and compared to find the central component, and then fused into categories.
5. Next, the final categories were compared to avoid obvious overlapping and, in a last step, the categories were compared and analysed in order to reveal possible relationships or hierarchies between them.

4.8 ETHICAL APPROVAL

Ethical approval for all the studies was obtained from the Regional Ethical Review Board in Stockholm (DNR 2011/718-31/2, 2011/1847-32 and 2014/1736-32).

5 RESULTS

5.1 STUDY I

Of 353 eligible individuals, 279 (79%) answered the questionnaires. The vast majority of patients (78%) were women, the mean age was 51 years and half of the patients reported one or more comorbidities. Surgery was the primary treatment reported by all the patients; a further 105 (38%) stated that they had received radioiodine treatment and additionally five (2%) reported receiving external radiotherapy.

5.1.1 HRQoL compared with the general population

HRQoL scores from SF-36 were compared with an age- and sex-matched Swedish general population. The patients showed statistically and clinically significant poorer HRQoL on three of eight SF-36 domains: vitality, social functioning and mental health (all p-values < 0.001). Interestingly, DTC patients reported significantly better physical role functioning compared with the general Swedish population (p < 0.001). This specific domain answers questions regarding how much of the time the patients have had problems performing work and other activities as a result of their physical health.

5.1.2 Comorbidities, recurrence and fear of recurrence

Comorbidities were, as expected, associated with lower HRQoL. Patients with one comorbidity reported poorer HRQoL on four of the SF-36 domains compared with those with none. Furthermore, patients with at least two comorbidities reported worse HRQoL on all eight domains compared with those with none (all p-values < 0.001). All differences were also clinically significant.

Only 19 (7%) of the patients reported a recurrence, which is low compared with the general risk of recurrence [38]. However, as many as 134 (48%) stated that they had a fear of recurrence. The HRQoL in those with a recurrence was lower than those without fear of recurrence on five of eight domains (p < 0.001-0.049) and, similarly, patients with fear of recurrence reported poorer HRQoL than those without fear on five of eight domains (p < 0.001-0.002). All these differences were also clinically significant. Patients with recurrence had similar HRQOL to those with a fear of recurrence, thus, fear of recurrence might be an important cause of decreased HRQoL.

5.1.3 View of life

Those 30 (11%) patients who stated that their disease had given them a negative view of life reported remarkably poorer HRQoL on all eight domains compared with those who reported a positive or unchanged view of life (all p-values < 0.001–0.030). Among the 19 patients with a recurrence, 12 (63%) stated that their disease had a positive influence on their view of life and only two reported that the disease had negatively affected their view of life, and thus recurrence seems to be an unusual cause for a negative view of life.

5.2 STUDY II

The study population in Studies I and II was the same and the patient characteristics have been presented previously. The remaining patient characteristics analysed in this study are thus presented: the majority (85%) had at least 10 years of education and half of the women were pre-menopausal. There was no statistical difference between responders and non-responders regarding age and sex.

5.2.1 Thyroid-related symptoms

Thyroid-related symptoms probably related to thyroid disease or levothyroxine treatment were defined as fatigue, sleeping disorders, irritability, lower stress resistance, muscle weakness, bodily restlessness, sweating, palpitations and flushes. Those symptoms with a probable relationship to a given treatment were; xerostomia, hoarseness, dysphagia, numbness in the operation area, and salivary gland problems. The majority (88%) of patients reported at least one of these symptoms. Almost half (42%) reported major symptoms, and 46% reported moderate symptoms. All patients with major thyroid-related symptoms had a significantly lower HRQoL on all SF-36 domains compared with patients without these symptoms ($p < 0.001$), both statistically and clinically. Additionally, all the differences were >20 points corresponding to a major difference on all domains but physical functioning. The HRQoL in patients with moderate thyroid-related symptoms compared with patients with no symptoms was significantly lower both statistically and clinically on half of the domains ($p < 0.001$-0.02).

5.2.2 Symptoms related to thyroid disease or levothyroxine treatment

Between 35% and 77% of patients (depending on symptom) reported symptoms related to thyroid disease or levothyroxine treatment. Regarding each symptom separately, all patients with moderate or major symptoms grouped together had significantly lower HRQoL compared with patients without that symptom ($p < 0.001$). All comparisons were clinically significant with >10 points difference on all SF-36 scores. When comparing patients with no symptoms with major symptoms, the difference was >20 points except for palpitations, sweating, and flushes. These differences are regarded as considerable clinical differences.

The most prevalent symptoms were fatigue, sleeping disorders, and irritability. These symptoms affected more than half of the patients, and had a large, negative effect on HRQoL. Comparing patients with major and no symptoms, SF-36 scores differed by >20 points, corresponding to a clinically considerable difference ($p < 0.001$). Figure 1 shows the differences according to fatigue.

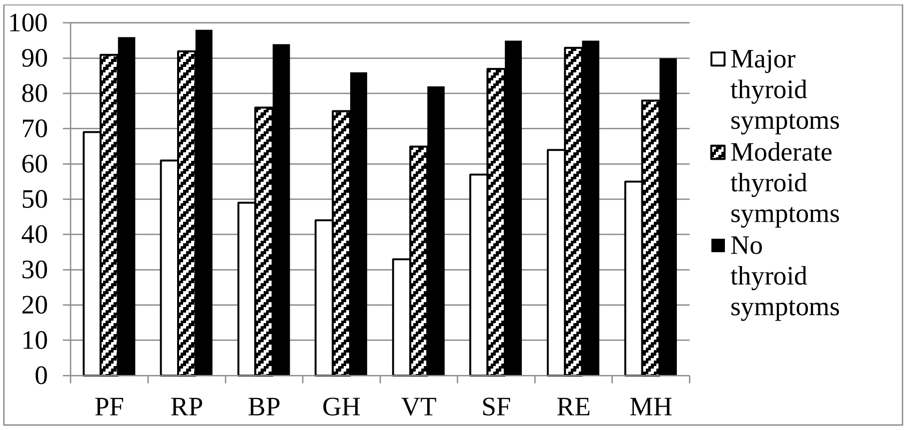

Figure 1. Differences in long-term HRQoL measured with SF-36 in DTC patients analysed on fatigue. HRQoL in patients without fatigue is compared with HRQoL in patients with moderate and major symptoms of fatigue.

