Universiteit
Leiden
The Netherlands

Differentiated thyroid carcinoma : treatment and clinical consequences of therapy

Hoftijzer, H.C.

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General introduction

Parts of this chapter will be published in Clinical Investigation volume 1, Issue 2 as the paper: Tyrosine kinase inhibitors in differentiated thyroid carcinoma: review of the clinical evidence

Hendrieke C. Hoftijzer, Ellen Kapiteijn, Tatiana Schneider, Guido C. Hovens, Hans Morreau, Hans Gelderblom, Johannes W.A. Smit

Contents

I. Introduction

Thyroid cancer is the most common endocrine malignancy; however it is still a low prevalent disease with an incidence of 2-10/100.000 persons per year. The incidence has increased during the last decades, and this trend appears to be continuing (1-3). In the Netherlands this represents approximately 320 new patients per year, with a 3 times higher incidence in women (4). However, the prevalence is higher because of a rather good prognosis (4).

Thyroid cancer is a heterogeneous disease which is classified into differentiated thyroid carcinoma (DTC), medullary thyroid carcinoma (MTC) and undifferentiated (anaplastic) thyroid carcinoma (ATC). Differentiated thyroid carcinoma is most common (95%) and includes papillary (80%), follicular (10-15%) and subtypes follicular variant of papillary thyroid carcinoma and Hürthle cell carcinoma. Mean age at diagnosis is between 45 and 50 year (5). The overall 10-year survival rates are about 90-95% (6). This is because of a combination of favorable biological (i.e. indolent) behavior of the tumor as well as the availability of effective therapy consisting of near-total thyroidectomy followed by radioactive iodine-131 (RaI) ablative therapy.

Once distant metastases have occurred, the prognosis of DTC becomes worse. This is the result of dedifferentiation of thyroid cancer cells. The subsequent loss of the ability to accumulate RaI leads to unresponsiveness to the only curative treatment option. Metastases are not immediately life threatening, but may impair quality of life considerably. In this situation, only palliative treatment options remain and include external beam radiation therapy or resection of symptomatic metastasis (7,8). Recently, increasing knowledge in tumor biology has led to the identification of potential targets and novel treatment options with tyrosine kinase inhibitors, including sorafenib and sunitinib (9,10). These multikinase inhibitors show promising results in patients with progressive metastatic DTC, refractory for RaI.

During routine follow-up for differentiated thyroid carcinoma patients are regularly withdrawn from thyroxine therapy to perform TSH stimulated whole body RaI scanning and measurement of thyroglobulin, a disease specific biomarker. This creates a state of controlled hypothyroidism. This and the fact that DTC patients are treated with TSH suppressive thyroxine replacement therapy makes DTC patients an interesting model to study the metabolic effects of thyroid hormone. There is no interference by endogenous thyroid hormone, because patients are treated with total thyroidectomy. Moreover there is no interfering effect from thyroid disease, like in patients treated with thyroxine for autoimmune thyroid disease.

In this introduction a general overview of DTC, the diagnosis, treatment and clinical consequences of therapy will be provided and the questions addressed in this thesis will be introduced.

II. Differentiated thyroid carcinoma

1. Pathogenesis

Human thyroid tumors originate from epithelial follicular cells or from parafollicular C-cells. Follicular cell-derived tumors represent benign adenomas, differentiated (follicular and papillary) and undifferentiated (anaplastic) carcinomas. Genetic alterations are involved in the pathogenesis of thyroid carcinoma. The identification of these alterations is important for the diagnosis of DTC and also for the understanding of the pathophysiology of thyroid disorders (11-17). Recent developments have provided a detailed map of these genetic alterations (**Figure 1**).

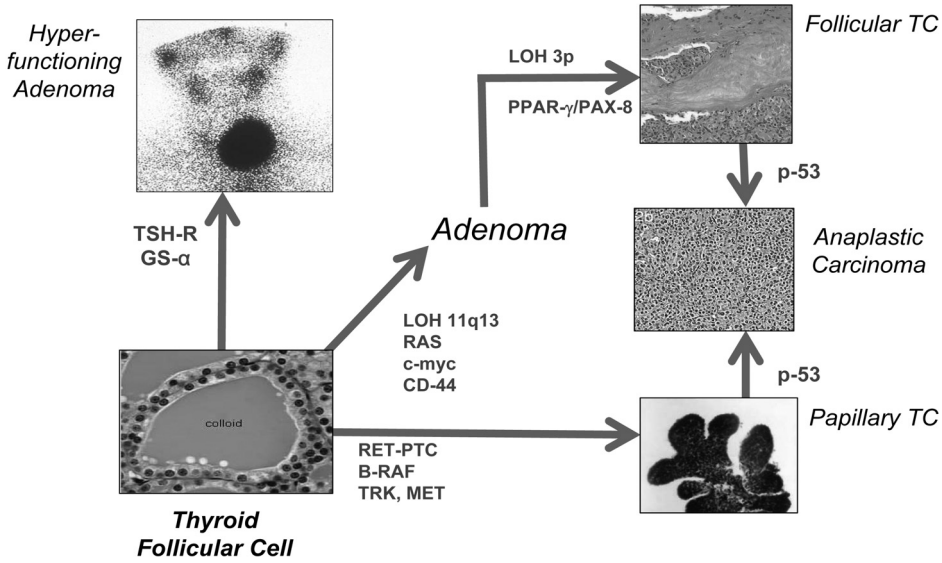

Figure 1
Pathogenesis of differentiated thyroid tumors

In DTC, genetic alterations that have been identified, and involve tyrosine kinase signaling pathways (12,15,16). In nearly all cases of papillary thyroid carcinoma (PTC), genetic defects involving the RET, RAS, and RAF protein kinase signaling cascade are identified. The BRAFV600E mutation has been found in 29–69% of PTC and has been associated with aggressive features including extrathyroidal extension and advanced stage (18). Translocations of RET observed in PTC result in a chimeric protein consisting of an activated RET tyrosine kinase domain (12,17,19-30).

