LONG-TERM OUTCOME OF PATIENTS WITH LOW-RISK PAPILLARY OR FOLLICULAR THYROID CARCINOMA

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ACADEMIC DISSERTATION

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To my family

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1 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred in the text by their Roman numerals:

I Pelttari H, Laitinen K, Schalin-Jäntti C, Välimäki MJ.
Long-term outcome of 495 TNM stage I or II patients with differentiated thyroid carcinoma followed up with neck ultrasonography and thyroglobulin measurements on T4 treatment.
Clin Endocrinol (Oxf). 2008 Aug; 69(2):323-31.

II Pelttari H, Välimäki MJ, Löyttyniemi E, Schalin-Jäntti C.
Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study.
Eur J Endocrinol. 2010 Nov; 163(5):757-63.

III Pelttari H, Schalin-Jäntti C, Arola J, Löyttyniemi E, Knuutila S, Välimäki MJ.
BRAF V600E mutation does not predict recurrence after long-term follow-up in TNM stage I or II papillary thyroid carcinoma.
APMIS. 2012 May; 120(5):380-6.

IV Pelttari H, Sintonen H, Schalin-Jäntti C, Välimäki MJ.
Health-related quality of life in long-term follow-up of patients with cured TNM stage I or II differentiated thyroid carcinoma.
Clin Endocrinol (Oxf). 2009 Mar; 70(3):493-7.

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2 ABBREVIATIONS

AGES Age Gender Extent Size

AMES Age Metastasis Extent Size

BRAF B isoform of RAF kinase

DTC Differentiated thyroid cancer

DxWBS Diagnostic whole-body scan

FNAB Fine-needle aspiration biopsy

FTC Follicular thyroid cancer

GBq Giga-Bequerel (10^9 Bequerel)

HRQoL Health-related quality of life

HUCH Helsinki University Central Hospital

MACIS Metastasis Age Completeness of resection Invasion Size

MMP Matrix metalloproteinase

NCCN National Comprehensive Cancer Network

NIS sodium-iodine symporter

PET Positron emission tomography

PTC Papillary thyroid cancer

RAI Radio-active iodine

rhTSH Recombinant human TSH

RRA Radio-active iodine thyroid remnant ablation

RxWBS Post-treatment whole-body scan

TG Thyroglobulin

TNM Tumour Node Metastasis

TSH Thyroid-stimulating hormone or thyrotropin

TTE Total thyroidectomy

UICC Union Internationale Contre le Cancer (International Union Against Cancer)

US Ultrasonography

VEGF Vascular endothelial growth factor

WBS Whole-body scan

WDTC Well-differentiated thyroid cancer

3 ABSTRACT

The goal of initial therapy in differentiated thyroid cancer (DTC) is to minimize disease related mortality and morbidity by surgically removing the primary tumour and all metastasized tumour tissue. A second goal is to minimize risk of recurrence and metastatic spread by facilitating post-operative radio-iodine ablation (RRA), permitting accurate long-term surveillance. Recurrences are relatively common even in patient population at low-risk for cancer-specific death, occurring in 10-40% of cases. The treatment and follow-up schemes have varied between centres and there is ongoing debate about appropriate methods for primary therapy and surveillance. With the increasing incidence of DTC, the need for new factors prognostic of disease recurrence is growing; most of the prognostic systems have been validated with cancer-specific death as outcome.

We designed an observational retrospective study to assess the outcome of a large cohort of patients with low-risk thyroid carcinoma and with a uniform primary therapy. All patients belong to TNM stage I or II and were considered disease-free after initial therapy. We evaluated the safety and efficacy of a surveillance paradigm, comprising yearly thyroglobulin (TG) measurements on L-T4 therapy and neck ultrasonography (US) every second year, with an increase in TG to a detectable level being an indication for further investigations. We examined the health-related quality of life (HRQoL) of the patient cohort after long-term follow-up using a validated multidimensional method (15D®).

We studied factors correlating with disease recurrence, including patient demographics, tumour characteristics and parameters with primary therapy, in 495 low-risk patients treated at Helsinki University Central Hospital over a 15-year period. Post-operative and post-ablative TG concentrations, age, tumour size, local infiltration and nodal metastasis at primary surgery, number of neck US, fine-needle aspiration biopsies (FNABs) and operations performed, presence of BRAF mutation in papillary tumour tissue, disease recurrences and cancer-specific deaths were evaluated.

The majority of patients had total thyroidectomy and radio-active iodine remnant ablation as initial treatment. The median follow-up was 16 (range 10–24) years. Fifty-one patients (10.3%) experienced disease recurrence during follow-up. A combination of neck US and high TG revealed most recurrences.

In multiple logistic regression analysis, post-ablative measurable TG concentrations (odds ratio (OR) 3.72, confidence interval (CI) 1.71–8.05, P = 0.0009) and presence of local infiltration on primary surgery (OR 2.66, CI 1.03–6.90, P = 0.04) were the only

independent predictors of recurrence. BRAF V600E mutation is common (prevalence 67%) in this low-risk papillary thyroid cancer patient group but does not predict recurrence after long-term follow-up after initial treatment with total thyroidectomy (TTE) and RRA.

HRQoL was preserved in DTC patients compared to a large age- and gender-standardized sample of the general Finnish population (*n* = 6001). After long-term follow-up, overall HRQoL is comparable with that of the general population. DTC patients demonstrate an age-related decline in HRQoL, similar to that seen in the population in general.

We conclude that post-ablative TG concentration is a strong predictor of disease recurrence in DTC. Although longer follow-up is needed, monitoring low-risk differentiated thyroid carcinoma patients with neck US and TG measured on L-T4 appears safe and effective.

4 INTRODUCTION

Primary thyroid carcinoma is not a single disease, but is a heterogenic group of conditions with a wide variation in behavior and prognosis; both the most indolent and most aggressive of malignant tumours are of thyroid origin. Among the generally treatable thyroid tumours are papillary and follicular carcinomas, designated "differentiated thyroid carcinoma", or DTC, together with medullary carcinoma. Papillary and follicular carcinomas account for the majority of thyroid carcinomas (85 - 95%) and are of follicular cell origin (Schlumberger 1998). These are well differentiated, treatable and often have little effect on the patients´ life expectancy.

Differentiated thyroid carcinomas are today generally being diagnosed at an earlier stage (Davies and Welch 2006, Kent et al. 2007), which has resulted in the need to adapt the treatment and follow-up strategies to a less aggressive disease. The diagnostic procedure is formed and characterized by the very widespread use of ultrasonography (US) and US-guided fine-needle aspiration biopsies (FNABs). Thyroidectomy remains the cornerstone of initial treatment of DTC, but the post-operative administration of radio-iodine ablative therapy is considered most beneficial for patients at a higher risk of thyroid cancer-related death (Cooper et al. 2006, Cooper et al. 2009, Sacks et al. 2010). Despite general treatability and early potential to be cured, even the most indolent thyroid cancers have the potential to recur as late as decades after primary therapy. Thus, the main goal for follow-up is to detect recurrent or persistent disease at the earliest stage possible, while simultaneously avoiding unnecessary tests for the patient and unnecessary costs for health care units. A number of prognostic scoring systems based on independent prognostic factors have been developed; however, most of these systems were validated using cancer-specific survival as the outcome (Cady and Rossi 1988, Hay et al. 1993). Since the majority of DTC patients are at a low-risk for cancer death, novel factors prognostic of disease recurrence are needed to guide the clinician today.

Due to the relative infrequency, indolence and long natural course of papillary and follicular DTC, most of the management strategies have been based on large retrospective studies and on consensus opinions of experts. At Helsinki University Central Hospital (HUCH), treatment and surveillance of low-risk DTC patients have already for two decades been carried out according to a uniform protocol much in the manner now discussed in and adapted by the international literature.

The aims of this work were to investigate retrospectively whether the treatment and especially the surveillance scheme in HUCH have succeeded in providing safe and efficient care for DTC patients. We analysed the long-term outcome of a large cohort of 495 DTC patients at low-risk of cancer-specific death, uniformly treated at one institution. The initial treatment consisting of near-total thyroidectomy and post-

operative radio-iodine ablation can be seen as active and in light of the current shift of treatment towards a more selective use of radio-iodine (RAI), as rather aggressive. The current work adds to the discussion of how to best balance benefits and harms in the use of RAI. With the increasing incidence and prevalence of DTC, the number of patients needing long-term follow-up is growing. Another important goal of this work has been to find novel prognostic factors for disease recurrence in low-risk DTC to guide surveillance in the future.

5 REVIEW OF THE LITERATURE

5.1 Histopathology of differentiated thyroid carcinoma

The normal thyroid gland weighs about 15–20 g and is macroscopically composed of two lobes connected by the isthmus. Each lobe can be regarded as an independent entity due to ipsilateral blood supply and lymph drainage. The basic cellular unit of the thyroid is the follicle, which is lined with epithelial cells (follicular cells) and filled with a colloid. Epithelial neoplasms arising from these follicular cells include benign follicular adenomas, malignant follicular carcinomas, papillary carcinomas and undifferentiated and anaplastic carcinomas. The calcitonin (CT) -producing parafollicular cells or C-cells account for only about 0.1% of all thyroid cells and are the origin of medullary carcinomas. The stroma between follicles is highly vascular.

5.1.1 Papillary thyroid carcinoma

Papillary thyroid carcinoma (PTC) is macroscopically a firm tumour that is unencapsulated or partly encapsulated (Hay 1990). PTC may be cystic or partly necrotic, and extension beyond the thyroid capsule is reported in about 8 - 30% of cases. PTC is also often multifocal in a single lobe and is bilateral in up to 60% of cases (Cooper et al. 2006). Characteristic microscopic findings are papillary structures lined with a single layer of epithelial cells. Pathognomic to PTC are psammoma bodies, calcified structures in the core of papillae. The nuclei of PTC cells are large and overlapping with irregular borders. This distinctive appearance of "ground glass nuclei" permits the diagnosis also from cytological material. PTCs invade the lymphatic vessels early in the course of the disease, and lymphatic metastases are found in 20 - 80% of cases at diagnosis, depending on the extent of lymph-node dissection and examination of surgical material. Vascular invasion is rare and distant metastases (in 5 - 10% of cases) are allegedly mostly the result of lymphatic spread. Lungs are the predominant site of distant metastasis in PTC, but involvement of bone, soft tissue, liver and occasionally the brain are also seen.

5.1.2 Variants of papillary thyroid carcinoma

The World Health Organization (WHO) defines *papillary thyroid microcarcinoma* (PTM) as PTC measuring up to 1.0 cm in diameter. The incidence of PTM in autopsy material ranges from 4% to 36% (Harach et al. 1985, Hay 1990). The *encapsulated*

variant of PTC is characterized by a tumour capsule but local invasion. Both of these variants carry a very good prognosis.

In *the follicular variant* of PTC, follicles are predominant over papillae but carry the same nuclear features as classical PTC. This variant is more frequently found in younger patients and was detected in 20% of the post-exposion childhood thyroid cancers after the Chernobyl nuclear accident (Furmanchuk et al. 1992).

Occurring at a younger age, *the diffuse sclerosing variant* constitutes 2% of papillary carcinomas. Diffuse involvement of one or both lobes occurs with sclerosis, patchy widespread lymphocytic infiltration and abundant psammoma bodies (Soares et al. 1989). Lymph node metastases are almost always present and lung metastases often occur.

The tall cell variant occurs mostly in elderly patients and is characterized by large size, vascular invasion and frequent metastasis. Microscopically, it presents with well-formed papillae covered with tall cells.

The columnar cell variant is rare and presents with intrathyroidal metastasis. *Papillary carcinoma with squamous cell or mucoepidermoid carcinoma* is a rare, combined form of PTC, usually with an aggressive clinical course.

5.1.3 Follicular thyroid carcinoma

Follicular thyroid carcinoma (FTC) is defined as a malignant epithelial tumour with follicular differentiation, but no diagnostic features of PTC. FTC is less frequent than PTC and usually presents as a solitary tumour. Microscopically, FTC may appear as well-formed follicles or solid growth. Capsular and/or vascular invasion confirms the malignant nature and is the basis for diagnosis. Confirmation with a needle biopsy specimen is impossible, and thus, a histological sample is always needed to diagnose FTC. FTC is usually divided into two categories with different prognosis according to the degree of invasiveness; minimally or widely invasive. FTC readily invades blood vessels and only rarely lymphatic vessels, and distant metastases are seen in lungs, bone and brain.

5.1.4 Variants of follicular thyroid carcinoma

Clear cell carcinoma is a rare variant of FTC, with clinical behaviour similar to classic FTC.

The oxyphilic variant of FTC (Hürthle cell) occurs mainly in elderly patients and presents with cells with oncocytic features. Macroscopically, it presents as a solitary

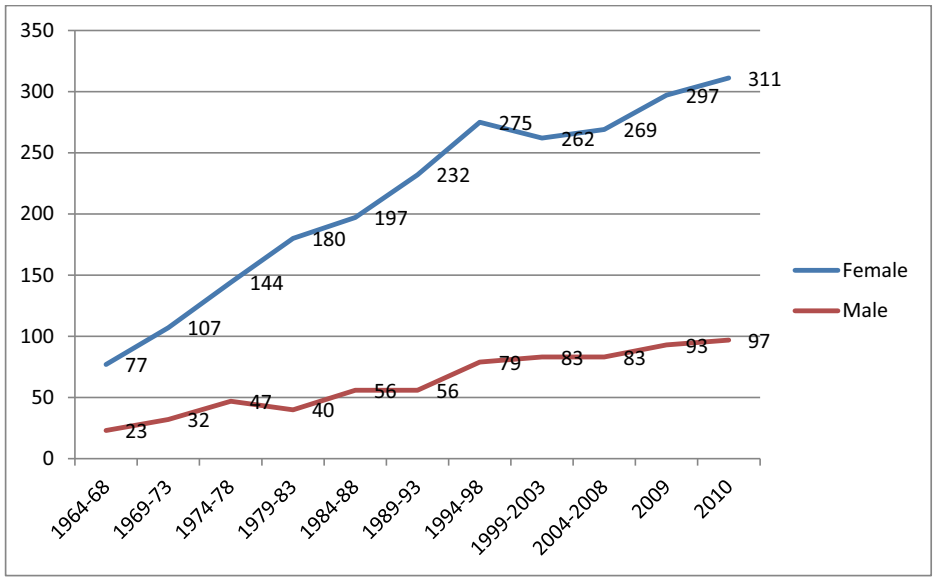
tumour with potential for extrathyroid extension and both lymph node and distant metastases.