5.2.3 Symptoms related to surgery or radioiodine treatment

Only a few patients reported symptoms with a possible relation to surgery or radioiodine: xerostomia (16%), hoarseness (13%), dysphagia (10%), numbness in the operation area (5%), and salivary gland problems (4%). All patients with major symptoms had statistically and clinically lower HRQoL on all eight SF-36 domains compared with patients with no symptoms ($p < 0.001$).

5.2.4 Association between thyroid-related symptoms and patient characteristics

The only patient characteristic associated with thyroid-related symptoms was comorbidity. Both those with one and those with two or more comorbidities had significantly more thyroid-related symptoms ($p < 0.001$). There was a clear correlation between thyroid-related symptoms and a decrease in HRQoL on all SF-36 domains. A statistically significant difference was demonstrated between patients with no thyroid-related symptoms and patients reporting major thyroid-related symptoms ($p < 0.01$). These differences remained after adjustment for age, sex, comorbidities, and education.

5.3 STUDY III

In this population-based prospective study, 349 (72%) patients answered the HRQoL questionnaires at diagnosis and were thus included. Of those, 250 had fulfilled a follow-up time of one year. In total, 235 (94%) had answered the HRQoL questionnaires at the one-year follow-up, and were thus included in Study III. The majority was women (70%) and the mean age was 51 years, both corresponding to incidence figures. During the first year of follow-up, 6% were diagnosed with loco-regional recurrences, 4% developed distant metastases and another five patients (2%) had abnormal Thyroglobulin-values.

5.3.1 TSH suppression and HRQoL

As the suppression of TSH has been suggested as one reason for decreased HRQoL in thyroid cancer [182] we conducted associations between the level of suppression and HRQoL. The majority (79%) had moderate or complete suppression. According to our results, those with moderate or complete suppression (TSH<0.1) had even slightly better HRQoL compared with the mildly suppressed patients (TSH 0.1-<0.4), with significantly better results on three of eight SF-36 domains (physical functioning, role physical and bodily pain), which was unexpected.

5.3.2 View of life, fear of recurrence and recurrence

Patients with a negative view of life were compared with patients with a positive or an unchanged view of life. Those with a negative view of life had a lower HRQoL both at diagnosis and at one-year of follow-up on eight and seven SF-36 domains, respectively, and the differences were also clinically significant. Fear of recurrence was common and seemed to affect HRQoL substantially. The majority of patients had a fear of recurrence both at diagnosis (75%) and after follow-up (69%). Those who reported a fear of recurrence “often” had a significantly lower HRQoL on five SF-36 domains at diagnosis and on seven domains after one year, and the differences were also clinically significant. In addition, those with an actual recurrence had a significantly lower HRQoL on seven of eight SF-36- domains.

5.3.3 HRQoL during follow-up

As expected, according to previous studies [47], HRQoL was higher after one year of follow-up, with significantly higher levels on six of eight SF-36 domains. One important question is which factors at diagnosis can affect HRQoL in the future, while these might be possible to affect early in the disease trajectory. In a bivariate analysis, age over 50 years, lower education, living alone, comorbidities, a fear of recurrence and HRQoL at diagnosis were associated with decreased HRQoL at one year of follow-up on some domains. In the subsequent multivariate analyses, only poor HRQoL at diagnosis was predictive of poor HRQoL at one year of follow-up for each respective SF-36 domain ($p < 0.01$).

5.4 STUDY IV

In the last study in this thesis, a qualitative method was used. With the aid of semi-structured interviews, patients' anxiety, fear of recurrence and protective strategies were explored. Altogether, 21 patients were interviewed. The majority was women (62%), the mean age was 49 years and mean time since diagnosis was 4 years (range 3 months-18 years). All patients had been treated with at least thyroidectomy and RAI. Five patients had loco-regional or distant recurrences. Categories and sub-categories are shown in Table 2.

Table 2. Categories and sub-categories

Anxiety	
	Contradictions - hidden anxiety
	Distrust as a source of anxiety
Protective strategies	
	Everyday life, routines and strategies
	Information and control

5.4.1 Anxiety

Anxiety was not restricted to any particular patient characteristics and physical manifestations were mentioned as consequences of anxiety. Several informants, both with and without a known recurrence, stated that they experienced anxiety both for the actual disease and also for future risks. Anxiety was in addition related to, and triggered by, follow-up procedures and temporarily decreased by successful investigations.

"I am a little anxious before the visits. It is a relief to leave the hospital with positive information about the disease. It is good to see the doctor regularly."

Some patients minimised anxiety at the beginning of the interview, but later during the interview the cancer turned out to be a major trigger of anxiety. This kind of hidden anxiety might be difficult to reveal during short consultations and is one of the major difficulties in patient-doctor communication.

Initially:

"…//I wouldn't say it [the cancer] affects me."

Later in the same interview:

"…[of course] everything, also my cancer, contributes to my worries."

At the end of the interview:

"It [worries and anxiety over her cancer] is of course present all the time."

5.4.2 Distrust

Several patients mentioned distrust in the healthcare system as a source of increased anxiety. Previous negative experiences were a reason for distrust and the anxiety was aggravated by a fear of the possibility that future recurrences would be delayed in being detected.

"What happens if they don't detect the next recurrence, they don't know where or how they should look for the recurrence…?"

In addition, a perceived lack of information increased anxiety, and the feeling of not being told the whole truth about the disease or investigations also added to the patients' feelings of anxiety.

…//"Why are they not telling me [about the results of examinations] or do they not want to tell me?" "What are they looking for or what are they worried about?"