Follicular thyroid carcinomas (FTC) frequently harbor mutations in one of the three RAS genes. The RET–RAS–RAF pathway is interconnected with the epithelial

growth factor receptor (EFGR) activated cascade that among others leads to vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) synthesis. Therefore, compounds targeting the activated RET–RAS–RAF pathway and beyond may be effective in non-RaI avid DTC. Other genetic alterations in FTC include PAX8-PPAR-gamma rearrangement. This is a unique combination of genes that traditionally are associated with thyroid development (PAX-8) and cell differentiation and metabolism (PPAR-gamma) (13, 31). This chimeric protein acts as a dominant negative competitor for PPAR-gamma and is associated with more aggressive growth and propensity for invasion (31). The follicular variant of PTC (FVPTC) shares some of the molecular features of follicular tumors, but less common also BRAF mutations are reported (11). Anaplastic carcinomas are frequently associated with mutations of the p-53 tumor suppressor gene (32).

The genetic alterations involved in the pathogenesis of DTC result in loss of thyroid specific gene expression and loss of thyroid specific protein expression. Thyroid peroxidase (TPO), which liberates iodide for addition onto tyrosine residues on thyroglobulin for the production of thyroxine (T_4) or triiodothyronine (T_3) is thought to diminish in an early phase. The Sodium-Iodide-Symporter (NIS) expression is subsequently lost. Herewith, the thyroid cell loses its ability to accumulate iodide, and thus becomes refractory for RaI therapy.

2. Diagnosis

Most differentiated thyroid carcinomas present as asymptomatic thyroid nodules. Carcinoma should be suspected if a hard irregular thyroid nodule is found, ipsilateral lymph nodes are enlarged and/or there is a history of progressive increase of the size of the nodule (5). Despite increasing standards of imaging techniques like ultrasound, fine needle aspiration (FNA) is still the procedure of choice in patients presenting with a thyroid nodule (33). The sensitivity of FNA for DTC is 90-95%. The specificity is lower (60-80%) when all patients with a non-benign FNA are referred for surgery (34). It is difficult to make the distinction between benign and malignant follicular tumors by FNA, since the essential criterion for FTC is capsular invasion, which cannot be determined by cytology. In addition, the distinction between a follicular adenoma and a follicular variant of a papillary thyroid carcinoma (FVPTC) is also difficult, because the crucial criterion here is the aspect of the nuclei. The consequence is that 70-80% of the patients with suspicious results from FNA, who undergo a hemithyroidectomy, have a benign tumor (35). The use of molecular markers (e.g. BRAF, RAS, RET/PTC, PAX8-PPARgamma or galectin-3) may be considered for patients with indeterminate cytology on FNA to help guide management (35-42).

After hemithyroidectomy the microscopical distinction between benign and malignant neoplastic thyroid nodules by conventional histology remains difficult as these lesions may share overlapping histological characteristics. Therefore, it is important to identify new markers to distinguish benign from malignant thyroid tumors. In recent years, several immunohistochemical markers have been studied to improve the differential diagnosis of thyroid lesions, using both candidate markers and unbiased approaches (43-54).

The expression of retinoid receptors may be interesting for the differentiation between benign and malignant thyroid tissues. Retinoids are important for growth, differentiation, and morphogenesis in vertebrates (55). Retinoids are derivatives of vitamin A (i.e. retinol). Retinoid receptors belong to the family of nuclear receptors and can be distinguished in retinoic acid receptors (RAR) and retinoid X receptors (RXR). According to the literature, retinoid receptors appear to be differentially expressed in benign and malignant thyroid tissues, the general picture being decreased expression of retinoid receptor subtypes in thyroid cancer (56-62), which may also have therapeutic implications (7,57,61,63-65) **(Chapter 2)**.

After primary diagnosis, the Tumor-Node-Metastases classification system (**Table 1 and Table 2**) is used for staging of the disease. This system is based on pathologic findings and divides patients into four stages (**Table 3 and Table 4**), with progressively poorer diagnosis and survival with increasing stage.