Poorly differentiated FTC is an intermediate group of tumours between differentiated and anaplastic carcinomas with a characteristic histological picture of small cells and solid growth with patches of necrosis and vascular invasion.

5.2 Epidemiology

Although thyroid carcinoma only accounts for 1% of all malignancies, it is the most common endocrine tumour (Davies and Welch 2006). The annual incidence of thyroid cancer per million inhabitants differs widely between countries and ranges from 12 to 40 in men and from 20 to 50 in women. The lowest incidence rates have been reported in Denmark and the Netherlands and the highest in France, Japan and the USA. In USA, there has been a 2.4-fold increase in the incidence of thyroid cancer, from 3.6 per 100 000 in 1973 to 8.7 per 100 000 in 2002 (Davies and Welch 2006, Kent et al. 2007). The increasing incidence of all thyroid cancers in Finland between 1964 and 2010 is illustrated in Figure 1 (data from the Finnish Cancer Registry).

Figure 1.Incidence of thyroid cancer in Finland in 1964-2010



The increase has been attributed to the rising incidence of particularly small low-risk DTC (Davies and Welch 2006, Kent et al. 2007). In an analysis of 4817 patients treated for DTC in one institution between 1969 and 2004, there was a significant increase in small tumours (< 1 cm) diagnosed between 1969 to 1989 and 1990 to 2004 (7.9% vs. 28.7% of all, respectively, p<0.0001) (Elisei et al. 2010). A significant decrease in the prevalence of both nodal (34.2% vs. 22.4%) and distant metastasis (5.4% vs. 2%) was also observed (Elisei et al. 2010). A registry-based study of 7422 thyroid cancer cases revealed a significant increase in small non-palpable tumours between 1990 and 2001 (Kent et al. 2007).

However, also recently, an increased incidence of all sizes of thyroid tumours has been reported in the United States. In 1988–2005, a significant increase was also observed for tumours >4 cm among men and women (Chen et al. 2009). These data indicate that increased diagnostic scrutiny is not the only explanation for this increase, but environmental influence should also be considered.

Tumours most often occur in individuals aged 20-50 years. The mean age at diagnosis for papillary cancer is slightly lower than for follicular cancer (mid-40s to early 50s and 50s, respectively). In adults, the female-to-male ratio of clinically diagnosed papillary carcinoma is 4:1 to 3:1 (Kent et al. 2007, Elisei et al. 2010).

5.3 Aetiology and pathogenesis

The aetiology of DTC is largely unknown. A higher risk for differentiated thyroid carcinoma correlates with a number of genetic disorders. A 4- to 10-fold increased risk of thyroid cancer in first-degree relatives of patients with thyroid cancer suggests a genetic basis for these tumours (Malchoff and Malchoff 2002). A familial predisposition for PTC has been supported by epidemiological studies (Galanti et al. 1997, Hemminki and Dong 2000). Also, a parallel incidence has been described in monozygotic twins (Malchoff and Malchoff 2002). A number of familial syndromes with an increased risk for PTC are known, among them familial adenomatous polyposis and its subtype Gardner's syndrome, which are caused by inherited mutations of a tumour suppressor gene (Giardiello et al. 1993, Malchoff and Malchoff 2002). A correlation between papillary thyroid carcinoma and some types of human leukocyte antigen (HLA) has also been observed (Porto et al. 2006).

5.3.1 Ionizing radiation

Ionizing radiation is the only known external predisposing factor for thyroid cancer. External radiation to the neck increases the incidence of papillary carcinoma of the thyroid later in life, and irradiation during childhood has been associated with the greatest risk for acquiring papillary thyroid cancer (Ron et al. 1995).

Recently, data have become available from studies of over 4000 people who developed thyroid cancer after the Chernobyl nuclear accident in 1986 (Nikiforov 2006). They have revealed that radiation exposure during childhood carries an increased risk of thyroid cancer and that the risk is radiation dose-dependent. As many as 9% of children with radiation exposure have developed thyroid cancer over a period of 20 years (Retetoff et al. 1975, Nikiforov 2006). The youngest children (<15 years) are most sensitive to radiation-induced carcinogenesis, and the minimal latent period for thyroid cancer development after exposure is as short as 4 years (Nikiforov 2006). The vast majority of these cancers are papillary carcinomas. On the molecular level, chromosomal rearrangements (such as *RET/PTC*) are more common than point mutations of BRAF and other genes. Radiation exposure only increases the risk of developing thyroid cancer; it does not affect the prognosis or the aggressiveness of the tumour (Nikiforov 2006). However, treatment with radio-active iodine has not been shown to increase the incidence of thyroid cancers.

5.3.2 Iodine intake and thyroid cancer

Iodine intake does not seem to influence the incidence of thyroid cancer, but may have an effect on the histological type of cancer; in areas of low dietary iodine, follicular carcinomas are relatively more common (Feldt-Rasmussen 2001).

5.3.3 Genetic alterations

Activation of receptor tyrosine kinases (*RET/PTC*, TRK, MET), by rearrangement or gene amplification, appears to be specific for the transformation of thyroid follicular cells into papillary thyroid carcinomas (Adeniran 2006). These rearrangements produce chimeric proteins with tyrosine kinase activities that contribute to the development of the malignant phenotype. Approximately 40% of adults with sporadic papillary carcinoma have *RET* gene rearrangement, and about 15% have *NTRK1* rearrangement (Adeniran 2006). RET/PTC oncoproteins are believed to take part in several mechanisms that allow tumour growth and spread, including angiogenesis, invasion, metastasis and immune escape. The prevalence of *RET/PTC* in PTCs varies significantly in different studies and geographic regions (Menicali et al. 2012). Clonal RET/PTC rearrangements are found in 10–20% of adult sporadic papillary carcinomas. RET/PTC rearrangements occur with higher incidence in patients with a history of radiation exposure (50–80%) (Nikiforov 2011). Several studies have tried to associate the presence of a rearranged *RET* with clinical parameters, yielding controversial results. Some studies have indicated an association between *RET/PTC* and a poor prognosis. Conversely, others have found an association with a good prognosis (Nikiforov 2011).

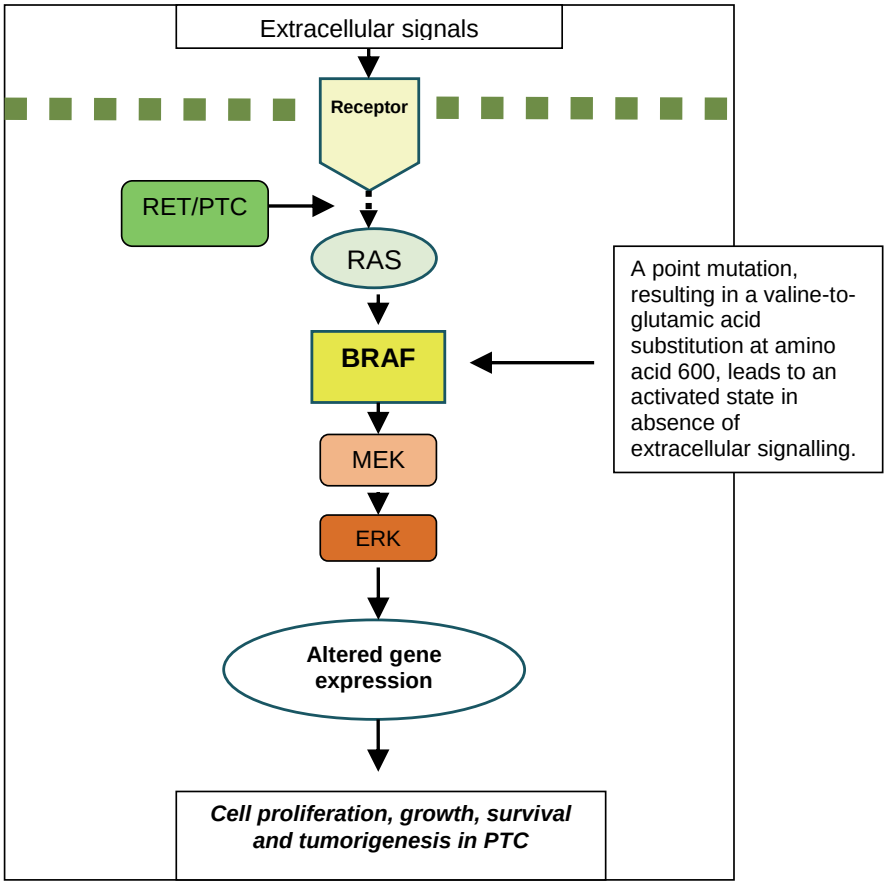
Follicular carcinomas commonly demonstrate RAS mutations (Nikiforova et al. 2003a, Nikiforov 2011). Additional mutations known to occur in poorly differentiated and anaplastic carcinomas involve the TP53 and CTNNB1 genes (Nikiforov 2011).

5.3.4 *Mutations of BRAF kinase*

In recent years, knowledge and understanding of the molecular mechanisms of WDTC have increased, and point mutations in the gene coding the protein kinase BRAF have been identified as a common genetic event in well-differentiated PTC (Cohen at al 2003, Kimura et al. 2003, Nikiforova et al. 2003b). Among the various histological subtypes of PTC, BRAF V600E mutation is commonly found in the conventional and also tall-cell variants.

BRAF is a member of the RAF kinase family that promotes signaling through the RAS-RAF-MAPK signal transduction cascade. A simplified schematic illustration of the MAPK pathway is given in Figure 2.

Figure2. RAS-RAF-MAPK signaling cascade with BRAF V600E mutation



An activating mutation located on exon 15 of the B isoform of the *RAF* kinase gene results in a valine-to-glutamic acid substitution at amino acid 600 (BRAF V600E). This mutation leads to destabilization of the kinase; it promotes a constitutively activated state, enhances BRAF kinase activity towards the MAPK kinase and promotes tumorigenesis through the MAPK pathway (Davies at al 2002). A higher expression of vascular endothelial growth factor in tumours harbouring the BRAF V600E mutation has been suggested (Jo et al. 2006), while other studies have reported down-regulation of VEGF-A and VEGF receptor (Durante et al. 2011).

In recent years, the BRAF mutation has strongly emerged as a molecular marker with potential utility in risk stratification for PTC patients (Xing 2007). Since its initial description (Cohen et al. 2003, Kimura et al. 2003, Nikiforova et al. 2003b), the BRAF V600E mutation has been widely found in PTCs, with a highly variable prevalence ranging from 29% to 83% in different publications (Xing 2005a, Fugazzola et al. 2006), and with a mean prevalence of 44% (Xing 2007).

5.4 Diagnosis

DTC usually presents itself as a solid, slowly growing non-tender nodule, often discovered by chance at a routine clinical examination. Thyroid nodules are relatively common, but only approximately 5% are cancers. The cornerstones of diagnostic work-up are neck ultrasonography (US) and sonographically guided needle biopsy. Fine-needle aspiration biopsy (FNAB) is indicated if the nodule is >1 cm or if there is clinical or ultrasonographic suspicion of malignancy (Pacini et al. 2010).

FNAB has an essential role in evaluating nodules detected in US. Papillary carcinomas have a distinct cellular appearance and can be diagnosed by a cytological sample obtained with fine-needle biopsy. In contrast, the malignancy of follicular neoplasm is defined by capsular invasion and cannot be diagnosed by cytological specimens; a histological specimen is always warranted. Pathological diagnostics of thyroid neoplasm require considerable expertise. The use of fine-needle aspiration cytology increases the diagnostic accuracy of thyroid malignancy cases (Table 1, Cibas and Ali 2009). Before the routine use of thyroid FNA, the proportion of surgically resected thyroid nodules that were malignant was 14%. With current thyroid FNA practices, the proportion of resected nodules that are malignant surpasses 50% (Cibas and Ali, 2009). A uniform system, the Bethesda system with diagnostic categories for reporting thyroid cytopathology, was developed in a process hosted by the National Cancer Institute (NCI) (Cibas and Ali 2009, Table 2).

Table 1. Risk of malignancy in thyroid fine-needle aspiration cytopathology (FNAC) (Bethesda system, Cibas and Ali 2009)

Diagnostic Category	Risk of Malignancy (%)
Non-diagnostic or unsatisfactory	1 – 4
Benign	0 -3
Atypia of undetermined significance *or* Follicular lesion of undetermined significance	5 -15
Follicular neoplasm *or* Suspicious for a follicular neoplasm	15 - 30
Suspicious for Malignancy	60 - 75
Malignant	97 - 99

Table 2. The Bethesda system for reporting thyroid fine-needle aspiration cytopathology

I. Non-diagnostic or unsatisfactory
Cyst fluid only
Virtually acellular specimen
Other (obscuring blood, clotting artifact, etc.)
II. Benign
Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis
Other
III. Atypia of undetermined significance or follicular lesion of undetermined significance
IV. Follicular neoplasm or suspicious for a follicular neoplasm
Specify if Hürthle cell (oncocytic) type
V. Suspicious for malignancy
Suspicious for papillary carcinoma
Suspicious for medullary carcinoma
Suspicious for metastatic carcinoma
Suspicious for lymphoma
Other
VI. Malignant
Papillary thyroid carcinoma
Poorly differentiated carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous cell carcinoma
Carcinoma with mixed features (specify)
Metastatic carcinoma
Non-Hodgkin lymphoma
Other

CT, MRI, and ^{123}I-scans performed for various indications occasionally reveal thyroid nodules, requiring a follow-up ultrasound and FNAB. Similarly, ^{18}F-fluorodeoxyglucose (FDG) avid nodules incidentally found on PET scans are occurring with increasing frequency and may require similar clarification. In addition to data in the literature demonstrating accurate detection of thyroid cancer by PET, one study proposed that PET may play a role in the management of patients with inconclusive cytologic diagnosis of a thyroid nodule (de Geus-Oei 2006). In this study, use of PET reduced the number of negative hemithyroidectomies by 66% (de Geus-Oei 2006).

Laboratory tests are generally not useful in diagnostic work-up of DTC.