5.4.3 Protective strategies

To decrease anxiety, everyday life and routines worked as important strategies to prevent frightening thoughts of the disease. Patients described the need of a "vacation" from the cancer and avoiding contact with the healthcare system for some periods of time helped them gather energy to cope with their disease.

"I try to avoid thoughts about the cancer. It is important to have these everyday routines, and to have people around me who I like and who like me."

In addition, information was an important factor for coping with the cancer. Patients described the need of clear-cut and honest information and receiving test results immediately was experienced as being important. On the other hand, the method of receiving the information was difficult. Telephone calls allow fast communication but, on the other hand, make it difficult to prepare questions.

"…The treatment has been exactly as the doctor told me…//…the information was exact, which I think is fantastic. [It was] very, very good information."

6 DISCUSSION

In this thesis we have studied HRQoL in thyroid cancer patients, both during short- and long-term follow-up. To explore HRQoL we analysed how patient characteristics, side-effects and symptoms were associated with HRQoL. As a complement to the quantitative perspective, we further made semi-structured interviews to deepen the understanding about anxiety and fear of recurrence. In this discussion, the general findings and interpretations are presented first, followed by clinical implications. Finally, the methodological aspects will be discussed.

6.1 FINDINGS AND INTERPRETATIONS

6.1.1 HRQoL in thyroid cancer patients during follow-up

In Study I, long-term HRQoL was measured in a population-based manner. The results were compared to a Swedish general population consisting of more than 4000 patients. The HRQoL in DTC patients was still lower compared with the general population, despite many years of follow-up and a low percentage of recurrences. These results are in good concordance with previous studies [172-174], although HRQoL similar to a general population has been shown in some studies [175,176]. The causes for the decreased HRQoL are probably multidimensional and might be related to the actual cancer itself, but the treatment and side-effects from levothyroxine could also be of importance. Interestingly, HRQoL in thyroid cancer is comparable to that of other cancer patients with even worse prognosis [177], which suggests that the disease is indeed one reason for the decreased HRQoL.

In Study III, HRQoL was measured at diagnosis and after one year of follow up. HRQoL was higher at the one-year follow-up, which was expected due to the timing of the first questionnaire. Similar results, with an increasing HRQoL during the first year have been demonstrated in previous studies [47,171]. The higher HRQoL after one year was probably related to a real improvement, but could be affected by a response shift. A response shift has previously been shown to affect HRQoL in cancer patients [213] and could complicate interpretation of the results.

One of the aims in Study III was to find factors at diagnosis predicting HRQoL during follow-up. Predictive factors could help the healthcare system to identify patients with the greatest needs and to offer interventions early in the disease trajectory. The only predictive factor for all SF-36 domains was the corresponding domain at diagnosis, and the results remained after adjustments for confounding factors. In the literature, personality is shown to be an important aspect affecting HRQoL [214] and could be one explanation for the predictive value of HRQoL at diagnosis. This is further supported by our findings in Studies I and III, where patients' with a negative view of life had significantly lower HRQoL, indicating that personality traits could be important for HRQoL.

6.1.2 Thyroid-related symptoms

In Study III, thyroid cancer patients reported several symptoms significantly affecting their HRQoL. The most common symptoms were fatigue, sleeping disorders, and irritability affecting 57-77% of the patients. In the literature, fatigue has been demonstrated to be the most frequent symptom in thyroid cancer patients [173,193,197] and it is significantly more common than in the general population [188]. In addition, fatigue in thyroid cancer is at least as frequent as in other cancers [189]. Three different methods of decreasing fatigue have been investigated in thyroid cancer patients: TSH restoration to non-suppressive doses [184], a combination of T_3 to T_4 treatment compared with traditional T_4 treatment [215] and, exercise [187]. Only exercise has been shown to decrease fatigue. The mechanisms of cancer-related fatigue are partly unknown, but inflammatory components play a role [216]. The effect of physical activity might be related to the known anti-inflammatory effect of exercise [217]. As physical activity has been shown to decrease fatigue in both thyroid and other cancer patients [218], this might play an important role in thyroid cancer rehabilitation in the future.

In addition to fatigue, sleeping problems are reported as one of the most frequent symptoms in thyroid cancer [173,196,197]. Both in comparisons with a general population and healthy controls, thyroid cancer patients have significantly more sleeping disturbances [173]. Sleeping problems are frequently reported in cancer patients in general [219] and also co-exist with fatigue and tiredness during the daytime [220]. Suggested causes for the sleeping problems are cancer treatments but also the disease itself, and distress and a fear of recurrence can aggravate the symptoms [221]. A recent randomised trial showed a positive effect of exercise on sleep quality in breast cancer patients [222], and this makes physical activity even more appealing in cancer rehabilitation.

Study II showed, that thyroid cancer patients still, more than 10 years after diagnosis, suffered from many thyroid-related symptoms, including fatigue and sleeping disturbances. Those with symptoms had significantly worse HRQoL and the impact on HRQoL remained after adjustments for common confounders such as age and comorbidities. This study highlights the importance of carefully asking patients about symptoms and, if possible, they should be offered help with treatable symptoms.

6.1.3 TSH and HRQoL

In Study III the relationship between TSH suppression and HRQoL was investigated. After one year of follow-up, the majority of patients were under moderate or complete TSH suppression. We demonstrated that these patients had better HRQoL compared with those with mild suppression, and were similar to those with no suppression. These results support previous findings that TSH suppression is not correlated with decreased HRQoL [185]. In addition, restoration to normal TSH does not increase HRQoL [184]. Although TSH does not seem to be associated with a decrease in HRQoL, patients still have significant levels of symptoms often seen in hyperthyroidism. One suggestion for our findings is that those patients with mild suppression could have had pronounced symptoms from complete TSH suppression. Therefore, they might have been prescribed lower doses of levothyroxine to decrease these symptoms.

Another aspect of TSH suppression is the correlation with an increased risk of cardiovascular mortality [60] and osteoporosis [61] in thyroid cancer patients with lower TSH values. Consequently, there might still be unknown hormonal factors that could explain both thyroid-related symptoms and cardiovascular morbidity.