In studies in this thesis, the 5th edition of the TNM classification system is used. Recently, the 6th edition has become available (66). The most important difference with the 5th edition is the fact that the dimension of T1 has been extended to 2 cm and that tumors with limited extrathyroidal extension are designated T3 instead of T4, which

Table 1: TNM Classification system 5th edition

T0	No evidence of primary tumor
T1	Tumor 1 cm or less in greatest dimension limited to the thyroid
T2	Tumor > 1 cm, but not more than 4 cm in greatest dimension, limited to the thyroid
T3	Tumor more than 4 cm in greatest dimension limited to the thyroid
T4	Tumor of any size extending beyond the thyroid capsule
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
N1a	Metastasis in ipsilateral cervical lymph node(s)
N1b	Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node(s)
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 2: TNM classification 6th edition

T0	No evidence of primary tumor
T1a	Tumor 1 cm or less
T1b	Tumor more than 1 cm but not more than 2 cm
T2	Tumor > 2 cm, but not more than 4 cm, in greatest dimension limited to the thyroid
T3	Tumor > 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroidal extension
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels. All anaplastic carcinomas are considered T4 tumors
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
N1a	Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 3: TNM staging system 5th edition

Under 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
45 years and older			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

has implications for the prognosis (67). Also the classification of regional lymph node metastases has changed. Some experts propagate to continue the use of the 5th edition.

3. Initial therapy

a. Surgery

Recent guidelines of the European Thyroid Association (ETA) and the American Thyroid Association (ATA) give an up-to-date overview of the treatment strategies

Table 4: TNM staging system 6th edition

Under 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
45 years and older			
Stage I	T1	N0	M0
Stage II	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

for DTC (33,68). Initial therapy consists of near-total thyroidectomy, followed by RaI ablative therapy of thyroid remnants. Although there is still some controversy about the extent of thyroid surgery, there are strong arguments in favor of total or near-total thyroidectomy in all patients (69), this to permit accurate long-term surveillance for disease recurrence. Only very low risk patients (PTC, T1N0M0, unifocal, intrathyroidal) may be treated with hemithyroidectomy. In tumor stages of T2 and higher a total thyroidectomy is indicated (70-72). In these patients near-total thyroidectomy results in lower recurrence rates because many papillary tumors are multifocal and bilateral (73,74). During follow-up both measurement of serum Tg as a tumor marker and RaI whole body scanning are explicitly affected by residual thyroid disease and warrant near-total or total thyroidectomy (33). The argument against total thyroidectomy is that it increases the risk of surgical complications such as recurrent laryngeal nerve injury (2%) and hypoparathyroidism. The latter occurs in 1/3 of the patients after total thyroidectomy, but persists only longer than 3 months in 2% of the patients (68). The experience of the surgeon plays an important role in determining the risk of complications (75-77).

b. Radioiodine-131 ablation therapy

Controversy also exists about the routine use of RaI ablative therapy for thyroid remnants. There are three reasons for post-surgical RaI therapy. First, as already stated above, ablative therapy destroys remaining normal thyroid tissue, which increases the specificity of detectable serum Tg and whole body scanning (72,78). Second, the use of high dose RaI permits post ablative scanning to detect persistent carcinoma or metastatic disease (79,80). The third reason is that RaI may destroy microscopic metastasis and carcinomas, thereby decreasing the risk of recurrence (72,81,82).

A number of large, retrospective studies show a significant reduction in the rates of disease recurrence and cause specific-mortality after RaI ablative therapy (71,83,84-86). However, other studies show no benefit, especially not in patients with small (<1.5 cm), intrathyroidal tumors (6,71,87-90). The beneficial effect is probably only present in patients with high risk or irradical surgery (91). Moreover, various papers reported a relation between RaI therapy and non-thyroidal carcinoma, so the use of it should be applied carefully (92-97). Thus RaI ablation is not indicated in T1N0M0 disease, but still the treatment of choice in patients with high risk of recurrence/mortality, gross extrathyroidal extension of the tumor, documented lymph node metastases, incomplete tumor resection and distance metastases as proposed by recent ATA and ETA guidelines (33,68).

The efficacy of RaI therapy depends on the radiation dose delivered to the thyroid remnant tumor or metastases and these are based on responsiveness of DTC to TSH. Therefore high TSH levels have to be established by either thyroid hormone withdrawal or by therapy with recombinant human TSH (rhTSH) (98,99). In addition, RaI uptake is increased by depletion of plasma inorganic iodide before RaI therapy through a low iodide diet (100-102).

In addition, efficacy of RaI ablative therapy of thyroid remnants is comparable between rhTSH and thyroxine withdrawal (68,103,104). In recent American Thyroid Association guidelines for the treatment of thyroid cancer it is recommended that ablation can be performed following either thyroxine withdrawal or rhTSH (33), and rhTSH is especially advised for patients unable to tolerate hypothyroidism.

c. TSH suppressive therapy

After initial therapy, all patients with DTC are treated with high doses of thyroxine aiming at suppressed TSH levels. The rationale for this approach is based on the potential harmful effects of TSH on tumor recurrence (83,105,106). Thyroid cancer cells express the TSH receptor on the cell membrane and respond to TSH stimulation by increasing the expression of thyroid cancer specific proteins and by increasing the rate of cell growth (107). A recent analysis by our institution indeed showed that TSH levels are positively associated with thyroid cancer associated death and relapse (108). Long-term TSH suppression however, may be associated with harmful effects on various systems including bone metabolism (109-111), glucose metabolism (112,113), cardiac function including higher risk of ischemic heart disease and increased risk of atrial fibrillation (114,115) and quality of life (116-118).