5.5 Prognostic factors and classifications

Main prognostic factors include tumour size, patient's age, extrathyroidal spread and histological variant. The presence of vascular invasion, even within the thyroid gland, is associated with a more aggressive disease at diagnosis and has a higher incidence of tumour recurrence (Nishida et al. 2002). Age is recognized to be the most important prognostic factor: age rather than extent of the disease determines the stage in the TNM staging system (Cancer Staging Manual, 6th edition, 2002.). Multifocality is relatively common, especially in PTC, and has been demonstrated to correlate with poor prognosis in some studies (Mazzaferri and Jhiang, 1994). Genetic alterations, especially BRAF mutations, have emerged as potentially useful prognostic markers. As discussed earlier, many studies have demonstrated significant associations between BRAF mutation and high-risk clinicopathological characteristics of PTCs (Xing et al. 2005, Xing 2007, Knauf et al. 2009), while some researchers have reported that the BRAF mutation has no relationship to poor prognosis (Kim et al. 2005b, Liu et al. 2005, Fugazzola et al. 2006, Ito et al. 2009).

Many staging systems have been developed to predict the prognosis of the DTC patient. These systems quantify various characteristics of the tumour and the patient at the time of diagnosis. Most prognostic classification systems are created and validated using cancer-specific death as the outcome.

The most commonly used staging method is the combined American Joint Committee on Cancer (AJCC) and International Union against Cancer (UICC) TNM classification. The Mayo Clinic has described a prognostic scoring system for papillary tumours based on the presence of distant metastasis, patient's age, completeness of resection, tumour invasion and size (MACIS) (Hay et al. 1993). Cady and Rossi (1988) described a completely clinical classification based on age of patient, presence of distant metastases and the extent and size of the tumour (AMES). Pasieka et al. (1992) modified AMES risk-group classification to include DNA ploidy (DAMES). In most staging methods, age is a major factor determining prognosis. The TNM and MACIS staging methods, primarily predicting the risk for cancer death, are further described below.

TNM. Tumour, node and metastasis (TNM) for papillary carcinoma of the thyroid are classified as follows:

Primary tumour (T)

- TX: Primary tumour cannot be assessed.
- T0: No evidence of primary tumour is found.
- T1: Tumour size is 2 cm or less in the greatest dimension and is limited to the thyroid.
- T2: Tumour size is greater than 2 cm but less than 4 cm and tumour is limited to the thyroid.

- T3: Tumour size is greater than 4 cm, and tumour is limited to the thyroid or any tumour with minimal extrathyroidal extension (extension to sternothyroid muscle of perithyroid soft tissues).
- T4a: Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.
- T4b: Tumour invades prevertebral fascia or mediastinal vessels or encases the carotid artery.

Regional lymph nodes (N)

- NX: Regional nodes cannot be assessed.
- N0: No regional node metastasis is found.
- N1a: Metastasis is found in level VI (pretracheal and paratracheal, including prelaryngeal and Delphian) lymph nodes.
- N1b: Metastasis is found in unilateral, bilateral or contralateral cervical or upper/superior mediastinal lymph nodes.

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed.
- M0: No distant metastasis is found.
- M1: Distant metastasis is present.

Table 3. TNM stages of thyroid carcinoma

	Age under 45 years	*Age 45 years or older*
Stage I	Any T, Any N, M0	T1, N0, M0
Stage II	Any T, Any N, M1	T2, N0, M0
Stage III		T3, N0, M0, T1, T2, T3, N1a, M0
Stage IVa		T1, T2, T3, N1b, M0, T4a, N0, N1, M0
Stage IVb		T4b, any N, M0
Stage IVc		Any T, any N, M1

MACIS: MACIS scoring system for papillary tumours was developed at the Mayo Clinic from a cohort of 1779 PTC patients (Hay et al. 1993). The analysis included five variables: distant Metastasis, Age, Completeness of surgery, Invasion/Infiltration of extra-thyroid tissue and Size of tumour. The MACIS score is calculated as follows: 3.1 (if age < 40) or 0.08 x age (if ≥ 40) + 0.3 x tumour size in cm + 1 (if incompletely resected) + 1 (if locally invasive) + 3 (if distant metastases present). A MACIS score below 6 indicates a 20-year cause-specific survival of 99% (Hay et al. 1993).

In addition to established prognostic factors (age, tumour histology, tumour diameter and metastasis), BRAF V600E mutation has strongly emerged as a molecular marker with potential utility in risk stratification for PTC patients (Xing

2007). Since its initial description (Cohen et al. 2003, Kimura et al. 2003, Nikiforova et al. 2003), BRAF V600E has been widely found in PTCs, with a mean prevalence of 44% (Xing 2007). Although some researchers have reported that the BRAF mutation has no relationship to poor prognosis (Kim et al. 2005b, Fugazzola et al. 2006, Ito et al. 2009), many studies have demonstrated significant associations between BRAF mutation and high-risk clinicopathological characteristics of PTCs in overall analyses of tumours of all sizes (Xing et al. 2005, Xing 2007, Knauf et al. 2009). Some reports have even found a significant association of BRAF mutation in preoperative FNAB specimens with poorer clinicopathological outcomes of PTC (Xing et al. 2009). Studies on immunohistochemical markers have not shown prognostic capacity (Siironen et al. 2005).

Classification into high- and low-risk categories can aid in the determination of appropriate primary therapy. The need for prognostic factors to classify patients with papillary carcinoma into high- or low-risk categories for mortality and, importantly, recurrence is ongoing, and much of current clinical research on papillary thyroid carcinoma focuses on this. Headway is being made in the identification of genetic markers in tumour cells that indicate prognosis in general, as well as the tendency of the cancer to metastasize. Gene expression patterns have been found that can differentiate between benign thyroid tissue and papillary thyroid carcinomas, and between papillary and follicular carcinomas (Lubitz at al 2006).

The prognostic factors and classifications proposed for disease recurrence are discussed later (section 5.8.1).

5.6 Primary treatment

5.6.1 Surgery

Thyroidectomy remains the standard treatment for DTC. The extent of surgery in primary therapy is a balance between minimizing complications and improving prognosis. Total thyroidectomy is recommended if the primary tumour is 1.0 cm or greater, or if extrathyroid extension or metastasis is present (Cooper et al. 2006, Pacini et al. 2010). In this surgical procedure, all thyroid tissue is removed so that postoperative iodine-131 can be effectively used to eliminate the risk of leaving occult disease in the thyroid, and allow serum thyroglobulin levels to be more sensitive in detecting recurrent or persistent disease. A near-total thyroidectomy can be performed to decrease the risk of damage to the recurrent laryngeal nerve or parathyroid glands. Some thyroid tissue is left during the resection and subsequently can be ablated with iodine-131. Although the risk of surgical complication is higher than that of hemithyroidectomy or near-total thyroidectomy, most experts agree

that the risk of recurrent disease is lower and the survival rate is higher after total thyroidectomy (Hay et al. 2002, Bilimoria et al. 2007).

It has been much debated whether hemithyroidectomy is the most appropriate treatment for small (<1 cm) low-risk papillary carcinoma that is macroscopically localized in one lobe or for patients with occult papillary thyroid cancers (Haigh et al. 2005, Bilimoria et al. 2007, Ogilvie et al. 2010). Less extensive surgery may be justified in case of a small (<1 cm) DTC diagnosed after surgery for a benign condition (Pacini et al. 2010). According to the revised American Thyroid Association guidelines, for patients with thyroid cancer >1 cm, the initial surgical procedure should be a near-total or total thyroidectomy unless there are contraindications to this surgery (Cooper et al. 2009). Thyroid lobectomy alone may be sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical nodal metastases (Cooper et al. 2009). Lobectomy may also sometimes be a good choice for patients who may not be compliant with thyroid hormone replacement postoperatively. However, a significant increase in recurrences locally or in the contralateral lobe has been observed in patients who have had only a lobectomy (Bilimoria et al. 2007).

An even more conservative approach of non-surgical observation has been suggested for the most benign, incidentally detected papillary thyroid microcarcinomas (Sugitani et al. 2010). This includes follow-up with neck US and lobectomy and a more radical surgical approach in case of observed growth.

Cervical lymph node involvement is common in papillary thyroid carcinoma, with positive adenopathy or micrometastatic lymphatic deposits in approximately 35% (25 – 60 %) of cases. However, long-term survival has been the norm even in the setting of extensive neck disease (Mazzaferri and Jhiang 1994).

Prophylactic central neck dissection (PCND) is defined as the removal of seemingly normal lymph nodes during the initial operation. The rationale for PCND rather than a selective approach is that ability with preoperative US or with intra-operative assessment to adequately evaluate the central neck compartment has been questioned. A comprehensive review and meta-analysis on the subject are pending.

Elective neck dissection rates vary in different centres. Performing elective central node dissection in the setting of larger (>1 cm) and multifocal papillary thyroid carcinomas may have advantages. These have been suggested to be the following (Guerrero and Clark 2011):

- Provides more accurate tumour staging
- Decreases rate of local recurrence
- Reduces likelihood of a more challenging reoperation carrying a higher risk of complications

- Reduces local tumour load, which may increase radio-active iodine uptake in distant metastatic foci, if present
- Renders more patients athyroglobulinemic, again by reducing local tumour load, allowing better surveillance.

Treatment with total or near-total thyroidectomy results in a higher surgical complication rate, while more conservative measures result in a higher rate of postoperative cancer recurrence. The most common significant complications of thyroid surgery are permanent recurrent laryngeal nerve palsy and permanent hypoparathyroidism. In experienced centers, they occur in 1–2% of the procedures (Pacini et al. 2010).

5.6.2 *Postoperative radio-iodine ablation*

Thyroid tissue has the ability to accumulate iodine from the bloodstream via an active, energy-dependent transport process, the sodium/iodide symporter (NIS). Accumulation is 20- to 40–fold in the thyroid gland, beginning rapidly after iodine ingestion. The radiation dose delivered to the thyroid gland is 1000- to 10000–fold that of surrounding tissues. This is the basis for using radio-active iodine (RAI) in the treatment of DTC. RAI is produced in nuclear reactors by neutron irradiation of tellurium or as a product during fissioning of uranium. At ingestion and uptake to thyroid tissue, physically unstable radio-active ^{131}I reverts to a stable state by ejecting beta particles. This beta radiation has a capacity to penetrate only up to 2 mm into the surrounding tissue. Beta particles account for about 90% of the radiation delivered by RAI, the rest is gamma radiation which leaves the patient mainly via the skin surface. Beta radiation is responsible for the treatment effects of radio-iodine, whereas gamma radiation allows for scanning the effects. The outcome of radio-iodine therapy is dependent on the uptake and retention of iodine by thyroid tissue. ^{131}I ablation allows the eradication of thyroid remnants and improves the diagnostic value of serum TG determination both on and off L-T4 treatment for surveillance (Toubeau et al. 2004, Kim et al. 2005a).

Despite the widespread use of RAI, data on effectiveness are controversial. Cohort studies have shown improved survival and reduced tumour recurrence when iodine-avid, advanced-stage, well-differentiated thyroid cancer is treated with radio-active iodine (DeGroot et al. 1994, Mazzaferri 1997). RAI has also been shown to reduce disease-specific mortality in high risk DTC in several studies (Mazzaferri and Kloos 2001, Sacks 2010). For low-risk DTC, the data are less clear.

A recent meta-analysis concluded that substantial evidence suggests that RAI is not associated with improved survival in low-risk or low-stage DTC (Sacks et al. 2010). This review of 79 published studies on RRA concluded that the majority of studies did not find a statistically significant improvement in mortality or disease-specific survival in low-risk patients treated with RAI (Sacks et al. 2010). Evidence regarding

recurrences was mixed, with half of the studies showing a significant relationship and half showing no relationship (Sacks et al. 2010). In another large retrospective analysis of 1298 low-risk DTC patients with a median follow-up of 10.3 years RRA, was not associated with improved overall survival or disease-free survival (Schvartz et al. 2012).

According to the American Thyroid Association recommendations, radio-iodine remnant ablation (RRA) after total thyroidectomy for DTC is indicated in patients with moderate to high risk of recurrent or persistent disease, based on age, tumour size, extrathyroidal extension, lymph node status and histology (Cooper et al. 2009). In contrast, for low-risk patients the use of RAI remains controversial and the benefit for survival or recurrence-free survival is more uncertain (Sawka et al. 2004, Sawka et al. 2008) and thus a more selective use is encouraged (Cooper et al. 2009). RRA is not indicated in patients with very low-risk tumours (Table 4, Pacini et al. 2010). The recommendations and the evidence are summarized in Table 5.

Table 4. Risk stratification for DTC patients according to the European Consensus Report (Pacini et al. 2010)

Very low-risk	Low-risk	High risk
Intrathyroidal tumour T1 ≤ 1 cm	Intrathyroidal tumour T1 > 1 cm and T2	Intrathyroidal tumour T3
No aggressive histology	Aggressive histology	Microscopic or macroscopic invasion (T3-T4)
No local or distant metastasis	No local or distant metastasis	Locoregional metastasis Distant metastasis
Complete surgery	Less than total thyroidectomy	Incomplete resection

Table 5. Major factors impacting decision-making in radio-iodine remnant ablation (adapted and modified from Cooper et al. 2009)

		Expected benefit according to current evidence		
Factor	**Description**	**Decreased risk of death**	**Decreased risk of recurrence**	**RAI ablation usually recommended**
T1	1 cm or less, intrathyroidal or microscopic multifocal	No	No	No
	1–2 cm, intrathyroidal	No	Conflicting data	Selective use
T2	>2–4 cm, intrathyroidal	No	Conflicting data	Selective use
T3	>4 cm	No		
	<45 years old	No	Conflicting data	Yes
	≥45 years old	Yes	Yes	Yes
	Any size, any age, minimal extrathyroidal extension	No	Inadequate data	Selective use
T4	Any size with gross extrathyroidal extension	Yes	Yes	Yes
N1	<45 years old	No	Conflicting data	Selective use
	≥45 years old	Conflicting data	Conflicting data	Selective use
M1	Distant metastasis present	Yes	Yes	Yes

The optimal administered activity of RAI to ablate the thyroid remnant remains controversial. The administered activities have varied widely between centres and have been determined either empirically or with dosimeter tools.

Prospective randomized studies comparing different activities of RAI (1.1 GBq vs. 3.7 GBq, e.g. 30 vs. 100 mCi) have been published in recent years (Mäenpää et al. 2006, Mallick et al. 2012, Schlumberger et al. 2012). In these studies, successful ablation rates were comparable between the groups, with better tolerability and shorter need for radiation protection in the 1.1 GBq group (Mäenpää et al. 2006). Two studies additionally compared preparation for ablation with rhTSH with thyroid hormone

withdrawal and found the ablation rate equivalent between the two methods (Mallick et al. 2012, Schlumberger et al. 2012).