6.1.4 Fear of recurrence

In Studies I and III fear of recurrence was reported by more than 70% of the patients during diagnosis and almost half of the patients throughout follow-up. Fear of recurrence and fear of developing another cancer were also important findings in the interviews in Study IV. In addition, fear of recurrence was associated with a significantly decreased HRQoL, and is thus an important factor for the patients' well-being.

Despite the good prognosis, thyroid cancer patients have similar levels of fear of recurrence when compared with other cancer patients [134]. This can partly be explained by the remaining life-long risk of recurrence, which most patients should be aware of. Younger patients, having children, a shorter time from diagnosis and suspected or proven recurrence are factors associated with fear [223]. Interestingly, these are mostly the same factors which are associated with lower HRQoL [178]. The life-long treatment with levothyroxine and the follow-up visits may add to the fear.

One important aspect could be the experience of having a "good cancer", which has been reported in qualitative studies [201,202]. As a consequence of this "good cancer", patients experience their disease to be trivialised, and they do not feel they have the right to psychosocial support. This might make the coping process more complicated and add to their fear.

6.1.5 Anxiety

In Study IV, anxiety was described by the majority of the patients, regardless of disease stage. Anxiety is known to be common in cancer patients, both in those cured from their disease and in patients with metastases [141,143]. Surprisingly, anxiety and depression are higher in thyroid cancer compared with several other cancer diagnoses with a poorer prognosis [144]. From a physician's point of view, DTC has an excellent prognosis and is often communicated to the patients as a "good cancer" [201,202]. To be diagnosed with a cancer can be considered a death threat and the term "good" is, for them, conflicting when it appears to invalidate their fears of having a cancer [202]. The need for long-term follow-up might add to the anxiety and, in our study, follow-up procedures were mentioned as one source of anxiety. The increasing distress around planned follow-up is shown in several cancer diagnoses [224,225] and the follow-up visits remind the patients of their disease, thus increasing anxiety. In Study IV, anxiety was also associated with a fear of recurrence and, in addition, persistent Tg values. Tg is a sensitive tumour marker and important for monitoring the disease. However, in patients with persistent Tg, the frequent follow-ups of abnormal laboratory tests might be a source of severe anxiety.

One important finding was the partly hidden anxiety, when patients denied anxiety at the beginning of an interview, but then admitted it later on. These kind of contradictions have been shown earlier, when patients denied anxiety one moment, but then openly talked about death anxiety in the next sentence [226]. This could be of great importance in the clinical setting, when consultations are often short and hidden anxiety might be missed. During consultations, patient-physician communication is predominantly concerned with medical issues, and symptoms and anxiety are discussed to a lesser extent [227]. This highlights the importance of also focusing on anxiety and other symptoms especially in thyroid cancer patients, who both might deny anxiety and also feel they do not have the right to complain about it due to the good prognosis.

Lack of information was mentioned as one source of anxiety in Study IV. Some patients felt that doctors gave evasive answers to their questions and, in addition, did not share with them the whole truth about their disease. Others mentioned that communication regarding test results was a problem, that a delay in receiving the results was increasing their anxiety. Previous studies have shown that unmet information needs are a frequent problem in thyroid cancer [228] and, on the other hand, those patients who are satisfied with their information needs experience less distress [229]. In Study IV, good information was described as an important part of coping with the disease. Clear-cut information created a sense of control, which resulted in decreased levels of anxiety. To ask the patients what kind of information they wish to receive and how they want it to be delivered could probably decrease their anxiety.

6.2 CLINICAL IMPLICATIONS

Based on the results in our studies, how can we help Lena, the 40-year-old woman with increasing anxiety before her follow-up visits?

According to our findings, patients with DTC have several reasons for anxiety and decreased HRQoL; fear of recurrence, lack of information, thyroid-related symptoms, and a life-long need of follow-up. All these factors could increase Lena’s anxiety. In the first place, she should be offered a consultation with the physician responsible for her treatment, as a good patient-physician relationship is vital for communication. The visit should not address medical issues alone, but also her anxiety and fears. In addition, possible thyroid-related symptoms affecting her HRQoL should be discussed as, for example palpitations and sleeping disorders could be possible to treat.

As DTC patients might not have been offered psychosocial support during the disease trajectory due to the “good cancer” perception, this should be offered to Lena. Adequate information about the favourable prognosis is obviously important, but to normalise her fears and anxiety could help Lena cope with her disease. The term “good cancer” should be avoided, and instead the term low-risk cancer is an option.

What kind of follow-up should Lena be offered? Lena is frightened and anxious before visits and appears to have a low-risk cancer. Thus, she could be offered individualised follow-up with less frequent visits and laboratory tests replacing some follow-up visits. If telephone calls are offered for test results, then it is crucial to offer answers in a timely fashion.

How can the initial care be organised to avoid anxiety? Adequate information about the prognosis without using the term "good cancer" is vital. To offer psychosocial support early on could be recommended, but unfortunately no good predictive tools for patients at risk of decreased HRQoL or anxiety exist. Thus, good patient-physician communication allowing patients' psychosocial needs to be addressed during consultations could be one possibility of decreasing anxiety.

6.3 METHODOLOGICAL CONSIDERATIONS

6.3.1 Internal validity

In quantitative studies, validity is important to assess and internal validity is defined as how well the study results have been measured, that is, the absence of systematic errors. Systematic errors do not decrease if the sample size is increased, as the errors remain during measurements. On the contrary, random errors are reduced by increasing the sample size. Systematic errors are often called bias, and are divided into three main groups; selection bias, information bias and confounding [230].

Selection bias

Selection bias refers to the differences between study participants and non-participants, thus the participants are not representative of the whole target population. Because the difference is unknown, the selection bias cannot be observed but is suspected [231].