The European Consensus on thyroid cancer (119,120) recommends that not all patients with DTC should be indiscriminately treated with TSH suppressive therapy, because of these negative effects of subclinical hyperthyroidism. Recent ATA thyroid cancer guidelines recommend initial TSH suppression below 0.1 mU/L for high risk

and intermediate risk thyroid cancer, while maintenance of TSH at or slightly below the lower limit of normal (0.1-0.5 mU/L) is appropriate for low-risk patients (33). In the future, TSH suppression may be achieved with thyroid hormone analogues that suppress pituitary TSH secretion with less effect on the cardiovascular system and the bone (121-123).

4. Follow-up

The purpose of follow-up protocols in DTC is the early detection of tumor recurrence or metastatic disease in order to optimize additional treatment. Most patients during follow-up have been cured definitely and have a low pre-test probability for recurrent disease. Therefore, the sensitivity of the diagnostic tests must be adequate to detect the few patients with evident remnant carcinoma whereas specificity must also be high to avoid unnecessary treatment in patients without recurrent disease. Recurrence is usually detected during the early years of follow-up, but may be detected later. Therefore, in our center thyroid carcinoma patients are followed-up for 15 years after initial diagnosis, with tighter screening during the first years.

a. Thyroglobulin

Thyroglobulin (Tg) is a glycoprotein that is produced only by normal or neoplastic thyroid follicular cells and is stimulated by TSH. In patients treated with total thyroidectomy and RaI ablative therapy, Tg should be undetectable. The type of analysis (RIA or immunometric assay) affects the interpretation of serum Tg values (124). The clinical interpretation of Tg is hampered by analytical problems. First, there is lack of universal standardization, leading to significant inter-assay variability and a high intra-assay variability. Second, "hook" effects which primarily affect the immunometric assay method can lead to inappropriately low-or normal range Tg values (125). Dilution of the serum can detect this problem. Third, the presence of Tg auto-antibodies can lead to under- or overestimation of the serum total Tg concentration (126-129).

The Tg auto-antibody interference is the most serious diagnostic problem affecting serum Tg measurements. The incidence of serum Tg auto-antibodies in DTC is approximately 15-30%. Despite these analytical problems, Tg measurements are still the basis in the follow-up in DTC, because in the absence of antibody interference, serum Tg has a high degree of sensitivity and specificity to detect thyroid cancer, with highest degrees following thyroxine withdrawal or rhTSH stimulation (100). A single TSH stimulated serum Tg <0.5 ng/mL has an approximate 98-99.5% likelihood for the identification of patients completely free of tumor (130,131).

Several studies have been performed to determine the diagnostic value of Tg measurements. The application of receiver operator (ROC) curves is essential, since

a chosen cut-off level is a subjective choice based on the balance between a desired percentage of missed recurrences *versus* unnecessary therapies. Therefore, in the European Consensus paper, it was recommended to define institutional Tg cut-off levels (119). High sensitive Tg assays lead to a higher sensitivity at the cost of a lower specificity (132). It is generally believed that high sensitive Tg assays cannot replace the need for TSH stimulated Tg measurements.

b. RaI whole body scanning, ultrasound and FDG-PET

The result of iodine-131 whole body scanning (WBS) depends upon the presence and the ability of thyroid-cancer tissue to take up iodine-131 in the presence of a high serum TSH, which is achieved by withdrawal of thyroxine supplementation for 4 weeks or by recombinant human TSH stimulation. WBS is most useful during follow-up when there is little or no remaining normal thyroid tissue. It may be of value in high or intermediate risk patients, but has no use in low-risk patients with an undetectable Tg and a negative ultrasound (120,133,134). Diagnostic RaI WBS has a much lower sensitivity than ultrasound and Tg measurement. Therefore the routine use of RaI scintigraphy in the diagnostic follow-up of low-risk DTC patients is no longer recommended (33,135).

Ultrasound combined with FNA has the highest sensitivity (94%) for local recurrence and lymph node metastases (134,136) and thus, ultrasound has an important role in the follow-up of DTC.

Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be indicated in patients with elevated serum Tg levels, in whom no RaI uptake is observed after diagnostic or therapeutic whole body scanning, especially in patients with invasive or metastatic Hürthle cell carcinoma (137-139). ATA guidelines recommend FDG-PET as a prognostic tool for staging in high risk patients with metastatic disease or at risk for rapid disease progression (33).

The sensitivity of FDG-PET may be marginally increased with TSH stimulation, but the clinical benefit of identifying additional small foci is yet to be proven (138). However, high FDG-PET uptake in large tumor masses may have an unfavorable prognostic significance (140).

c. Thyroxine withdrawal and recombinant human TSH

Serum Tg measurements, RaI ablation and RaI diagnostic whole body scanning are based on the responsiveness of DTC to TSH. TSH stimulated Tg measurements have superior diagnostic value in DTC compared to Tg measurements on thyroxine replacement therapy (100). High serum TSH levels can be achieved either by thyroxine withdrawal or intramuscular injection of rhTSH. In the first option, 4 weeks thyroxine withdrawal results in a controlled state of profound hypothyroidism with low FT4 and

high TSH. This is poorly tolerated by patients and has negative effects on multiple organs and systems: it exacerbates neuropsychiatric illness and cardiovascular disease, negatively influences lipid metabolism, increases atherosclerotic risks and thus negatively influences quality of life (141). There is also a theoretical disadvantage in thyroxine withdrawal, which states that high TSH levels may be unfavorable with respect to enhancement of tumor proliferation (105). High TSH level as a result of injections of rhTSH has less impact on quality of life (142). RhTSH is an adequate method to detect recurrence or metastases (98,99,143). Tg measurements during rhTSH have comparable accuracy with thyroxine withdrawal (144). The sensitivity and negative predictive value of Tg after rhTSH injections combined with ultrasound are 96.3% and 99.5% respectively (135). Also whole body scans performed after rhTSH injections have a similar sensitivity and negative predictive value compared to thyroxine withdrawal (98,99,143).