The side-effects of RAI therapy may occur in many areas and organ systems. Acute and mostly transient adverse effects have included hypothyroidism-induced decreased quality of life before radio-active iodine treatment and local effects upon administration. Recent studies have demonstrated that use of rhTSH is highly effective and safe and that the rate of successful ablation is similar to that obtained with L-T4 withdrawal (Pacini et al. 2006a, Pilli et al. 2007). ^{131}I radio-active iodine is also associated with long-term dose-dependent adverse systemic and local effects, such as those on the salivary glands and nasolacrimal ducts, resulting in xerostomia and dental problems. In a series of 160 DTC patients comparing low vs. high activity of ^{131}I, Mäenpää et al. found that all acute adverse effects were mild (grade 1 or 2) except for nausea, which was severe in four patients(6%) in the low activity and in seven patients (10%) in the high activity group. All adverse effects also decreased in the three-month follow-up.

Radio-active iodine may also have serious long-term health risks. NIS gene is expressed in tissues besides the thyroid gland, which appears to result in an increased risk of second primary malignancies after radio-iodine treatment, as shown in recent studies (Rubino et al. 2003, Sandeep et al. 2006). In a European pooled cohort, a relationship was found between ^{131}I administration and occurrence of bone and soft tissue, colorectal and salivary gland cancers (Rubino et al. 2003). The association was seen even in low-risk patients, the greatest risk being for leukaemia (2.5-fold increase). Results are controversial regarding breast cancer, stomach cancer or other solid tumours. Some authors have demonstrated that patients with DTC have an overall increased standardized incidence rate for second primary tumours, but not for second primary tumours following ^{131}I therapy (Verkooijen et al. 2006). These findings suggest a common mechanism for these cancers, aetiologic and/or genetic, instead of a causal relationship with RAI.

In a pooled cohort analysis, an increasing risk for both solid tumours and leukaemias was seen with increasing cumulative dose of ^{131}I; an excess of 4% per GBq was calculated (Rubino et al. 2003). Use of external radiotherapy did not influence the relationship; i.e. the excessive risk remained the same (Rubino et al. 2003).

Infertility and gonadal failure have also been studied in correlation with ^{131}I therapy. After RRA, transient amenorrhea in women and azoospermia in men have been observed. With multiple treatments, the effects in male reproductive organs may be permanent (Pacini et al. 1995).

5.6.3 Thyroxine therapy

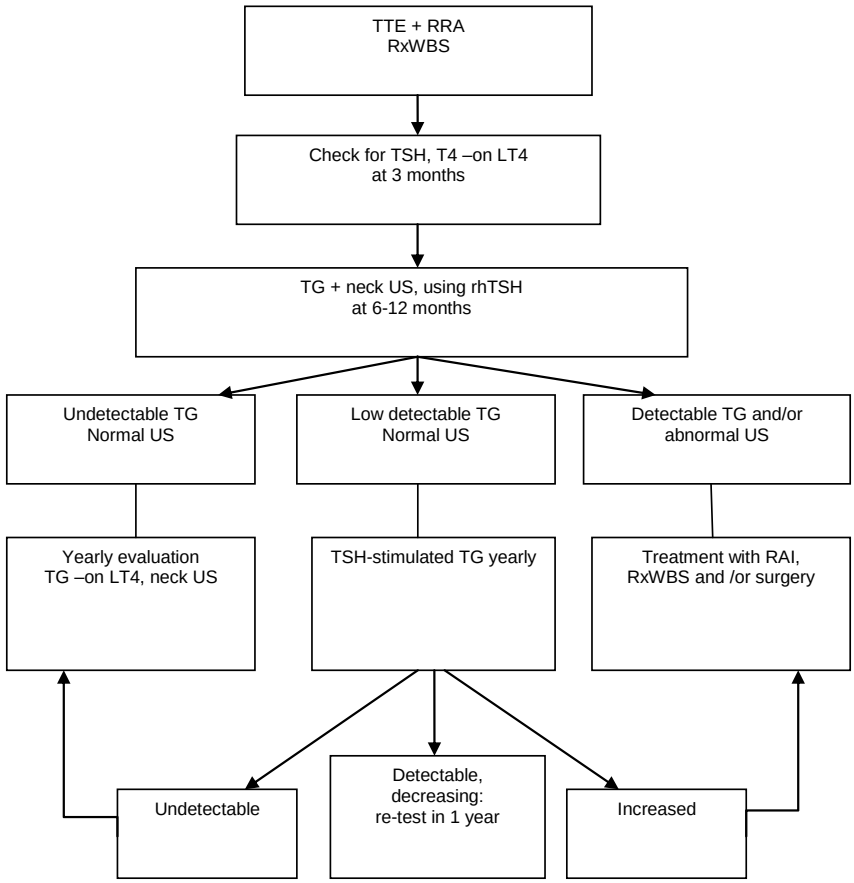
After thyroidectomy, the need for thyroid hormone substitution is permanent. Thyroid-stimulating hormone (TSH) suppression therapy by administration of thyroxine has been used for many years. The correlation between TSH suppression and disease outcome remains somewhat controversial. In postoperative patients with low-risk papillary thyroid carcinoma, the recurrence rate and survival rate among TSH-suppressed and TSH-nonsuppressed individuals seem to be similar (Sugitani and Fujimoto 2010). Nevertheless, some studies have indicated that non-suppressed TSH is related to an increased risk of DTC recurrence independent of tumour type and TNM stage (Böhm et al. 1999). In advanced disease, however, TSH suppression has been shown to correlate with better disease outcome; in a study of 157 patients, DTC-specific survival was significantly better in patients with a median TSH level ≤0.1 mU/l (median survival 15.8 years) than in those with a non-suppressed TSH level (median survival 7.1 years) (Diessl et al. 2012).

Suppressive thyroxine therapy has also been correlated with a number of side-effects, though the evidence is inconsistent. A decreased bone mineral density, diastolic heart failure, cardiac arrhythmias, primarily atrial fibrillation and increased risk of thrombosis are among the possible side-effects (Toivonen et al. 1998, Horne et al. 2004, Heijckman et al. 2005, Smit et al. 2005). Most centres do not administer thyroid hormone to suppress TSH in patients with low-risk papillary thyroid carcinoma and recent guidelines also advise total suppression of TSH only in the high-risk patient group (Cooper et al. 2006, Cooper at al 2009, Pacini et al. 2006, Pacini et al. 2010).

5.7 Follow-up

The European guidelines for the management and follow-up of low-risk DTC patients were updated and published recently (Schlumberger et al. 2004, Pacini et al. 2006, Pacini et al. 2010). Their cornerstones are total thyroidectomy, ^{131}I ablation, post-therapy whole-body scan (WBS), and neck ultrasonography (US) and (rhTSH-stimulated) TG measurements without diagnostic WBS (DxWBS) 6-12 months after primary treatment (Figure 3). If TG is undetectable and neck US normal, indicating disease-free status, the patient will be followed only with TG measurement on L-T4 and neck US (Schlumberger 2005, Pacini et al. 2006, Pacini et al. 2010). The consensus report by American and European authors contains basically the same elements, but neck US is recommended only for those with rhTSH-stimulated TG above 2 µg/L (Pacini et al. 2002, Pacini et al. 2006, Cooper et al. 2009).

Figure 3. Proposed flow chart for the follow-up after initial treatment (adapted and modified from Pacini et al. 2006)



The European Society of Medical Oncology (ESMO) guidelines for DTC recommend basal and stimulated TG measurement 6-12 months after initial therapy together with neck US and with or without WBS to confirm remission (Pacini et al. 2010). If the patient is disease-free at this point, he/she is categorized as low-risk and followed up with TG measurements on thyroxin and neck US yearly (Pacini et al. 2010).

5.7.1 Serum thyroglobulin measurements

Thyroglobulin (TG) is produced only by thyroid follicular cells and serves as the prohormone for thyroid hormone production. Serum TG levels reflect three factors: the mass of thyroid tissue, the level of TSH stimulation and any damage or inflammation of thyroid tissue. Following total thyroid ablation, TG should be undetectable in serum and any detectable level then indicates the persistence or

recurrence of neoplastic disease. This is the basis for the use of TG as a postoperative tumour marker in the follow-up of thyroid cancer patients. After surgery and RRA, serum TG measurement is sensitive and specific; the mainstay for the follow-up of DTC patients (Schlumberger and Baudin 1998, Robbins et al. 2002, Faterni and LoPresti 2003, Kloos and Mazzaferri 2005, Mazzaferri et al. 2003). The significance of thyroglobulin levels may be lost in patients with circulating thyroglobulin antibodies.

Ongoing debate exists as to whether after primary evaluation of response, serum TG measurements should be performed on or off L-T4 or after the stimulation by rhTSH or thyroxine withdrawal (Rosario et al. 2005, Pacini et al. 2010). Recently, a large prospective study evaluating the prospective capacity of TG demonstrated that stimulated TG determination presented only a slightly higher sensitivity than TG determination on L-T4 (Brassard et al. 2011). The ESMO clinical guideline suggests no stimulated TG measurements for the very low-risk group and every 12 months for intermediate-, and high-risk groups (Pacini et al. 2010).

Thyroglobulin is today being measured by sensitive immunoassays. The availability of these second-generation assays has resulted in revision of the guidelines (Cooper et al. 2009) with regard to TSH stimulation. The need for stimulation may be reduced in low-risk patients with initial negative TG after primary therapy (Cooper et al. 2009). At the same time, with very sensitive assays, the risk for minimally measurable concentrations resulting in unnecessary procedures (radiology or radioisotope) is recognized.

5.7.2 *Diagnostic whole-body scan in follow-up*

In the past, routine DxWBS together with serum TG measurements was considered the main tool for detecting persistent or recurrent disease (Schlumberger 1998, Mazzaferri and Kloos 2002). In the past ten years, the sensitivity of DxWBS for this purpose has been questioned and demonstrated to be low (Cailleux et al. 2000, Pacini et al. 2002, Mazzaferri and Kloos 2002). Many studies have shown that DxWBS does not add much to the information gained from serum TG measurements on existing recurrence, especially when stimulation by rhTSH is used (Pacini et al. 2002, Mazzaferri and Kloos 2002, Baudin et al. 2003). Today, DxWBS is increasingly aimed only at ascertaining the completeness of primary RRA. For TG–positive and WBS–negative patients, FDG-PET is increasingly utilized (Salvatore et al. 2008, Ma et al. 2010).

5.7.3 *Neck ultrasonography*

Traditional techniques, DxWBS foremost, for surveillance of DTC have in the past ten years been found to be less sensitive than ultrasonography (US) in the detection of

neck recurrences. In the low-risk patient cohort, neck recurrences are most common. Neck US detects recurrences in patients with undetectable serum TG levels and negative WBS; neck US in combination with TG has been demonstrated to be an effective and sensitive surveillance method to detect recurrences (Frasoldati et al. 2002, Pacini et al. 2003, Torlontano et al. 2004). Most guidelines now agree that neck US should be performed as the first-line investigation in the follow-up of all DTC patients (Schlumberger et al. 2004, Pacini et al. 2006). Neck US should always be performed by experienced radiologists or clinicians.

Fine-needle aspiration biopsy (FNAB) has an essential role in evaluating nodules detected in US. Before the routine use of thyroid FNA, the proportion of surgically resected thyroid nodules that were malignant was 14%. With current thyroid FNA practices, the proportion of resected nodules that are malignant surpasses 50% (Cibas and Ali 2009).

5.7.4 Recombinant human thyrotropin

A relatively new discovery for postoperative DTC patients is the administration of recombinant form of human thyrotropin or TSH (rhTSH) without causing symptoms of hypothyroidism. rhTSH is a heterodimeric glycoprotein produced by recombinant DNA technology; it has comparable biochemical properties to pituitary TSH.

Today, rhTSH has been shown to effectively replace thyroid hormone withdrawal in thyroid remnant ablation and in the follow-up of thyroid cancer patients (Haugen et al. 1999, Robbins and Robbins 2003, Pacini et al. 2006a, Duntas et al. 2008). Patients may now be given rhTSH to prepare them for whole-body scanning or ablation (Figure 4) and to entirely avoid the 4– to 6–week ordeal of levothyroxine withdrawal, hypothyroidism-linked health problems and impaired quality of life (Schlumberger et al. 2002, Luster et al. 2005a). Pharmacoeconomic considerations are also important. The use of rhTSH carries potential economic savings from preserving the ability to work, which in many cases offsets the direct costs (Luster et al. 2005b).

Figure 4. Schematic example of rhTSH administration

Ablation schedule				
Day 1	Day 2	Day 3	RxWBS 5 to 7 days after administration of ^{131}I	
First rhTSH injection	Second rhTSH injection	Radio-iodine dose		
Diagnostic testing schedule				
Day 1	Day 2	Day 3		Day 5
First rhTSH injection	Second rhTSH injection	Radio-iodine dose		Measurement of serum TG +/- DxWBS

5.8 Outcome and recurrences

In general, the prognosis for differentiated carcinoma of the thyroid is excellent. Long-term survival rates of approximately 90% are usually given. However, up to 30–40% of patients develop tumour recurrence (Mazzaferri and Jhiang 1994). Two-thirds of recurrences occur within the first decade after therapy. Tumours recur outside the neck in about 21% of cases. The most common site for distant metastasis is the lung. Mortality rates are lower when recurrences are detected early based on radio-iodine scans rather than clinical signs.

In a recently published large population-based study of over 50 000 patients, the recurrence rates were 5.7% at 5 years and 9.4% at 10 years (Bilimoria et al. 2007). Both recurrence and survival were associated with tumour size; 10-year survival rates declined with increasing tumour size (Bilimoria et al. 2007).

5.8.1 Prognostic factors and risk group classification for disease recurrence

According to the American Thyroid Association, to assess the risk of recurrence, a three-level stratification to low-risk, intermediate-risk and high-risk patients can be used (Cooper et al. 2009):

Low-risk patients have the following characteristics:

- no local or distant metastases
- all macroscopic tumour has been resected
- no tumour invasion of locoregional tissues or structures

- the tumour does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion
- and, if ^{131}I is given, there is no ^{131}I uptake outside the thyroid bed on the first post-treatment whole-body RAI scan (RxWBS)

Intermediate-risk patients have any of the following:

- microscopic invasion of tumour into the perithyroidal soft tissues at initial surgery
- cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation
- a tumour with aggressive histology or vascular invasion

High-risk patients have the following characteristics:

- macroscopic tumour invasion
- incomplete tumour resection
- distant metastases
- and possibly thyroglobulinemia out of proportion to what is seen on the post-treatment scan

The European Society of Medical Oncology (ESMO) guideline for DTC recommends stratification to these three groups. The postoperative clinicopathological staging system should be used, in conjunction with the AJCC staging system to improve prediction of risk for recurrence and to dictate the most appropriate therapy (Pacini et al. 2010).