Studies using postal questionnaires are inexpensive in gathering data, but non-responders are a problem and decrease the accuracy of the data. Several ways of increasing participation exist; people can be contacted in advance, questionnaires can be sent by first class post, questionnaires can be made personal and kept short, compensation can be offered and reminders can be sent [232]. In Studies I, II and III most questionnaires were posted, and up to three reminders were sent to non-responders. The included letter was easy to understand and a pre-paid return envelope was enclosed. No compensation was offered. It is known that lower response rates are expected among men, younger, and rural inhabitants [233]. In Studies I and II the inclusion was population-based and there was no statistical difference between responders and non-responders regarding age and sex. However, in Study III, non-responders were younger (mean age 43 vs 51 years, $p = 0.03$) but with no difference in sex. Younger patients could have had better physical functioning, which might have affected the results. In Study III, the hospitals including patients did not start inclusion into the study at the same time. Thus, all eligible patients during the time period were not included. Patients were, however, included from all Swedish hospitals administering RAI treatment to DTC patients, and all disease stages, different age groups, and patients from both cities and rural areas were included. Loss-to follow-up was extremely low in Study III, with a response rate of 94% at the one-year follow-up. In Study IV, although it was a qualitative study and no statistical methods were used, it is worth mentioning that no patients refused to participate.

Information bias

Information bias, also called misclassification bias, is due to errors in collecting information from, or about, study subjects.

In Studies I and II, all the data was filled in by the patients, that is, sociodemographic factors, comorbidities, treatments and symptoms. There may have been possible information bias due to recall bias or because the patients could not understand the questions. To minimise language difficulties, the questionnaire was pilot tested on five patients, and no difficulties appeared. Regarding comorbidities, self-assessment has shown high concordance with medical records, and the method is therefore acceptable [234]. According to recommendations, no healthcare providers helped the patients to complete the questionnaires, but no information is available about possible family members or others helping them [81]. Information from medical records in Study III was obtained on a predefined protocol developed by the research group. All the medical records were reviewed by the first author to minimise misclassification.

At the beginning of our studies, no validated HRQoL questionnaire suitable for thyroid cancer patients was available in Swedish. Therefore, two different questionnaires were used, the SF-36 and the study-specific questionnaire. SF-36 is a well-validated HRQoL instrument, but does not include questions regarding specific thyroid cancer issues. While thyroid cancer patients are not expected to have typical symptoms from chemotherapy, radiotherapy, or other oncological treatments, a general HRQoL questionnaire was regarded as suitable. SF-36 is regarded as valid for the use in studies of thyroid cancer patients [45,47,112]. The study-specific questionnaire is not validated, but includes questions relevant for thyroid cancer patients, including questions about symptoms and side-effects from the disease and given treatment. The questionnaire was developed by the research group, with its relevant knowledge of thyroid cancer and its symptoms. Recently, a phase III study has investigated an EORTC QLQ-C30 thyroid-specific module THY34 [235], and as soon as it is validated in a phase IV study and translated to Swedish it should be a good alternative.

Confounding

Confounding refers to a “confusion of effects”, that is, finding an association of the wrong reason. A confounder is a factor interfering with both the exposure and the outcome, but not a causal factor. Randomisation and matching are methods of preventing confounding. In addition, adjustments for known confounders can be analysed statistically [230,231].

In Studies II and III, adjustments were discussed in the research group and the statistical method was discussed with a statistician. To accomplish adjustments SF-36 domains were dichotomised into “good” versus “poor”. Patients answering “no” or “little” symptoms/impact on HRQoL on all questions on one domain were categorised as having “good” HRQoL. They were otherwise categorised as having “poor” HRQoL. Multiple logistic regression models were used to adjust for confounding factors. The dichotomisation has not been validated, however, as the aim was to compare patients with no/few symptoms with those with more symptoms, the method seemed acceptable.

6.3.2 Random errors and precision

Random error is the influence of chance, thus referring to the variability in the data and providing information about the precision. Random errors can be estimated by confidence intervals (CI) and tested with p-values, that is, the analysis of significance. A commonly used CI is 95%, which is, if the study was to be repeated many times, for 95% of the time the CI would include the correct values of the measure. The width of the CI is related to the variability, and aids the investigator in deciding whether the difference is of clinical importance. The p-value is calculated from the same equation as the CI and measures whether the null hypothesis, which states that there is no relation between exposure and outcome, is true or not. The p-value answers the question: what is the probability to receive this result, or a more extreme one, if the null hypothesis is true? In medical research, a p-value of < 0.05 is commonly used as a significant level, although it is more of a convention and other possible levels such as < 0.01 or < 0.001 could be used [231].

No statistical testing is completely certain and there is always, therefore, a risk of errors being made. A Type I error occurs when a null hypothesis is rejected although it was true (false positive). On the contrary, a Type II error is when the null hypothesis is not rejected although it is false (false negative). The risk of Type I errors can be decreased by lowering the p-values and to decrease the risk of Type II errors a larger study population is needed. Another measure is power, which is 1-Type II error. Power is the probability of obtaining a statistically significant p-value when the null hypothesis is truly false [231,236].

In our studies we have set the level of a significant p-value to < 0.05, which might generate many significant p-values due to multiple testing. To add a clinical significance to the results, MID was used and no differences in SF-36 <5 points were regarded as significant. To reduce Type II errors the sample size in Studies I, II and III was more than 200 patients and the power is, therefore, satisfying.

6.3.3 HRQoL measurements

To assess HRQoL, the most appropriate questionnaires should be used. Generic instruments might not capture symptoms relevant for certain diseases, while disease-specific instruments could be complemented with a general questionnaire to better understand HRQoL changes over time. In addition, specific questions about certain symptoms, fears or life satisfaction could be added depending on the study [77]. By using the study-specific questionnaire as a complement to SF-36, disease-specific questions were added, when no disease-specific questionnaire was available. In addition, to address two clinically important questions not included in other instruments, fear of recurrence and change in view of life were added.