5. Therapeutic strategies for metastatic disease

a. Conventional treatment options

Distant metastases, usually in the bones and lungs, occur in approximately 10-15% of patients with DTC. Lung metastases are most frequent in young patients with papillary carcinomas. In general, bone metastases are more common in older patients and in those with follicular carcinomas. Metastatic thyroid cancer that has become inoperable or refractory to RaI therapy is associated with a poor 10 year survival of 5-10%. Because of the indolent character of DTC, metastases are not immediately life threatening, but may impair quality of life considerably (145).

In case of residual disease or metastases, surgery can be attempted when the lesion is accessible. In other cases high dose RaI therapy will be given in patients that accumulate RaI. The remission rate in pulmonary metastases treated with RaI is ~50%, varying from 90% in patients with microscopic metastases to only 10% in macronodular disease. The remission rates of bone metastases are worse, varying between 7 and 20% (5,146). The major problem in this category of patients is the dedifferentiation of thyroid cancer and with that the diminished or lost ability to accumulate RaI. Only palliative treatment options remain. These include external beam radiation therapy and chemotherapy, which have limited success (147).

External beam radiation can be used as palliative therapy in locally advanced disease and can reduce pain of bone metastases or dyspnea in case of airway obstruction. Many conventional chemotherapeutic protocols have been tried in progressive thyroid carcinoma, with overall disappointing results. The most frequently tested agent is doxorubicin. Doxorubicin alone or in combination with cisplatin and bleomycin may induce temporary remissions or stationary disease in about 30-50% of the

patients (147,148). Furthermore, responses are typically short-lived and associated with a high degree of toxicity (149,150).

b. Experimental additional treatments

Lithium has been associated with increased trapping of iodine by the thyroid gland, without impairing iodine uptake, thus enhancing RaI retention. However, despite an increase in RaI uptake in tumor deposits, there are no data that demonstrate a better outcome of patients treated with lithium as an adjunct to RaI therapy (151-152).

PPAR-gamma agonists have been introduced as anti-diabetic agents. Their proposed mechanism is the differentiation of pre-adipocytes, thereby increasing the fatty-acid storing capacity of adipose tissue. Altered expression of PPAR-gamma and *in-vitro* beneficial effects of PPAR-gamma agonists have been described in a number of malignancies. Although PPAR-gamma agonists showed promising results in pre-clinical models for thyroid cancer, they do not result in clinically benificial response (153).

Retinoids are derivates of vitamin A, and are important for growth, differentiation and morphogenesis in vertebrates (55). Beneficial effects of retinoids have been reported *in-vitro* in thyroid carcinoma (63,154-156) including increased NIS mRNA expression and iodine uptake in some thyroid cancer cell lines (154). Interestingly, the promoter of the NIS gene has a retinoic acid responsive element (157). A limited number of human studies have been performed on the effects of retinoids on RaI-131 uptake and reported variable results (64,65,158,159). The main conclusion however is that unfortunately retinoids are not able to restore susceptibility to RaI therapy (7).

c. Future treatment options

As a result of the increasing knowledge of the biologic mechanisms of thyroid cancer pathogenesis and progression, therapeutic agents that could target these mechanisms have been identified. **Table 5** gives an overview of the literature addressing the results of studies on tyrosine kinase inhibitors and DTC.

The anti-EGFR compound gefitinib was not successful in 27 patients with DTC, medullary and anaplastic thyroid carcinoma (160). In a phase II study in 60 thyroid carcinoma patients with various histologies, the VEGFR inhibitor axitinib showed a partial response of 30% (median progression free survival (PFS) 18 months) (161). Recently, 3 phase II studies have been published, using multi-kinase inhibitors (9,10,162). Motesanib diphosphate induced a partial response in 14% of 93 DTC patients (median PFS 40 weeks) (162). Sunitinib, an inhibitor of RET, VEGFR and PDGFR induced a response rate of 13% and 32 % in DTC and MTC patients (163, 164).

Two studies have been published using sorafenib. Sorafenib (BAY 43-9006) is an inhibitor of RET, C-RAF, wild-type and mutant (V600E) BRAF, VEGFR1, -2, -3, Flt3, and