Unlike staging according to the TNM staging system and others, depending on the clinical course of the disease and response to therapy, the risk of recurrence may change over time. Appropriate management requires an ongoing reassessment of the risk of recurrence and the risk of disease-specific mortality as new data are obtained during follow-up (Cooper et al. 2009).

Evidence has accumulated to support a more ongoing risk stratification, which takes into account the response to initial therapy. Successful ablation, measured by negative post-treatment scan and undetectable serum TG, has been shown to correlate with better outcome (Verburg et al. 2005). Undetectable serum TG after primary therapy by itself has also been reported to correlate with better outcome (Toubeau et al. 2004, Kloos and Mazzaferri 2005, Kim et al. 2005a, Brassad et al. 2011).

On this basis, patients can be classified as having an excellent, acceptable or incomplete response to therapy (Tuttle 2008). Patients with an excellent response (undetectable basal and stimulated TG, negative TG antibodies and negative neck US) should have a very low-risk of recurrence and their long-term follow-up is based on yearly physical examination and suppressed TG value. Patients with an acceptable response (undetectable basal TG, stimulated TG <10 ng/ml, trend of declining TG, TG-Ab absent or declining, substantially negative neck US) require a closer follow-up,

reserving additional treatment in the case of any evidence of disease progression. Patients with an incomplete response (detectable basal and stimulated TG, trend of TG stable or rising, structural disease present, persistent or recurrent RAI-avid disease present) require continued intensive follow-up with neck ultrasound, cross-sectional imaging, RAI imaging and FDG-PET imaging (Pacini et al. 2010).

5.9 Health-related quality of life (HRQoL)

Studies on health-related quality of life (HRQoL) after primary treatment of DTC patients are limited in number. Most studies have demonstrated some impairment of HRQoL (Botella-Carretero et al. 2003, Crevenna et al. 2003, Tagay et al. 2005, Hoftijzer et al. 2008). One study assessed HRQoL in 153 cured DTC patients with the validated health-related questionnaires SF-36, MFI-20, HADS and SDQ and compared the results with those of 113 healthy controls, selected by the patients themselves, and 336 age- and gender-matched controls from other local studies. Duration of cure varied considerably (0·3–41·8 years). Quality of life was impaired in DTC patients relative to the two control groups in 11 and 13 of 16 subscales, respectively (Hoftijzer et al. 2008). These studies include reports on the short-term effects of hypothyroidism or subclinical hyperthyroidism on quality of life in DTC patients (Botella-Carretero et al. 2003, Tagay et al. 2005, Tan et al. 2007).

The long-term effect of thyroid cancer on HRQoL has been the subject of only a few surveys. Schultz and colleagues have described the health profiles of 518 thyroid cancer survivors, as part of a large cancer survival survey (Schultz et al. 2003). The survey, which was designed for adult survivors of any cancer, consisted of questions concerning health effects of cancer on neurological, cardiovascular, musculoskeletal, gastrointestinal, genitourinary, pulmonary, integumentary, psychological, endocrine and sociocultural functions. In this study, thyroid cancer survivors reported more memory loss and psychological problems than survivors of other cancers, and more migraine headaches than other cancer survivors or the general population (Schultz et al. 2003). In a study of 150 DTC patients with a median time of 5.5 years from diagnosis, using the SF-36 survey, an impairment in HRQoL was seen during the first year after diagnosis. Thereafter, quality of life improved correlating with the time since initial diagnosis (Crevenna et al. 2003).

6 AIMS OF THE STUDY

The prevalence of particularly low-risk DTC is increasing, and the number of patients who need long-term follow-up is considerable. General guidelines are most suitable for low-risk patients; for high-risk patients, a tailored approach is always warranted. Identifying novel factors prognostic of disease recurrence is an important goal of current research activity. At HUCH, a uniform treatment and surveillance scheme of low-risk DTC patients has been used for more than 20 years, providing an adequate perspective on the follow-up of low-risk patients. Specific aims of this study were as follows:

- To analyse the long-term outcome of patients treated for TNM stage I or II low-risk differentiated thyroid carcinoma, and in remission, at HUCH between 1983 and 1997.
- To find factors prognostic of recurrence of patients with low-risk differentiated thyroid carcinoma.
- To evaluate the prognostic capability of BRAF V600E mutation for recurrence in a patient population with low-risk for cancer-specific death.
- To compare HRQoL of patients who have undergone treatment for low-risk DTC with the age- and gender-matched general population.

7 MATERIALS AND METHODS

The study was carried out at Helsinki University Central Hospital (HUCH) and the University of Helsinki between 2001 and 2011. HUCH provides specialist health care for a district with approximately 1 425 000 inhabitants (the Uusimaa region). Patients with DTC are treated and followed up at the Division of Endocrinology, Department of Medicine and Department of Oncology. Patients with persistent disease are followed up by oncologists, whereas those considered disease-free are referred to the Division of Endocrinology for five years. Thereafter, the follow-up takes place at the local hospital for additional five years.

All patient data were collected by reviewing the original patient records. Data on patients' current addresses were provided by the Finnish Population Registry Centre. Causes of death were provided by Statistics Finland.

7.1 Study approval

The study protocol was reviewed and approved by the Ethics Committee of HUCH.

7.2 Subjects and methods

For this study, the clinical records of 710 patients (571 female, 139 male) diagnosed with and treated for papillary or follicular thyroid carcinoma over a 15-year period from 1st January 1983 to 31st December 1997 in the HUCH district were reviewed. The study cohort comprises those DTC patients belonging to TNM stage I or II who were considered to be disease-free and in complete remission after initial treatment (n=495, 70% of all).

The major data collection time-points were in 2002 and 2007. These time-points were chosen so that all patients would have a follow-up period of five years or more and ten years or more, respectively.

Demographic data included patients' age at diagnosis, sex, date of operation and data on causes of any death, provided by the Finnish Population Registry. Data on tumour size, histological diagnosis and invasiveness, local and distant metastasis, postoperative and post-ablative thyroglobulin levels as well as data on primary treatment, including mode of operation, radio-active remnant ablation and activity of

RAI, external radiation and judgment of completeness of surgery, were collected. Records of all follow-up visits (n=2559) were reviewed, and data on all tests and examinations utilized were recorded (including laboratory, radiological and other parameters).

7.2.1 *Subjects in Studies I and II*

The study cohort in Studies I and II consisted of 495 (83.8% female and 16.2% male) patients with TNM stage I or II differentiated thyroid carcinoma and considered to be disease-free after initial therapy. Mean age at diagnosis was 40.6 years.

For BRAF mutation analysis (Study III), all patients with papillary tumours and disease recurrence (n=46) were considered. Age- and gender-matched controls were chosen.

For Study IV, 417 patients (84% of study cohort) were invited to participate in the HRQoL study. Patients with occult carcinomas or patients with lobectomy as initial treatment were excluded. Altogether 341 patients replied, resulting in a response rate of 81.1%.

7.2.2 *Tumour staging*

The tumours were staged according to the AJCC, 6th edition. The papillary tumours were additionally staged according to the MACIS prognostic scoring system.

7.2.3 *Disease recurrences*

A disease recurrence was defined as new evidence of disease after a disease-free period of 12 months or more. It included all sites of disease reported and confirmed by either imaging or surgery. A new uptake on DxWBS, a newly measurable TG, a clinical finding with histological conformation or a lesion in neck US with positive FNAB or histological finding were considered. A disease-free period of 12 months or more was necessary before the diagnosis of recurrence; otherwise, it was classified as persistent disease and excluded. Time to disease recurrence was calculated from the date of initial surgery. For TG, the detection limit of the method used at each time-point was used as cut-off value distinguishing between measurable and non-measurable findings.

A questionnaire was sent in 2002 and again in 2007 to all patients whose follow-up had been referred from HUCH to another hospital. The questionnaire clarified possible suspicion of recurrence and possible side-effects of primary treatment during follow-up. A separate standardized questionnaire, the 15D™ (Sintonen 2001), evaluating patients' HRQoL was also sent to all patients in 2002.

7.2.4 *Thyroglobulin measurements*

Until 1989, serum TG was measured by an RIA kit (Medix Laboratories Ltd., Kauniainen, Finland) with a detection limit of 3 mg/l, and after that by an immunometric sandwich assay using two MABs (AutoDelfia, Perkin Elmer, Wallac, Turku, Finland) with a detection limit of 1 mg/l. Prevalence of anti-TG antibodies was evaluated using the recovery method according to the manufacturer's instructions (Delfia TG (hTG), Perkin Elmer). A recovery of >80% was considered normal and excluded the presence of anti-TG antibodies.

7.2.5 *BRAF mutation (Study III)*

To evaluate the prognostic quality of BRAF mutation, original tumour tissue samples of PTC patients with a disease recurrence after a median follow-up of 16 years (n=46) were located. Twenty-six original tumour tissue samples were retrievable; these were re-evaluated by an experienced thyroid pathologist. Representative tumour slides with a minimum of 30% of tumourous tissue were chosen for further analysis. Age- and gender-matched controls with retrievable tissue samples and no disease recurrence were selected.

Paraffin-embedded tumour tissues were processed for DNA extraction. For the BRAF mutation V600E test, DNA was extracted by using the Quiagen mini extraction kit. For mutation analyses, ARMS (allelic-specific PCR) with Scorpions real-time PCR technology was applied according to the instructions given by the supplier (B-RAF Mutation Test Kit; BR-01, Qiagen DxS).

7.2.6 *Measurement of health-related quality of life (Study IV)*

HRQoL was measured by the 15D tool (Sintonen 2001). This is a generic, comprehensive, 15-dimensional, standardized, self-administered measure of HRQoL that can be used both as a profile and single index instrument. The 15D questionnaire consists of 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. Each dimension is divided into five ordinal levels, to assess the extent of the attribute. The subject chooses the level best describing his or her current health status for each dimension. The evaluation system of the 15D is based on an application of the multi-attribute utility theory. A set of utility or preference weights, elicited from the general public through a 3-stage evaluation procedure, is used to generate the within-dimension level values and the overall utility score, i.e., the 15D score (single index number) over all the dimensions on a 0-1 scale. The maximum score is 1 (no problems on any dimension), and

minimum score 0 (equal to being dead). The minimal clinically important difference of the 15D score is 0.03.

The 15D questionnaire was posted to the patients. The HRQoL data obtained were compared with that of a large, representative sample of the general Finnish population. The 15D data for the general population came from the National Health 2000 Health Examination survey representing the Finnish population aged 30 years and over (Aromaa and Koskinen 2004). For the present analysis, individuals who were in the age range of the patients (n=6001) served as a comparative population. This sample was weighted to reflect the age and gender distribution of the patients.

7.3 Statistical analysis

The statistical analyses were carried out using a NCSS 2000 software package (NCSS Statistical Software, Kaysville, UT, Study I) or S+ Software (Studies II, III and IV). A p-value less than 0.05 was regarded as statistically significant. All tests were performed as two-sided tests. The following tests were used:

Study I: For comparisons between patients with or without recurrence, Fisher's exact test for two proportions was used. The assumptions for Student's t-test were not fulfilled for the variables of age, size and MACIS, which were evaluated using Mann-Whitney U-test or Wilcoxon rank-sum test for difference in medians. Independent predictors for recurrence were studied using forward stepwise regression analysis.
Study II: The relationships between recurrence and explanatory factors were first examined using simple logistic regression. A multiple logistic regression model including all significant factors in the first analysis was created (hazard ratio with 95% confidence intervals). A p-value of less than 0.05 was considered statistically significant.
Study III: The relationships between recurrence and explanatory factors were examined using simple logistic regression for each factor separately. Comparison of patient and tumour characteristics according to BRAF V600E mutation status was performed with simple logistic regression, Fisher's exact test, Wilcoxon rank-sum test or two-sample *t*-test. In these analyses, BRAF V600E mutation status was handled as a factor. A p-value of less than 0.05 was considered statistically significant.
Study IV: Differences in the means of continuous variables were tested with independent samples *t*-test and in categorical variables with Pearson Chi-square test. Differences between the mean 15D scores and dimension level values between participants and the control group were tested with independent samples *t*-test. The variance in the 15D scores among the survey participants was explained by a Tobit regression model.

8 RESULTS

8.1 Patient and tumour characteristics

The study cohort of 495 low-risk DTC patients in studies I, II and IV consisted of 415 (83.8 %) females and 80 (16.2 %) males. Mean age at diagnosis was 40.6 years. A majority (93.1%) of the tumours were of papillary histology, 6.3% were follicular and 0.6% other (Hürthle-cell and mucoepidermoid variants). Median tumour size was 1.8 cm (range 0.3 to 6.0 cm) for all tumours and 1.6 cm (0.3 to 6.0 cm) for papillary and 3.0 cm (0.6 to 6.0 cm) for follicular tumours. The follicular tumours were significantly larger in diameter than the papillary tumours (P<0.0001). In 11 cases (2.2%), tumour size was not recorded in either surgical or histological reports.

Table 6. Tumour characteristics expressed as median (range) or number (percentage)

	All *n = 495*	Papillary *n = 461*	Follicular *n = 31*	Other *n = 3*
Size (cm)	1.8 (0.3 – 6.0)	1.6 (0.3 – 6.0)	3.0 (0.6 –6.0)	1.5 (1.5 – 2.0)
Macroscopic infiltration	37 (7.4%)	36 (7.8%)	1 (3.2%)	0
Complete surgery	492 (99.4%)	458 (99.3%)	31 (100%)	31 (100%)
Nodal metastases at primary operation	62 (12.5%)	61 (13.2%)	0	1 (33.3%)
Distant metastases at diagnosis	1 (0.2%)	0	1 (3.1%)	0

The majority (94.6%) of the patients underwent near-total thyroidectomy as the initial surgical procedure. A selective lymphadenectomy or a modified neck dissection was performed for patients with confirmed nodal metastases by diagnosis (n=62, 12.5%). Hemithyroidectomy or a resection of varying extent was performed on

27 patients, most of whom had a small incidental tumour when operated on for other causes. All but three of these tumours were ≤ 1 cm in diameter.