Scoring

The questions in SF-36 are answered on an ordinal scale with three to six response alternatives and transformed to a scale ranging from 0-100. The transformation could be questionable, while certain answers can only become specific numbers from 0-100. If a larger number of response categories are offered, respondents tend to choose different answers during repeated testing and, thus, four to five response categories are recommended. In SF-36, all the questions are multi-item, that is, the same domain is composed of several questions, and this gives a greater precision.

In the study-specific questionnaire we have used five response categories for the symptoms related to thyroid disease or levothyroxine treatment and three for the treatment-related symptoms. When measuring associations between symptoms and SF-36, the answers were grouped together into three categories: corresponding to "no", "moderate" and "major" symptoms. These three groups show clear-cut differences in HRQoL levels.

The questions about symptoms and side-effects can be discussed, at least after studies investigating and developing the EORTC QLQ-C30 THY34 disease-specific questionnaire [235]. Some of the questions are lacking in our disease-specific questionnaire used in Studies I, II and III, partly because we only intended to study specific symptoms and not the life impact of the disease. On the other hand, although we have fewer questions in our questionnaire, they cover important parts of the THY34 questionnaire. In addition, the symptoms-specific questions seem relevant, because the different levels with "no", "moderate" and "major" symptoms have significantly effect on the SF-36 domains. Moreover, the question regarding fear of recurrence showed similar associations to SF-36, where those with "often" had lower HRQoL compared with those reporting "seldom" and "no" fear of recurrence. Although fewer patients had a negative change in view of life, those reporting negative view had significantly lower HRQoL, making the question important.

Clinical significance

In medical research, p-values < 0.05 are often assessed as significant, but in HRQoL measurements, in addition, clinical significance is of great importance to the patients. Although the concept of QoL is understood by the readers, an understanding of the measurements in HRQoL studies is seldom well known to clinicians. Thus, reporting HRQoL data should include both statistical and clinical significance reported in a clear-cut way.

A difference of 5-10 points on a 100-point scale is often regarded as clinically significant [118]. There seem to be differences in the ability to experience improvement and deterioration of HRQoL. An improvement of 5% might be meaningful, whereas a 10% decline is required to be clinically significant [237].

In our studies we have used 5-10 points as a small clinical significance, 10-20 as a moderate and >20 as a major difference. In measuring HRQoL during the follow-up in Study III, which was increasing, the results should be clearly clinically important according to the lower required difference during improvements of HRQoL.

Response shift

Patients experiencing a serious illness learn to adapt to and cope with their disease and often report better HRQoL than expected, which is understood as a response shift. Clinicians are aware that their patients are adapting to their disease, but in HRQoL research it is difficult to take this into account. In Study III, HRQoL was measured at the time of diagnosis and after one year of follow-up. The increasing HRQoL during the first year might be affected by a response shift and thus overestimated, and the interpretation of the results is therefore challenging.

6.3.4 External validity

External validity refers to what extent the results from a study can be generalised to another population [231]. In Studies I and II, the inclusion was population-based and no differences according to age and sex were measured between the responders and non-responders. Thus, these results could be generalised to another thyroid cancer population in a country with a similar a healthcare system. The long follow-up time makes the results comparable to a large group of patients due to the longevity of the disease. However, the treatment and follow-up of thyroid cancer is changing, which makes the results more difficult to compare in patients with a shorter follow-up time. In addition, few recurrences were reported and the results cannot be generalised to patients with recurrent disease. In Study III, the inclusion was population-based, although it might be expected that more patients from urban areas were included and, in addition, non-responders were younger. The population-based inclusion does, however, offer generalisation to thyroid cancer patients with short-term follow-up, but not to other forms of cancer.

6.3.5 Trustworthiness

Corresponding to the terms validity and reliability in quantitative studies, the term trustworthiness is used in qualitative research. It is an assessment of how the study results can be trusted and if the findings are worth paying attention to. The terms used for trustworthiness are credibility, dependability and transferability [156]. In Study IV, we did take into account some important aspects of trustworthiness.

Credibility

Credibility assesses how well the data collection and the analysis process address the research question [156]. The aim of the study was to capture and describe the experience of thyroid cancer in depth, to find the variation and also the most common patterns. To increase credibility, patient selection was made by purposeful maximum-variation sampling according to age, sex, stage of disease, education, and time since diagnosis; to capture the width of the experience by as broad an inclusion as possible. To ensure that the most common themes were covered, saturation was assessed, that is, no new data was discovered after 15 interviews. Another six interviews were conducted to ascertain that no new information could be found. We did not include patients with smaller tumours. These individuals could be expected to have similar experiences of their disease, due to our results showing that disease stage did not affect HRQoL.

The method of analysis is another aspect of credibility. In our study, we have shown the different steps used during the analysis according to Hsieh [150]. While defining meaning units we have used the exact words from the interviews not to lose any meaning. In addition, dialogical intersubjectivity was aimed at [151], meaning that the authors analysed relevant interview segments separately and compared their findings. In case of any discrepancies, these were discussed, revised, and validated in discussion with the other author. To enable readers to judge similarities and differences between categories, representative quotations from the text were shown. During analysis for Study IV, the most apparent and common themes were anxiety and protective strategies. Thus, the analysis and reporting is based on those results. Those results not reported are therefore unknown for the readers, might contain aspects of interest. To avoid uncertainty, the method and the chosen themes were described in the paper for Study IV.

Dependability

Dependability refers to which codes and quotations are included in the categories. While data collection extends over time, and the interviewing is an evolving process, the interviews can be affected by the researchers. To ensure that the analysis is consistent, several researchers can cooperate [156]. In Study IV, several interview segments were analysed by two of the researchers, to ensure that the analysis was consistent and that different opinions were discussed. The aim was not to reach a consensus, but to find possible alternative interpretations.