Table 5: Literature on tyrosine kinase inhibitors in DTC

Drug	Target	Tumor type	Number of patients	Response Rate (%)	Stable Disease (%)	Progression free survival	Reference
Gefitinib	EGFR-RET	DTC + MTC	18 + 4	0%	24% (>24 weeks)	16 weeks	Pennell et al. (160)
Axitinib	VEGFR	DTC	45	31 %	42 %	18 months	Cohen et al. (161)
Motesanib	RET- PDGF -VEGFR-KIT	DTC	93	14 %	35% (>24 weeks)	40 weeks	Sherman et al. (162)
Sunitinib	RET, VEGFR, PDGFR	DTC	37	13 %	68 %	-	Cohen et al. (163)
		DTC + MTC	26 + 7	32 % (7 CR)	-	-	Carr et al. (164)
Pazopanib	VEGFR, PDGFR	DTC	26	32%	65 %	12 months	Bible et al. (167)
Sorafenib	RET-RAS-RAF-VEGF-VEGFR-PDGF-cKIT	DTC	41	15 %	56% (>24 weeks)	15 months	Kloos et al. (10)
			30	23 %	53 %	79 weeks	Gupta et al. (9)

c-KIT. In the first study, including DTC, anaplastic and medullary thyroid carcinoma patients, sorafenib induced a partial response in 23% (median PFS 79 weeks) (9). In the second study, including patients with DTC and anaplastic thyroid carcinoma, a partial response was observed in 11% (median PFS 4.5–16 weeks) (10). As bone metastases of DTC are poorly responsive to RaI, the response of bone metastases to the above-mentioned therapies is of interest. However, there are no separate analyses for patients with bone metastases in the above-mentioned studies.

In DTC, a relationship has been identified between genetic alterations in the RET, RAS, RAF cascade and loss of NIS expression (165,166). Interestingly, in an *in-vitro* study, sunitinib was able to reinduce NIS expression in RET/PTC transformed thyroid cells (168). In addition, sunitinib also increased RaI uptake in FRTL-5 cells. We therefore hypothesized that treatment with a multiple kinase inhibitor not only reduces tumor progression, but may also restore RaI uptake in non-RaI avid DTC. Therefore, we performed a single arm phase II trial to determine the efficacy of sorafenib in patients with iodine refractory metastatic DTC, focusing on the reinduction of RaI uptake and the efficacy in bone metastases **(Chapter 3)**.

Therapy with tyrosine kinase inhibitors is associated with alterations in thyroid hormone parameters. Sunitinib has been associated with hypothyroidism in 14–85% of the patients (169-174) and in some patients it induced hyperthyroidism (174-176). Both sunitinib induced hypothyroidism and hyperthyroidism may be caused by destructive thyroiditis, but other mechanisms, such as interference of sunitinib with thyroid peroxidase (177) or inhibition of thyroidal vascularization leading to thyroid

atrophy (178,179), have been proposed. Likewise, sorafenib was associated with TSH elevation in 18% of patients with metastatic renal cell carcinoma (180).

All these studies are performed in patients with intact thyroid function. However, thyroid function abnormalities have also been observed during therapy with imatinib (181,182), motesanib (162), and sorafenib (9) in athyreotic patients treated for medullary thyroid carcinoma and non-medullary thyroid carcinoma. Because an increased need of thyroxine is observed in athyreotic patients who are treated with tyrosine kinase inhibitors, the mechanisms of hypothyroidism may include alterations in thyroid hormone metabolism. Stepwise deiodination is the major route of thyroid hormone degradation and is mediated by iodothyronine deiodinases (D1, D2, and D3) (183) and by hepatic conjugating enzymes (184). To address this subject, we studied the effect of sorafenib on peripheral thyroid hormone metabolism in athyreotic humans **(Chapter 4)**.

III. Consequences of treatment of thyroid carcinoma

Patients with DTC who are treated with total thyroidectomy and RaI ablative therapy become completely dependent on exogenous thyroid replacement therapy. Because of the favorable effects on tumor recurrence, patients used to be treated with TSH suppressive doses of thyroxine (see *TSH suppressive therapy)* for approximately 15 years. Whereas this long-term TSH suppression is associated with an overall better prognosis (108,185), this subclinical hyperthyroid state is associated with deleterious effects on the cardiovascular system (114,115,186,187), carbohydrate metabolism (112,188) and psychological well-being (116,118,189,190).

During follow-up, DTC patients are regularly withdrawn from thyroxine therapy to evaluate recurrence and disease state with TSH stimulated whole body scintigraphy and Tg measurement. This creates a state of controlled hypothyroidism, which can exacerbate neuropsychiatric illness and cardiovascular disease, negatively influences lipid metabolism, and increases atherosclerotic risks and also has an impact on quality of life. The long-term subclinical hyperthyroidism combined with episodes of short-term hypothyroidism make DTC patients an interesting model to study the metabolic effects of thyroid hormone. Also, there is no interference by endogenous thyroid hormone, because patients are treated with total thyroidectomy. Moreover there is no inference from thyroid disease, like in patients treated with thyroxine for autoimmune thyroid disease.