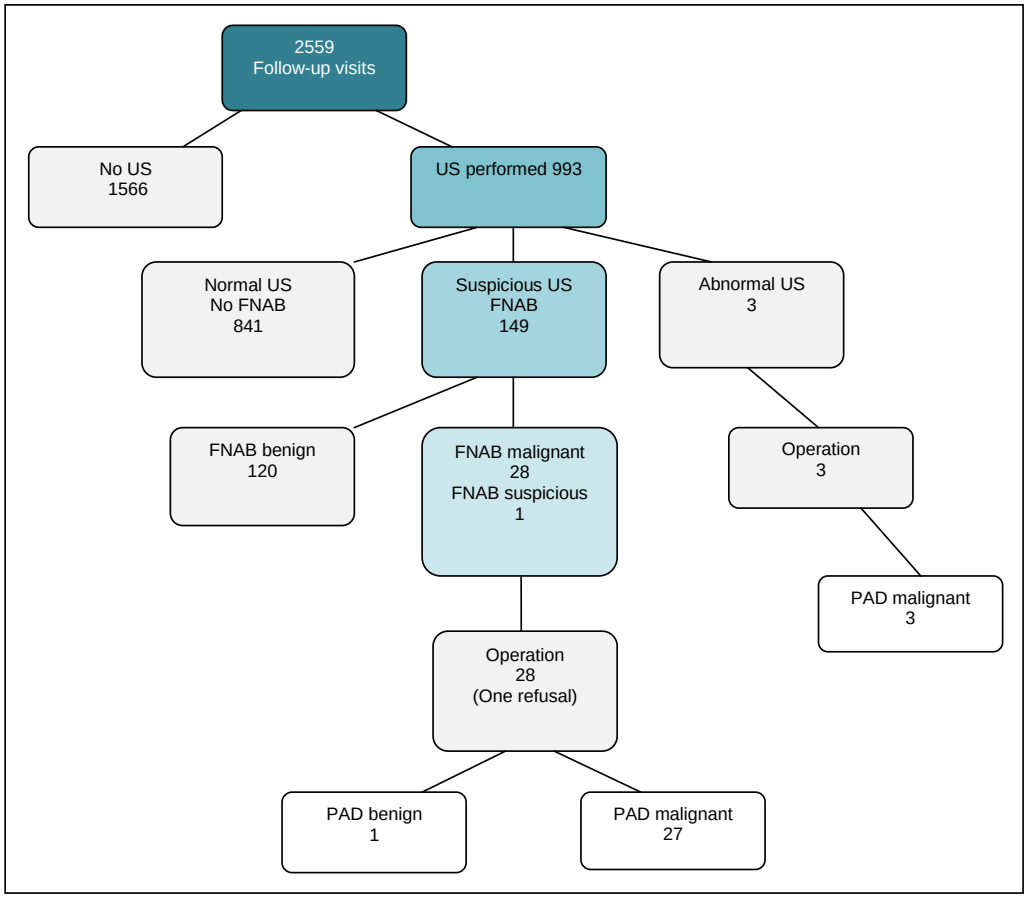
Of the patients, 80% received RRA. The initial treatment dose of ^{131}I varied from 1.11 – 4.44 GBq (30 – 120 mCi), depending on the uptake. Repeated doses of radio-iodine were administered if necessary (77 patients, 15.5%). The completeness of RRA was controlled 3-4 months later with DxWBS and TG measurement after withdrawal of L-T4.

Median follow-up time was 11.6 years (range 5–19 years) in Studies I and IV and 16 years (range 10 – 24) in Studies II and III.

8.2 Use of US and DxWBS in the follow-up (Study I)

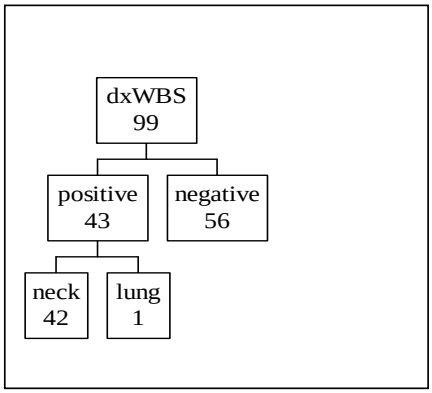
For this cohort, we reviewed the records of 2559 follow-up visits. Neck US was performed 993 times (38.8% of the follow-up visits). The radiologist proceeded to a FNAB in 149 (15.0%) of the examinations. In 28 of the 149 samples (18.8%), the cytological finding was considered malignant and in one suspicious (altogether 23 patients). One patient refused surgery and was referred to external beam radiation therapy. In 28 operations, malignancy was confirmed in all but one case (Figure 5). Additionally, three neck node operations were scheduled because of a suspicious finding in neck US without a suspicious FNAB (not performed in 2 cases, benign in one case), and all had a malignant finding at operation.

Figure 5. Number and findings of neck ultrasonography (US) and fine-needle aspiration biopsy (FNAB)



DxWBS with ^{131}I activity of 0.185 to 0.37 GBq (5–10 mCi) was performed at 99 follow-up visits (3.9%) of 75 patients (Figure 6). The scan was positive 43 times in 33 patients (44.0%) and negative 56 times. Of 43 positive scans, the uptake was located in the neck only in 42 cases (97.7%) and in the lungs and neck in one case (patient with first recurrence in the neck only, second recurrence in lungs and neck as indicated by a TG on T4 of 14 ug/l). Forty-five (45.5%) of the DxWBS were performed because of detectable TG on T_4. and the remaining 54 for other causes. These included serum TG increasing by 1 µg/l or more compared to the previous visit, without concomitant suspicious findings on neck US, and detection of anti-TG antibodies, which made TG measurements unreliable. DxWBS was also used in the surveillance of some patients, whose primary operation had indicated more aggressive disease (tumour invasion into surrounding tissues, suspicion of incomplete surgery, several nodal metastases)

Figure 6. Use of DxWBS in follow-up



8.3 Outcome of 495 patients (Studies I and II)

8.3.1 Disease recurrences

At the time of the first data collection point (median follow-up 11.6 years, range 5-24 years) in 2002, 44 patients (8.9%) had experienced their first disease recurrence (Table 7). All recurrences were located in the neck (Table 7). Median time to disease recurrence was 42 (range 12 –214) months. The clear majority of the recurrences, 93.1%, occurred within 10 years of the diagnosis and 70.7% within the first 5 years. Tumour histology was papillary carcinoma in 39 cases and follicular carcinoma in 5 cases.

Table 7. Characteristics of patients at diagnosis with and without tumour recurrence after 11.6 years (median).

	With recurrence *n = 44*	Without recurrence *n = 451*	*P*
Male sex	12 (27.3%)	68 (15.1%)	*0.051*
Age (median with range)	32.5 (6 –83)	40 (15 - 73)	*0.0038*
Follicular histology	5 (11.4%)	26 (5.8%)	*0.180*
Size in cm (median with range)	2.3 (0.5-5.0)	1.6 (0.1-7.0)	*0.019*
Complete surgery	44 (100%)	448 (99.3%)	*1.00*
Total thyroidectomy (TTE)	43 (97.7%)	426 (94.4%)	*0.498*
Local infiltration in primary surgery	9 (20.5%)	28 (6.2%)	*0.0029*
Nodal metastasis in primary surgery	12 (27.3%)	50 (11.1%)	*0.0044*
Radio-active remnant ablation (RRA) given	36 (81.8%)	362 (80.3%)	*0.847*

At the time of renewed data collection (median follow-up 16 years), the cumulative number of recurrences had risen to 51 (10.3%). The duration of disease-free period after primary treatment, the primary diagnostic tool of the recurrence, localization of the recurrence for each patient after a median follow-up of 16 years are presented in Table 8. The majority of recurrences were located in the cervical lymph nodes (LN; 94.1%), were detected with neck US (54.9%) and were confirmed histopathologically. The diagnosis of a smaller number of recurrences (31.4%) was confirmed with a definite new uptake on diagnostic WBS (Table 7). In one case each, recurrence was detected based on increased TG concentration on T4 combined with palpable nodes, or a suspect US finding and the appearance of TG antibodies indicated by declining recovery. In two cases, increasing concentration of TG without radiological or clinical findings provided an indication for therapeutic activity of RAI, and the recurrence was confirmed in subsequent RxWBS.

Table 8. Disease recurrences

Age at diagnosia	Gender	Location of recurrence	Diagnostic method	Months to recurrence
30	Male	Cervical LN	DxWBS	16
36	Female	Cervical LN	US/FNAB	16
31	Female	Cervical LN	US/FNAB	18
53	Female	Cervical LN	US/FNAB	18
30	Female	Cervical LN	US	18
49	Female	Cervical LN	US/FNAB	21
24	Female	Cervical LN	US	21
20	Male	Cervical LN	US/FNAB	21
16	Female	Cervical LN	TG + palpation	22
21	Female	Cervical LN	US	24
42	Female	Cervical LN	DxWBS	24
18	Female	Cervical LN	DxWBS	24
53	Female	Cervical LN	US/FNAB	25
27	Male	Cervical LN	US/FNAB	26
52	Female	Cervical LN	DxWBS	27
42	Female	Cervical LN	US/FNAB	30
43	Male	Cervical LN	US/FNAB	33
39	Male	Cervical LN	DxWBS	35
53	Female	Cervical LN	DxWBS	35
27	Male	Cervical LN	US	36
33	Female	Cervical LN	DxWBS	38
51	Female	Cervical LN	US/FNAB	48
40	Female	Cervical LN	DxWBS	48
27	Female	Cervical LN	US/FNAB	52
25	Female	Cervical LN	US/FNAB	58
69	Male	Cervical LN	DxWBS	58
26	Female	Cervical LN	DxWBS	59
60	Male	Cervical LN	DxWBS	59
39	Female	Cervical LN	US	60
17	Female	Cervical LN	DxWBS	60
20	Female	Mediastinal LN	TG-on-T4	65
40	Female	Cervical LN	US/FNAB	66
73	Female	Cervical LN	DxWBS	67
21	Male	Cervical LN	US/FNAB	69
19	Female	Cervical LN	DxWBS	71
26	Female	Cervical LN	US/FNAB	92
35	Female	Cervical LN	DxWBS	93
19	Female	Cervical LN	TG /US	108
54	Female	Cervical LN	TGWBS	108
34	Male	Cervical LN	US/FNAB	108
27	Male	Cervical LN	US/FNAB	110
41	Female	Cervical LN	New TG-AB	113
43	Female	Cervical LN	US/FNAB	116
6	Female	Cervical LN	US/FNAB	121
16	Female	Cervical LN	US/FNAB	131
19	Female	Cervical LN	NA	132
44	Female	Cervical LN	US/FNAB	144
32	Male	Cervical LN	US/FNAB	144
27	Female	Cervical LN	US/FNAB	149
65	Female	Cervical LN	TG-on-T4	212
32	Male	Cervical LN	DxWBS	263

8.3.2 Cancer death

At the time of second data analysis, thyroid carcinoma was registered as the cause of death in one patient (Statistics Finland), diagnosed with follicular carcinoma at the age of 42 years; this patient had diagnosed with a benign follicular adenoma five years earlier. The malignant diagnosis was made from a local tumour of 1.2 cm in diameter, with no nodal or distant metastases (TNM stage I). A retrospective analysis of the primary histological sample revealed capsular invasion. After total thyroidectomy, RRA (3.7 GBq (100mCi)) was administered, post-treatment scan (RxWBS) showed no uptake and serum TG on and off L-T4 was undetectable. The patient died of thyroid cancer 8 years after the malignant diagnosis.

8.4 Prognostic factors

After a median follow-up of 11.6 years (Study I), predictors of recurrence in univariate analysis were male sex (p=0.051), age (p=0.0038), tumour size (p=0.019), local infiltration (p=0.0029) and nodal metastases (p=0.0044) at primary operation. Also MACIS predicted recurrence (p=0.045). In multivariate analysis, independent predictors for recurrence were age (p=0.031), male sex (p=0.028) and local infiltration at primary operation (p=0.002).

In Study III, with a median follow-up of 16 years, simple logistic analysis of predictive factors for disease recurrence revealed that compared with patients without recurrence, patients who experienced disease recurrence were younger (p<0.0057), more often males (p<0.035) and more often had detectable post-surgical and post-ablative TG levels (p=0.0251 and p<0.0001, respectively). Patients with recurrence also had more nodal metastasis (p=0.0008) and local infiltration (p=0.005) at primary surgery. Multiple logistic regression analysis including all statistically significant variables revealed that only infiltration at primary surgery (OR 2.66, CI 1.03 – 6.90, p=0.04) and post-ablative detectable TG concentrations (OR 3.7, CI 1.71 – 8.05, p=0.009) were independent predictors of disease recurrence.

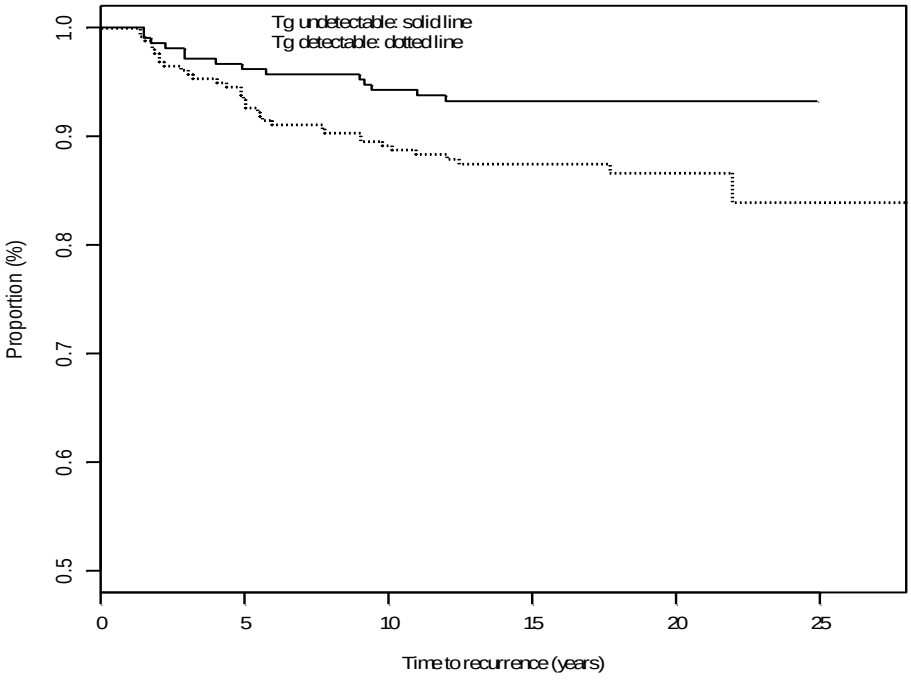
8.4.1 Serum thyroglobulin (Study II)

Post-surgical TG levels were recorded in 468 cases (94.5%). After primary total or near total thyroidectomy, 250 cases (52.9%) demonstrated post-surgical TG levels above the detection limit. Of the 51 patients with disease recurrence, 71% (n=34) had a post-operative TG level above the detection limit, as compared with 54% (n=225) of the 420 patients without recurrence (p=0.0251). Post-operative TG did not correlate

with postoperative TSH concentrations (p=0.056). The post-operative median TSH concentrations did not differ between patients with and without recurrence (76 and 73 mU/l, respectively, p=0.39).