Transferability

Transferability refers to what degree the findings in a qualitative study can be applied beyond the bounds of the project, and is similar to external validity in quantitative research. To enable the readers to judge transferability the method section importantly contains a clear description of the context in which the study was carried out, participant selection criteria used, and a clear description regarding the analysis [156]. For Study IV, patient selection is clearly described and, in addition, a description of where the interviews were conducted and methods of analysis were provided. For readers, the transferability is difficult due to different healthcare systems, varying follow-up routines and other cultural expressions when dealing with crisis and anxiety.

7 CONCLUSIONS

Some conclusions that can be drawn from the studies in this thesis

- Long-term HRQoL in patients with DTC is lower compared with the general population measured 14-17 years after diagnosis.
- Half of the patients have a fear of recurrence both at diagnosis and during long-term follow-up.
- Thyroid-related symptoms affect, depending on symptom, 35-77% of thyroid cancer survivors, and these symptoms affect HRQoL negatively.
- Negative view of life affects HRQoL significantly.
- Short-term HRQoL increases during the first year of follow-up.
- TSH-levels do not seem to affect HRQoL in DTC patients.
- HRQoL at diagnosis is a predicitive factor for HRQoL during follow-up.
- Anxiety is a major concern for thyroid cancer patients.
- Protective strategies help patients to cope with their anxiety.

8 FUTURE RESEARCH

Decreased HRQoL in thyroid cancer patients both at diagnosis and during follow-up is an important finding in this thesis. These patients have a significant symptom burden and increased anxiety affecting their HRQoL. In order to assess further information about how HRQoL develops over time, a follow-up of the prospective study is warranted. We are continuously gathering data from the patients included in Study III and, follow-up is planned both at three and five years after inclusion. These data will provide a further insight into the development of HRQoL over time. As population-based follow-up results are not, to the best of our knowledge, yet published, this will contribute substantially to the understanding of HRQoL in DTC patients. During follow-up a careful review of medical records is made, enabling further exploration of tumour characteristics, treatment-related factors, and laboratory tests affecting HRQoL. One of the most interesting findings will be the effect of TSH values on medium-term HRQoL.

In the qualitative study, increased anxiety and different ways of coping with the cancer were major findings. Several patients experienced anxiety related to follow-up visits. To further investigate these findings, additional interview data is available. Further qualitative analyses of the patient-physician relationship and the patients' experiences of healthcare could give important insights both into their thoughts and attitudes about their disease and its treatment, and also about their opinions concerning the healthcare system.

Further, the question not answered is how personality affects HRQoL and how patients in the greatest needs are offered help. Our intention is to find a predicitve tool for decreased HRQoL at diagnosis and offer those patients psychosocial counseling. The best possible study would be a randomised trial offering counseling and structured information to DTC patients in combination with thorough measurements of HRQoL and distress over time.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

9.1 BAKGRUND

Sköldkörtelcancer, eller tyreoideacancer, utgör endast 1 % av alla cancerfall i Sverige, men är en av de snabbast ökande cancerformerna. Ungefär 3 av 4 som drabbas är kvinnor och medelåldern vid insjuknandet är under 50 år, alltså betydligt lägre än vid de allra flesta cancersjudomar. De två vanligaste typerna av tyreoideacancer är den papillära och den follikulära, som tillsammans utgör den differentierade tyreoideacancern. Härefter används tyreoideacancer i betydelsen differentierad tyreoideacancer.

Tyreoideacancer har en mycket god prognos med en överlevnad på över 90 % och i kombination med tidigt insjuknande är det många som lever med sjukdomen. Sjukdomen upptäckts oftast som en knöl på halsen. Behandlingen består av operation, där sköldkörteln och ibland även närliggande lymfkörtlar, avlägsnas. Som efterbehandling ges ofta radioaktivt jod, vars syfte är att avlägsna eventuella kvarvarande cancerceller. När patienterna har opererat bort sin sköldkörtel, kommer de att behöva livslång medicinering med sköldkörtelhormon. Behandlingen av tyreoideacancer har relativt få biverkningar, som inte är jämförbara med andra cancerbehandlingar såsom cellgifter eller strålbehandling. Prognosen för patienter med tyreoideacancer är mycket god. Således förväntas sjukdomen ha en liten inverkan på patienternas livskvalitet.

Flera tidigare studier har visat att patienter med tyreoideacancer trots detta har sämre livskvalitet än normalbefolkningen. De har ungefär motsvarande livskvalitet som andra cancerpatienter, trots att prognosen vid tyreoideacancer ofta är påtagligt bättre. En stor andel av patienterna med tyreoideacancer har oro för återfall, vilket påverkar deras livskvalitet negativt. Eftersom prognosen är så bra, har sjukvården en tendens att klassa den som en ”snäll cancer”. Det kan uppfattas av en del som något positivt, men många upplever det som jobbigt. Att få en cancersjukdom är livsomvälvande oberoende av om prognosen är god och om sjukdomen är ”snäll”. Patienterna kan uppleva att de inte får samma typ av psykosocialt stöd som andra cancerpatienter och de känner att deras rädsla inte blir tagen på allvar p.g.a. den ”snälla cancern”.

Således drabbas dessa patienter av försämrad livskvalitet, men varken orsaken till den försämrade livskvaliteten eller hur den utvecklas över tid är klarlagt. Syftet med denna avhandling var att studera hur livskvaliteten hos patienter med tyreoideacancer ser ut och hur den utvecklas över tid och därtill att identifiera faktorer som påverkar livskvaliteten på kort- och långsikt.

9.2 METOD

När man studerar livskvalitet relaterat till sjukdom och de symtom som beror på sjukdomen, kallas detta för hälsorelaterad livskvalitet. Hälsorelaterad livskvalitet mäter hur sjukdomen påverkar patienternas fysiska och psykiska hälsa samt hur deras förmåga att utföra dagliga aktiviteter påverkas. Livskvalitet mäts oftast med frågeformulär. Dessa frågeformulär är olika utformade beroende på syftet med studien. Generella formulär mäter livskvalitet hos patienter med olika sjukdomar och även friska människor, vilket innebär att jämförelser kan göras mellan olika patientergrupper och med normalbefolkningen. Sjukdomsspecifika formulär är utformade för att mäta symtom som är specifika för vissa sjukdomar.