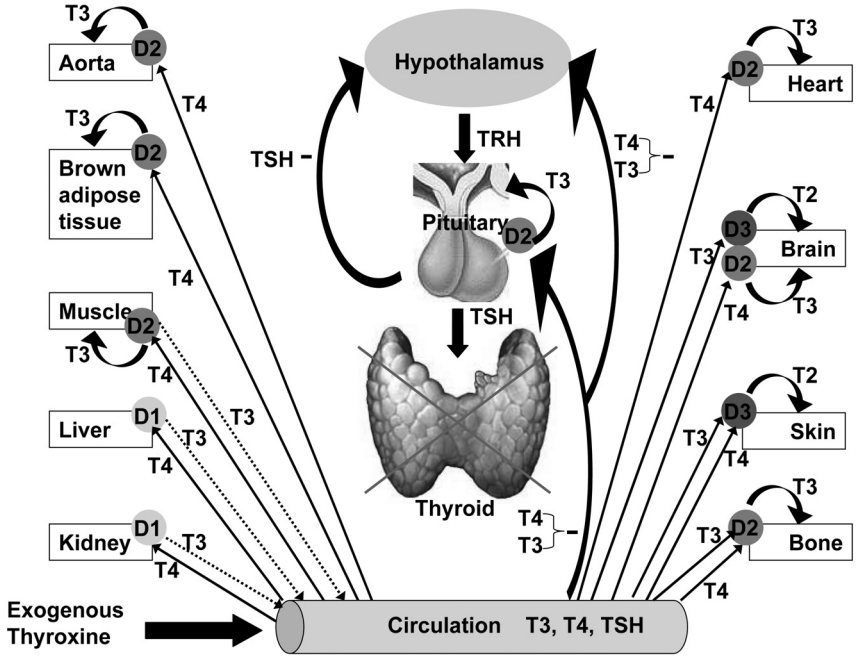

Figure 2
Thyroid hormone production and homeostasis in thyroidectomized patients

1. Thyroid physiology

The production of thyroid hormones is regulated by the hypothalamus-pituitary-thyroid axis (**Figure 2**). Thyrotropin releasing hormone (TRH), which is produced by the hypothalamus, stimulates the secretion of thyrotropin (TSH) by the anterior pituitary. TSH promotes the thyroid to synthesize the prohormone thyroxine (T4). Iodine is actively taken up by the thyroid gland by the sodium-iodide-symporter NIS. The expression and activity of NIS is controlled by TSH. Thyroglobulin, which is synthesized by the follicular cells, is then iodinated with one or two iodides to form monoiodotyrosine (MIT) or diiodotyrosine (DIT). This process is catalyzed by the enzyme thyroid peroxidase (TPO). Two DIT molecules are then coupled to form T4 and one DIT and one MIT are coupled to form T3. The thyroid secretes 90% T4 and 10% T3. T3 is the active form of thyroid hormone. The majority of T3 is formed after conversion of T4 in T3 in peripheral tissues like liver, kidney and muscle. T4 and T3 have a negative feedback mechanism on TRH secretion by the hypothalamus and the TSH production by the pituitary.

Peripheral thyroid metabolism is mainly regulated by the iodothyronin deiodinases D1, D2, and D3 (183,191) **(Figure 2**). D1 is present in the thyroid, liver and kidneys. It converts T4 to T3, and is involved in the serum T3 production. In addition, it plays a role in the breakdown of rT3 (192,193). D2 catalyzes local T3 production

in various tissues. It is present in brain, skeletal muscle, thyroid, pituitary, brown adipose tissue, aortic smooth muscle cells, osteoblasts and the heart (194-196). In the brain, D2 is expressed mainly in astrocytes in the cerebral cortex, hippocampus and amygdala (197). D2 in skeletal muscle may also contribute to plasma T3 production. D3 inactivates T3 and T4 and thus regulates the clearance of T3 and T4. It is present in the brain, skin, placenta and fetal tissues. It is thought that it contributes to thyroid hormone metabolism by protecting tissues from excess thyroid hormone. The deiodinases adjust the thyroid hormone levels of individual tissues in response to various conditions.

Several polymorphisms in D1 and D2 have been described, of which some are associated with circulating levels of T4, T3 and TSH (198-200), with most studies investigating the consequences of the D2-Thr92Ala polymorphism (rs225014). Two polymorphisms in the D1 gene, D1-C785T (rs11206244) and D1-A1814G (rs12095080), have been associated with changes in the balance of thyroid hormones in the serum, with raised T3, low T4 and low rT3 levels, but these changes have not been associated with differences in TSH. This implies that the net effect is perceived by the hypothalamus and pituitary as "neutral" (192,201,220).

Controversy exists about the functional implications of the D2-Thr92Ala polymorphism, which has been associated with a decreased D2 activity in some *in-vitro* experiments (198) but not in others (199,200). So far no associations are found between the D2-Thr92Ala polymorphism and serum thyroid hormone levels in studies in healthy subjects (192,198-200).

Torlontano *et al.* reported in thyroidectomized differentiated thyroid carcinoma patients that homozygous carriers of the D2-Ala92 allele need higher dosages of T4 (202). This difference was most prominently observed in the group with near-suppressed TSH (TSH values between 0.1 and 0.5 mU/l). This study has various limitations, because actual values of serum TSH levels for wild type and homozygous groups within the near-suppressed TSH group are not given. It is, therefore unclear whether TSH levels in both groups are indeed identical, which would be a key finding to ascribe the slight differences in thyroxine dose to the polymorphism. We therefore performed a study to reconfirm the findings of Torlontano *et al.* We studied the association between the D2-Thr92Ala polymorphism and thyroid hormone levels and T4 dosage in 154 patients treated for DTC and 141 patients substituted with T4 for Hashimoto thyroiditis **(Chapter 5)**.

In healthy blood donors the D2-ORFa-Asp variant (rs12885300) was associated with lower levels of serum T4, fT4 and rT3, but not with plasma T3 and TSH levels (203). This suggests that the D2-ORFa-Asp polymorphism leads to higher activity of D2 at the pituitary level. However, this association was not seen in elderly men (203).