RRA was performed on 414 of the 472 patients who had undergone total or near-total thyroidectomy (49 patients with subsequent recurrence and 365 without recurrence). Post-ablative TG levels were recorded in 401 cases (96.9%) and were detectable after the initial RRA therapy in 51 cases (12.7%, median 10.0 μg/l, range 1-500). All patients with detectable TG after initial RRA received repeat doses of RAI until TG became undetectable and there was no evidence of disease on post-therapy WBS or subsequent DxWBS. Total ^{131}I activity administered varied between 2.2 and 25.9 GBq (60–700 mCi). After ablation, TG was measurable in 36.4% of patients with subsequent recurrence compared with 9.8% of patients without recurrence (p<0.0001; Table 2). The corresponding post-ablative median TSH concentrations were 44 and 36 mU/l, respectively (p=0.36). Disease recurrence was diagnosed significantly more often in patients with detectable TG after initial RRA than in patients in whom TG was undetectable (Figure 7, p=0.021).

Figure 7. Proportion of recurrence-free patients without (n = 350) and with (n= 51) detectable TG after first ablative radio-iodine treatment as a function of time



In 79 cases with undetectable TG after RRA, a low recovery (<80%) indicated TG antibodies. Nine of these patients subsequently developed disease recurrence. No significant difference was present in the prevalence of TG antibodies between patients with and without recurrence (p=0.3029).

8.4.2 Prevalence and predictive value of BRAF V600E mutation (Study III)

Original tissue samples were retrievable in 26 (57%) of 46 patients who had experienced a disease recurrence. Tissue samples from 25 age- and sex-matched patients from the same cohort, who had not experienced a recurrence during follow-up served as controls. Prevalence of the BRAF V600E mutation in the 51 samples analyzed, representative of the whole cohort, was 67% (34/51).

The 26 patients with later disease recurrence for whom original tissue samples were retrievable did not differ from the 20 patients with disease recurrence for whom samples could not be retrieved. No significant differences were observed with regard to median age, male gender, primary tumour size, nodal metastasis or local infiltration at presentation, time to disease recurrence, detectable TG after RRA , number of RRA treatments or mean RRA activity administered (all p=NS).

Prevalence of the BRAF V600E mutation did not differ between patients with and without recurrence (65% vs. 68%, p=0.84). Patients with recurrence more often (p= 0.053) had detectable TG concentrations after RRA than patients without recurrence, but did not differ significantly with regard to primary tumour size or nodal metastasis in primary surgery. Four patients (15%) with recurrence were characterized by local infiltration at presentation compared with none of the patients without recurrence. No difference existed between the groups in the proportion of patients receiving RRA as part of the initial therapy. Repeated treatment was more often needed in patients with later disease recurrence than in patients without, but the difference was not significant. Mean initial RRA activity was higher in patients with than patients without later disease recurrence, but this difference did not quite reach statistical significance [6.9 GBq (189 mCi) vs. 4.3 GBq (116 mCi), p=0.059].

When patients with and without recurrences were combined, of the 34 BRAF mutation-positive patients, 50% experienced a disease recurrence compared to 53% of BRAF negative patients (p=NS). Median time to disease recurrence was 52 months for patients with and 36 months for those without the mutation. This difference did not reach statistical significance (p=0.15). Median age, prevalence of male gender and tumour size were also similar in both groups. Nodal metastasis (21% vs. 35%) and local infiltration (6% vs. 12%) at presentation appeared to be more frequent in BRAF mutation-negative patients, but the differences were not significant (p=0.26 and p=0.47, respectively). Number of radio-iodine treatments needed initially or mean

treatment activity of ^{131}I did not differ between the groups (p=0.67 and p=0.70, respectively).

8.5 HRQoL after treatment for differentiated thyroid carcinoma (Study IV)

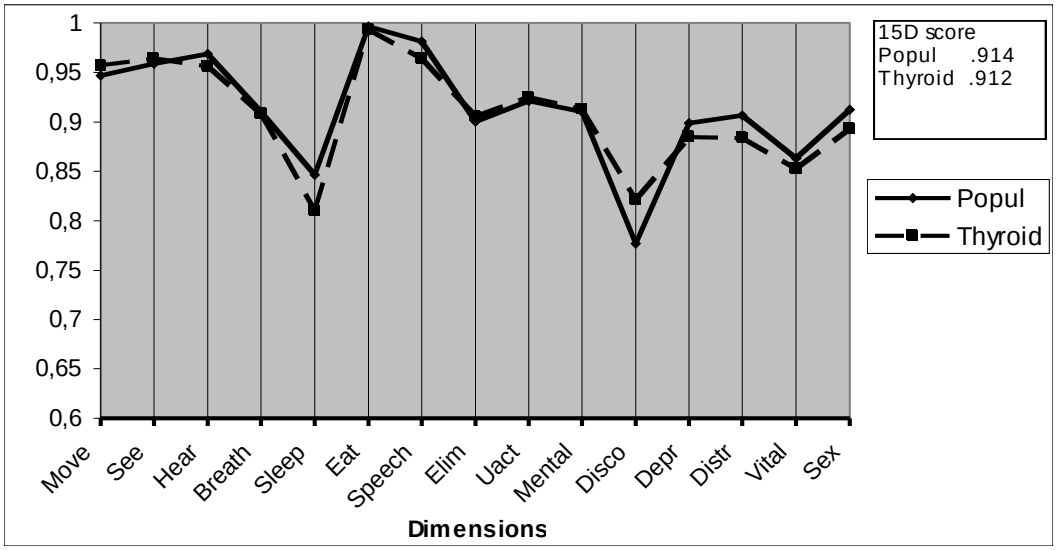
HRQoL for 341 patients (48 men, 293 women) aged 23–93 years (mean 52 years) was analysed. The majority of patients had papillary tumours (94.5 %), 18 patients (5.3%) had follicular carcinoma and one patient had a Hürthle-cell carcinoma. Five patients had vocal cord paralysis (0.05%) and six patients prolonged or permanent hypoparathyrodism as a surgical complication (0.018%). Eighty-five percent (290 patients) had received postoperative radio-iodine ablation, 60 of them (20.7%) more than one treatment. The daily dose of thyroxine varied from 0.093 mg to 0.400 mg (mean 0,171 mg). Median follow-up time from initial surgery was 12.4 (range 5–19.5) years. Thirty-three patients (9.6%) had experienced a disease recurrence.

The patients who participated in the HRQoL survey were significantly older than those who did not return the questionnaire (52 vs. 42 years; p<0.001). There were no statistically significant differences between the two groups in other characteristics (gender distribution, number of radio-iodine treatments, disease recurrence, and duration of follow-up).

No significant difference between the mean total 15D score of the patients (0.912) and that of the age- and gender-standardized general population (0.914) was found. With regard to single dimensions, patients were worse off than the general population on the dimensions of sleeping, speech and distress (p= 0.001, 0.002 and 0.012, respectively). With regard to discomfort and symptoms, patients were better off than the general population (p<0.001, Figure 8).

Of the different parameters, only the negative marginal effect of age at the time of initial treatment reached statistical significance (p<0.001). The data suggest that the higher the patients' age at the time of initial treatment, the lower the HRQoL at the time of the survey. Duration of follow-up showed a similar negative marginal effect on HRQoL; however, this was not significant. The marginal effect of daily dose of thyroxine on HRQoL was positive, but did not quite reach statistical significance (p=0.087). The marginal effects of disease recurrence, number of radio-iodine treatments and vocal cord paralysis were negative, but again not significant.

Figure 8.



For variance in the level values of the dimensions of sleeping, discomfort and symptoms, a similar result was obtained. Age at the time of initial treatment was the only explanatory variable, with a negative marginal effect that was significant. With regard to distress and speech, none of the explanatory variables had a significant marginal effect (Table 9).

Table 9.

Variable	Marginal effect	*P*-value
Gender (0=female, 1=male)	0.0061	0.6771
Number of radio-iodine ablations	-0.0019	0.8306
Recurrence (0=no, 1=yes)	-0.0087	0.5813
Daily dose of levothyroxine	0.0027	0.0868
Duration of follow-up (years)	-0.0017	0.1962
Age at initial treatment (years)	-0.0018	<0.0001
Vocal cord paralysis (0=no, 1=yes)	-0.0100	0.8004

9 DISCUSSION

9.1 Study population

The increasing prevalence of thyroid cancer can be attributed to the increasing incidence of low-risk DTC (Kent et al. 2007, Pacini et al. 2010). This work presents the long-term follow-up data of a cohort of 495 patients at low-risk of thyroid cancer-specific death according to the AJCC-UICC prognostic classification and who were disease-free after primary therapy. All patients belong to the favourable TNM stage I or II, representing the clear majority of patients in everyday clinical practice. We did not include those TNM stage I or II patients who could not be classified as disease-free after primary therapy: patients with low measurable TG values but no detectable disease, patients who would need a tailored and more intensive follow-up.

The cohort is representative of this patient group, with a median age of 40 years and a female-to-male ratio of 4:1.

A considerable number of patients, all uniformly treated and followed up according to a uniform strategy and a long follow-up, can be seen as strengths of the study. With the presently ongoing shift of treatment paradigms towards a more selective use of radio-iodine, this work offers valuable data on long-term outcome of low-risk patients treated with thyroidectomy and RRA.

9.2 Neck US, DxWBS and TG in follow-up

The cornerstones of the treatment scheme in HUCH have been total or near-total thyroidectomy, followed by RRA therapy destroying thyroid remnants and possible remaining tumour cells and rendering most patients' TG levels undetectable on and off L-T4 treatment. In surveillance of patients, neck US was frequently used; every two years routinely and additionally whenever clinically indicated. TG measurements were performed on L-T4 treatment without rhTSH stimulation, with an increase in TG to a detectable level being a prompt indication for further investigations. Naturally, the treatment and follow-up paradigms have evolved over the years, and at least at the beginning of the study period occasional deviations occurred. However, the relatively large patient cohort, long follow-up time and routine use of neck US over 20 years give a solid background to evaluate the surveillance scheme.

In the last ten years, most surveillance protocols have acknowledged the sensitivity of neck US in detecting local recurrences. Pacini et al. (2003) found that rhTSH-

stimulated TG values alone have a sensitivity of 85% for disease detection, rising to 96.3% when combined with neck US, with a negative predictive value of 99.5%. In a series by Mazzaferri and Kloos (2002) of 107 patients with tumours of all stages, nine patients with persistent disease were identified with an rhTSH-stimulated serum TG level greater than 2 μg/L. However, four of these patients had a detectable, although low TG level on L-T4, and in three additional patients neck US located the recurrence to the neck (Mazzaferri and Kloos 2002). Accordingly, the surveillance protocol would have revealed seven persistent tumours, without rhTSH stimulation tests.

The present study does not support the notion that liberal use of neck US would lead to unnecessary FNABs and operations at increased costs and discomfort for the patients. Of 993 neck US performed, only 15% led to FNAB, and of 149 FNABs 28 to further surgery, with a malignant finding in all but one of the cases. Neck US must always be performed by experienced examiners to ensure reliability. It could also be argued that using very low TG cut-off levels for further evaluations would lead to a large number of additional investigations, with detrimental psychological effects for patients. However, in our study, TG on L-T4 was detectable in only 67 patients, and further investigations confirmed recurrent tumour in 23 and persistent disease in four of these subjects.

When increasingly more small low-risk differentiated cancers are treated with surgery only (Vaisman 2011), neck US is more sensitive than any other method in detecting a recurrence in follow-up (Durante and Filetti 2011). For patients who do not undergo RRA, thyroglobulin assays are difficult to interpret. Neck US also has excellent negative predictive value in patients with very low-risk DTC (Durante et al. 2010).

Sonographic criteria for identifying metastatic involvement of the cervical nodes have been well-defined; these include cystic appearance, hyperechoic punctuations, loss of hilum, and peripheral vascularization (Leboulleux et al. 2007). As an integral part of thyroid cancer follow-up, neck US examination should always be conducted by experienced and adequately trained physicians.

In summary, the updated versions of many international guidelines now follow principles similar to those studied here. According to recent ESMO guidelines, at 6–12 months the follow-up aims to ascertain whether the patient is free of disease and is based on physical examination, neck US and basal and rhTSH-stimulated serum TG measurement with or without diagnostic WBS (Pacini et al. 2010). The subsequent follow-up of patients considered disease-free at the time of their first follow-up consists of a physical examination, basal serum TG measurement on LT4 therapy and neck US once a year. No other biochemical or morphological tests are indicated unless some new suspicion arises during evaluation (Pacini et al. 2010). The American Thyroid Associations guidelines recommend neck US at 6 and 12 months after initial surgery together with TG measurement to assure remission. Thereafter, neck US is

recommended yearly for 3-5 years (Cooper et al. 2006, Cooper et al. 2009). Diagnostic WBS in this setting can be omitted (Cooper et al. 2006, Pacini et al. 2010).

9.3 Long-term outcome

During the study period 51 patients (10.3%) experienced a recurrence and one patient died of thyroid carcinoma. This concurs with recurrence rates seen in other large series and is steadily approaching the 14-15% seen in a 30-year follow-up in a large Mayo Clinic cohort (Hay 2007). In another retrospective series of 1528 DTC patients, 23.5% of patients experienced a recurrence after median follow-up of 16.6 years (Mazzaferri and Kloos 2002). In patients treated with thyroidectomy and RAI, the number of recurrences was comparable with our series (Mazzaferri and Kloos 2002). In a large prospective series with a median follow-up of 6.2 years and patients of all TNM stages, the 5-year recurrence rate was 4,2% (Brassard et al. 2011).