Denna avhandling omfattar fyra delarbeten. I **delarbete I, II och III** har vi studerat livsvalitet med frågeformulär och i **delarbete IV** har vi intervjuat patienter. Då patienter med tyreoideacancer inte förväntas ha samma symtom som andra cancerpatienter, har vi i denna avhandling använt ett generellt frågeformulär, som kallas SF-36. Som komplement har vi utvecklat ett eget studiespecifikt frågeformulär för att mäta de symtom och biverkningar som kan uppkomma efter behandling av tyreoideacancer.

I delarbete I och II har vi skickat frågeformulär till patienter med tyreoideacancer 14-17 år efter diagnos, för att studera deras livskvalitet på lång sikt. I delarbete III har vi inkluderat patienter vid diagnos och följt dem efter ett år, då de svarat på samma frågeformulär som i delarbete I och II. I delarbete IV genomförde vi intervjuer med 21 patienter för att ytterligare öka kuskapen om hur patienter med tyreoideacancer mår.

9.3 PATIENTER OCH RESULTAT

Delarbete I och II

I delarbete I och II har vi inkluderat 279 patienter med tyreoideacancer. Dessa hade sämre livskvalitet jämfört med en jämförande grupp från den svenska befolkningen. Därtill hade hälften av patienterna oro för återfall, trots många år sedan diagnos. De patienter som hade oro för återfall hade påtagligt sämre livskvalitet än de utan oro.

I delarbete II har vi undersökt vilka symtom dessa patienter lider av. Majoriteten av patienterna hade symtom som skulle kunna vara relaterade till den cancerbehandling de fått och det sköldkörtelhormon som alla patienter får. De vanligaste symtomen var trötthet, sömnsvårigheter och irritationskänsla. De patienter med symtom hade påtagligt sämre livskvalitet än de utan symtom. Eftersom symtomen kunde bero på många andra faktorer än sjukdomen, som ålder, kön, andra sjukdomar och cancers allvarlighetsgrad, gjordes ytterligare statistiska analyser. Analyserna visade att den negativa inverkan på livskvalitet av trötthet, irritationskänsla och sömnssvårigheter faktiskt berodde på dessa symtom och inte på andra faktorer.

Delarbete III

I delarbete III inkluderades 235 patienter i samband med att de fick sin cancerdiagnos. Deras livskvalitet mättes vid diagnos och efter 1-års uppföljning. Livskvaliteten förbättrades påtagligt under det första året, vilket var förväntat. Majoriteten av patienterna hade oro för återfall både vid diagnos och vid uppföljning, vilket påverkade deras livskvalitet negativt. För att identifiera om någon faktor vid diagnos kunde förutspå patienternas livskvalitet efter 1 års uppföljning analyserades bl.a. följande faktorer: ålder, kön, utbildning, oro för återfall och livsvalitet vid diagnos. Den enda faktorn som vid diagnos kunde förutspå livskvalitet vid 1 års uppföljning var livskvaliteten vid diagnos.

Delarbete IV

För att fördjupa kunskapen om hur oro för återfall och ångest påverkar patienternas livskvalitet, utförde vi i delarbete IV intervjuer med 21 patienter. De flesta patienterna, oberoende av ålder, kön eller sjukdomens allvarlighetsgrad, upplevde ångest. Denna ångest var relaterad till oro för återfall och många upplevde att ångesten ökade i samband med återbesök. De flesta patienterna hade strategier för att minska ångesten. Det vardagliga livet med arbete och barn hjälpte dem att inte tänka på sin cancersjukdom. Bra och fullständig information om sjukdomen och dess behandling gav patienterna en känsla av kontroll och hjälpte dem att bearbeta sin sjukdom.

9.4 DISKUSSION

Patienter med tyreoideacancer upplever sämre livskvalitet jämfört med en generell population i Sverige, trots den goda prognosen. Orsaken är antagligen mångfacetterad, och torde vara relaterad till själva cancersjukdomen. Detta stöds av att patienter med tyreoideacancer har en likvärdig livskvalitet jämfört med andra cancerpatienter, som har betydligt sämre prognos.

Majoriteten av patienterna upplevde symtom som trötthet och sömnproblem. Dessa patienter hade påtagligt sämre livskvalitet än de utan symtom. Trötthet är det vanligaste symtomet även hos andra cancerpatienter men orsaken är inte klarlagd. Många av patienterna hade också sömnproblem, vilket kan vara en förklaring till tröttheten. Sömnproblemen förvärras ofta av oro relaterat till själva cancersjukdomen, och således är det viktigt att efterhöra symtom för att bäst kunna avhjälpa dessa.

Den livskvalitet patienterna upplevde vid diagnos var den enda faktorn som verkade förutsäga hur livskvaliteteten är vid 1 års uppföljning. En förklaring till detta fynd kunde vara att personlighet påverkar livskvaliteten. I studier gällande många olika cancersjukdomar har man visat att en mera negativ personlighet ger upphov till sämre livsvalitet.

Många patienter hade rädsla för återfall, både vid diagnos och under uppföljning. Denna rädsla är lika vanlig hos patienter med tyreoideacancer som hos andra cancerpatienter med betydligt sämre prognos. Oron ger både en försämrad livskvalitet och är också en källa till ångest. Denna oro kan förvärras av att patienterna fått höra att de har en ”snäll cancer”, vilket gör att deras rädsla och ångest inte tas på allvar. Således är det viktigt att fånga upp patienternas upplevelser, och istället för att prata om en ”snäll cancer” kan ordet lågrisk cancer användas. Att erbjuda psykosocialt stöd även vid tyreoideacancer är oerhört viktigt, då många patienter kan ha blivit negligerade vid diagnos p.g.a. den goda prognosen.

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12 APPENDIX

12.1 STUDY-SPECIFIC QUESTIONNAIRE