The clear majority of the recurrences, 93.1%, occurred within 10 years of the diagnosis and 70.7% during the first 5 years. This suggests that 10 years after the initial treatment the surveillance could mainly focus on adequate L-T4 therapy and utilize TG measurements or neck US at a reduced frequency or when clinically indicated.

Together, these numbers stress that follow-up should indeed aim at early detection of disease recurrences, as the majority of these patients are at low-risk of thyroid cancer-specific death. For the majority of DTC patients, who also will never experience a recurrence, the long-term follow-up should serve to reassure that eradication of the tumour is complete. At the same time, the tests should be able to detect persisting or recurrent disease at the earliest possible stage. Delayed detection of local recurrences has been seen to result in significant personal suffering and increased mortality, with inoperable tumours that are resistant to radiotherapy and chemotherapy. The majority of DTC patients are of working-age, which should be factored into the pharmaco-economic considerations of surveillance schemes.

Another important objective of continuous surveillance is to maintain adequate thyroxine therapy permanently.

9.4 Factors prognostic of disease recurrence

After a median follow-up of 11.6 years, univariate analysis indicated that several factors, such as age, male gender, tumour size, local infiltration and node metastasis in primary surgery and tumour stage according to MACIS predicted recurrent

disease. However, in multivariate analysis only age, sex and extracapsular infiltration were independent predictors of recurrence. These factors have been established in many large retrospective studies (Hay et al. 1993, Jukkola et al. 2004, Siironen et al. 2005). In line with the present study, Jukkola et al. (2004) found in a retrospective analysis of 499 DTC patients that an accurate definition of risk could be achieved by using only two parameters, age (cut-off value 50 years) and extracapsular invasion of the thyroid gland.

9.4.1 Prognostic quality of serum thyroglobulin

After a long surveillance (median 16 years), infiltration at primary surgery and detectable serum TG concentration off thyroxine after the initial RRA were the only independent predictors of a later recurrence in this cohort. Consequently, these factors should be taken into account when trying to identify DTC patients at increased risk of local recurrence among the larger group of patients at low-risk of cancer-specific death. The data imply that in patients treated according to this protocol more emphasis should be placed on the follow-up of patients with detectable post-ablative TG concentrations, while a lighter follow-up scheme is probably indicated in patients with undetectable post-ablative TG. This would also help to individually tailor the surveillance scheme and its duration for high-risk patients and increase the cost-effectiveness of the surveillance system.

Local infiltration is included in nearly all classification systems for predicting cancer-specific death, but only a few studies have examined the possible role of post-surgical or post-ablative TG concentrations on disease outcome (Hall et al. 2003, Toubeau et al. 2004, Kim et al. 2005a).

In a study of 268 patients (TNM stage I to III) with a median follow-up of 5.7 years (Kim et al. 2005a), the recurrence rate was 13%, and the authors concluded that post-operative serum TG has a complementary role in predicting disease persistence or recurrence. They found a good correlation between post-surgical and post-ablative TG concentrations, but no association between post-ablative concentrations and recurrence rate (Kim et al. 2005a). In a 5.1-year follow-up study of 212 TNM stage I to III patients by Toubeau et al. (2004), recurrence rate was 9% and, in line with the present study, post-ablative but not post-surgical TG emerged as a strong predictive factor of disease recurrence, in addition to lymph node invasion. Hall et al. (2003) studied 212 DTC patients (TNM stages I to IV) for a median of 47 months; 12 % experienced recurrence at 11 months. They found that post-surgical TG greater than 20 pmol/l together with advanced tumour stage were independent predictors of disease recurrence (Hall et al. 2003).

Results on recurrence rate after a long-term prospective follow-up of 715 DTC patients in complete remission after primary treatment were recently published by Brassard et al. (2011). They assessed the predictive value of initial TG levels (after

primary treatment) for recurrence and found a negative predictive value of 99% for TG both on and off thyroxine therapy. They concluded that initial TG measurement allows predicting long-term recurrence with excellent specificity of 86–90% (Brassard et al. 2011). Our results support these findings.

The inclusion of stimulated TG concentrations measured 6-12 months after initial treatment in the surveillance scheme of DTC patients is strongly emphasized in a number of recent guidelines, not only to control the outcome of primary therapy but also to guide further surveillance (Cooper et al. 2006, Schlumberger et al. 2004, Pacini et al. 2006). The guidelines recommend TG measurements stimulated by recombinant human TSH (rhTSH) at 6-12 months after initial RRA. If TG concentrations are undetectable, follow-up can thereafter be based on yearly evaluation of serum TSH and TG on L-T4 treatment with or without neck US.

In simple logistics analysis, also post-operative TG level correlated with disease recurrence. Of the 51 patients with disease recurrence, 71% (n=34) had a post-operative TG level above the detection limit, as compared with 54% (n=225) of the 420 patients without recurrence (P=0.0251). In a study comparing low and high activity of ^{131}I in ablation, pre-ablative post-surgical levels of TG were predictive of success of RRA (Mäenpää et al. 2008).

Taken together, the data suggest that the response to initial treatment predicts recurrence-free survival and should guide follow-up of DTC patients. TG is a valuable tool in the setting of total thyroidectomy followed by RRA. Prophylactic neck compartment dissection has been suggested to be a surrogate for post-operative ablation. The advantages and disadvantages of each procedure remain to be compared and discussed.

The use of high-quality serum TG analysis can improve the cost-effectiveness of management and follow-up of DTC patients. Serum TG assay sensitivity has greatly improved in the last decades, lowering the analytical sensitivity from approximately 0.8 ng/ml to 0.01 ng/ml. This together with the reliability of the assays may result in less need for TSH stimulation in a setting of negative neck US. The main problem with this approach is the unrequested follow-up procedures in patients with minimal measurable basal TG levels (0.2–0.5 ng/ml) who, before the availability of the second-generation TG assay, were classified as disease-free with undetectable TG.

9.5 BRAF V600E mutation in low-risk PTC

Since it was first described in thyroid cancer, the BRAF V600E mutation has proven to be the most common genetic event in the onset of PTC, responsible for around 45% of cases. The mutation occurs exclusively in PTC or PTC-derived anaplastic tumours, but not in FTC or other types of thyroid tumours. This suggests a unique pathogenic

role of this mutation in the development of PTC. Up-regulation of VEGF, MMPS, resulting in tumour angiogenesis and invasion, has been observed, as has aberrant gene methylation, resulting in abnormal silencing of tumour suppressor genes (Xing 2007). Pathways leading to observed loss of radio-iodine avidity remain to be identified.

The relationship between BRAF V600E mutation and outcome of PTC has been extensively investigated (Xing et al. 2005, Xing 2007). Most studies have demonstrated a significant association between the mutation and the conventional high-risk clinicopathological characteristics of PTC (*e.g.* older age, advanced TNM stages, lymph node metastasis, distant metastasis, recurrence and persistence of disease) (Xing 2007). Of note, most of these prognostic factors have been validated with disease-specific death and not recurrence as the outcome. Some studies have demonstrated a significant association with tumour recurrence as well (Xing et al. 2005, Kebebew et al. 2007). These studies included patients of all TNM stages and have not clearly differentiated between recurrent and persistent disease.

In the present study, no correlation was seen between BRAF mutation and disease recurrence or time to recurrence. Furthermore, BRAF mutation was not associated with larger tumour size, invasion or nodal metastasis at presentation. A limitation of our study was that only 57% of the original tumour tissue samples of patients with recurrent disease were retrieved for determination of BRAF V600E status. To assure that these patients would be representative of all patients experiencing disease recurrence, we compared their characteristics with patients experiencing disease recurrence but with unknown BRAF status. No significant differences emerged between these groups in any of the characteristics. Another limitation is that for five patients with recurrence, BRAF mutation was determined from a nodal metastasis, as primary tumour tissue was unattainable. However, a close correlation between BRAF status in paired primary and recurrent PTC has been demonstrated (Barollo et al. 2010).

The results indicate that although common in Finnish PTC patients, BRAF mutation does not serve as a prognostic marker for later recurrence in a low-risk patient population treated with thyroidectomy and RRA. The question of whether a correlation would have been present had the patients not received active primary treatment with RRA, remains unanswered.

BRAF mutations have also been linked to loss of avidity for RAI. In a study of 50 DTC patients with recurrent disease, Barollo and colleagues (2010) found that 94% of BRAF V600E-positive recurrent patients were ^{131}I-negative. We wanted to test the association between BRAF mutation and sensitivity to primary RRA, but found no differences in the mean activity of RAI needed for ablation in this small patient cohort.

Mutated BRAF may in the future also be a therapeutic target for PTC. A number of BRAF inhibitors have been investigated as potential new agents for targeted therapies. One BRAF inhibitor (vemurafenib) has been authorized for use in BRAF mutant melanoma in 2011 and studies are ongoing in papillary thyroid cancer (www.clinicaltrials.gov). Other inhibitors of the MAPK pathway are also being investigated.

9.6 Health-related quality of life

Studies focusing on HRQoL of cured DTC patients are few (Botella-Carretero et al. 2003, Tagay et al. 2005, Crevenna et al. 2003, Giusti et al. 2005, Dagan et al. 2004, Schultz et al., Tan et al., Eustatia-Rutten et al. 2006, Hoftijzer et al. 2008).

Tagay and colleagues (2005) compared HRQoL in 130 hospitalized patients during 4-weeks of L-T4 withdrawal and in 100 outpatients on suppressive thyroxine therapy to that of a German reference population (n= 2914). Botella-Carretero et al. (2003) compared 18 DTC patients, both in the euthyroid state and during suppressive doses of L-T4, with 18 healthy controls using four validated HRQoL questionnaires. Mild or moderate impairment on several dimensions (sleep, mental health, energy, emotional, social functioning, total score) correlated with subclinical hyperthyroidism. In the biochemically euthyroid state, the results were more comparable with those of the healthy controls. Among 24 DTC patients with a disease history of at least 10 years, Eustatia-Rutten et al. (2006) compared the effect of continued TSH-suppressive thyroxine therapy (n= 12) with that of restored euthyroidism (n= 12) gained over 6 months. The results were compared with age-adjusted reference values. At baseline, patients demonstrated only minor clinically insignificant impairments in HRQoL on four validated questionnaires (SF-36, Mfi-20, HADS, SRS). The data indicate that HRQoL may not be impaired in DTC patients in long-term follow-up, even during TSH suppressive thyroxine therapy (Eustatia-Rutten et al. 2006).

Hoftijzer et al. (2008) assessed HRQoL with validated health-related questionnaires in 153 cured DTC patients and compared the results with those of 113 healthy controls, selected by the patients themselves, as well as with 336 age- and gender-matched controls from other local studies. Duration of disease-free period varied considerably (0.3 – 41.8 years). Quality of life was impaired in DTC patients relative to the two control groups in 11 and 13 of the 16 subscales, respectively. The HRQoL parameters were not influenced by serum TSH levels, but were inversely affected by duration of cure. Although the representativeness of the control groups can be challenged, the authors concluded, that in DTC patients quality of life was restored after 12-20 years of cure (Hoftijzer et al.).

In our study, we focused on patients who represent a clear majority in everyday clinical practice. The median duration of follow-up was 11.6 years. We used the 15D multidimensional validated generic instrument (Sintonen 2001) instead of cancer- or other disease-specific questionnaires to assess HRQoL to be able to compare the results with those of the general population. The instrument is highly sensitive (Saarni et al. 2006, Moock and Kohlmann 2008) and combines the advantages of a profile and single index instrument. The control population was large, consisting of a sample of 6001 age- and gender-standardized Finnish subjects.

In this study, overall HRQoL index score did not differ from that of the general population and the slight numerical difference observed has no clinical importance. Of the single dimensions, DTC patients reported a significant impairment in sleep, speech and distress. Sleep disturbances could be attributed to exogenous subclinical hyperthyroidism, while the disturbances in speech are more difficult to explain. The study cohort comprised only five cases of vocal cord paralysis (0.015%). One possible explanation is xerostomia in DTC patients, due to radio-iodine therapy. However, with regard to discomfort and symptoms, DTC patients were significantly better off than the general population. The findings are somewhat unexpected and difficult to explain. One explanation might be that DTC patients benefit from the once-yearly contact provided by the surveillance scheme, as opposed to the general population. Another explanation may lie in the impact of subclinical hyperthyroidism on subjective well-being. Within the DTC patient group, a statistically significant inverse effect of age at the time of initial treatment on overall HRQoL was observe; no other significant effects of the parameters included in the model (gender, number of radio-iodine ablations, recurrence, daily dose of thyroxine, duration of follow-up and vocal paralysis) were noted.

In long-term follow-up, cured TNM stage I and II DTC patients did not suffer from overall impaired HRQoL compared with the general population. DTC patients demonstrate an age-related decline in HRQoL, which is compatible with that seen in the general population.

10 SUMMARY AND CONCLUSIONS

The major findings of this work are as follows:

- In this uniformly treated cohort of low-risk TNM stage I or II DTC patients (n=495) with median follow-up of 16 years, 51 patients (10.3%) experienced disease recurrence, a finding comparable with other large international series. The clear majority of recurrences occurred in the first 10 years after primary treatment. The finding may be useful in modifying follow-up protocols for low-risk DTC.
- Predictors of disease recurrence in a low-risk patient group after long-term follow-up are tumour infiltration at diagnosis and post-ablative positive thyroglobulin levels. These findings add to the growing body of evidence that response to primary therapy is a significant prognostic factor. This can be used to guide surveillance.
- BRAF V600E mutation is a common finding, but does not appear to correlate with disease recurrence after treatment with total thyroidectomy and RRA among low-risk patients.
- Health-related quality of life after extensive primary treatment of low-risk DTC and long-term follow-up remains comparable with that of an age-adjusted general population.
- The surveillance scheme in use for low-risk DTC patients at HUCH for 20 years has proven efficient and safe after long-term follow-up. The same principles have now been adapted also by many international centres.
- Neck US combined with serum TG measurement on thyroxine therapy is a reliable and efficient way of monitoring DTC patients who have undergone near-total thyroidectomy followed by radio-iodine ablation and are disease-free after primary therapy. For intermediate-risk and high-risk patients, surveillance must be tailored.

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