Intraindividual variation in serum T4, T3 and TSH is narrow; however there is a considerable interindividual variability (204). A large body of evidence suggests that every individual has a unique thyroid function setpoint, compatible with a genetic influence on the regulation of the pituitary-thyroid axis (204-206). We hypothesized that polymorphisms in D1 and D2 could influence the setpoint of the hypothalamus-pituitary-thyroid axis. We tested this hypothesis in 151 patients treated for differentiated thyroid carcinoma (DTC). During follow-up of DTC, patients are treated with thyroxine substitution therapy in a dose intended to suppress TSH level, which results in a constant and precisely measurable supply of T4. During this period they regularly come for routine measurements of TSH and FT4, moreover they are regularly withdrawn from thyroxine to perform TSH stimulated radioactive iodine-131 whole body imaging, which leads to a wide individual range of combined measurements of TSH and FT4. These patients are therefore an ideal group to assess the relationship between polymorphisms in deiodinases and the setpoint of the hypothalamus-pituitary-thyroid axis **(Chapter 6)**.

2. Bone metabolism

The involvement of thyroid hormone in bone metabolism has been well documented clinically, ranging from decreased skeletal development in childhood hypothyroidism (207-209), accelerated growth in childhood hyperthyroidism (210) to an increased risk for osteoporosis in overt and subclinical hyperthyroidism (109,211-213).

Although clinical observations suggest a clear involvement of thyroid hormone in bone metabolism, the molecular mechanisms by which thyroid hormone acts on bone is so far only been partially uncovered. T3 promotes osteoblastic proliferation, differentiation and apoptosis and, by induction of interleukin 6 (IL-6), prostaglandins, and RANKL, probably also promotes osteoclast formation and activation. This suggests that osteoblasts are the primary target cells for T3 in the regulation of bone remodeling (208,209,213-217). A functional role of TSH on skeletal development and metabolism has been proposed on the basis of data obtained in animal studies (218-220) and in humans as well (221). This was however disputed by data obtained in thyroid hormone receptor (TR) deficient mice, which indicated that bone remodeling was predominantly mediated by T3 via TRalpha (222,223). It has also been reported recently that in humans there is a significant association between bone mineral density (BMD) and serum thyroid hormone concentrations rather than TSH (224).

Designing a study to address the potential role of deiodinases, including D2 on skeletal metabolism is difficult in humans. The study of the effects of functional D2 polymorphisms on BMD and bone turnover in humans may shed light on this role. Interestingly, a study by Canani *et al*. reported (198) that the maximal velocity of D2

was decreased by 3 to 10-fold in thyroid and skeletal muscle of carriers of the D2-Thr92Ala polymorphism. This effect was observed in the absence of differences in D2 mRNA level or in the biochemical protein properties of the 92Ala allele. Therefore, it was suggested that either a functionally relevant single nucleotide polymorphism occurs in linkage disequilibrium with the Thr92Ala polymorphism or the 92Ala allele affects protein translation or stability.

We therefore performed a study in an attempt to elucidate a potential role for D2 in skeletal metabolism and BMD by evaluating the relationship between the D2 Thr92Ala polymorphism, BMD and bone turnover markers in cured thyroidectomized differentiated thyroid carcinoma patients receiving thyroid hormone substitution. This human model has the advantage of having strictly regulated serum thyroid hormone levels which are kept in a relatively narrow range **(Chapter 7)**.

We have also designed a study in an attempt to discriminate between potential effects mediated by decreased thyroid hormone levels from those mediated by increased TSH levels in a human model in which the reciprocal relationship between thyroid hormones and TSH was interrupted. To this effect, we studied parameters of bone metabolism after parenteral administration of recombinant human TSH (rhTSH) resulting in exogenously increased TSH levels while preserving normal thyroid hormone levels by uninterrupted thyroid hormone substitution in athyroid differentiated thyroid carcinoma (DTC) patients. We studied the same parameters in age-, gender- and BMI matched athyroid DTC patients during short-term thyroxine withdrawal, resulting in decreased thyroid hormone levels and endogenously increased TSH levels, and after reestablishment of thyroid hormone substitution **(Chapter 8)**.

3. Cardiac function

Thyroid hormone has profound effects on the cardiovascular system. Hyperthyroidism induces cardiac arrhythmias, left ventricular (LV) hypertrophy and diastolic dysfunction, and enhances systolic function (225-227). Subclinical hyperthyroidism resulting from TSH suppressive thyroxine therapy, is associated with increased heart rate and supraventricular arrhythmias, including atrial fibrillation, increased LV mass (LVM) with a slightly enhanced systolic function, and diastolic dysfunction. Diastolic dysfunction is at least partly reversible after restoration of euthyroidism and is associated with an increase in mortality (114,228-230). Conversely, hypothyroidism is associated with bradycardia, mild hypertension, increased peripheral cardiovascular resistance, heart failure (225,227,231), decreased cardiac output and diastolic dysfunction (225,227,232-234). Long-standing hypothyroidism can even result in asymmetrical septal hypertrophy (235) and pericardial effusion (230). Hypothyroidism is also associated with coronary artery disease, presumably because of associated hyper-

cholesterolaemia, hypertriglyceridaemia and hypertension (225,227,236). Thyroxine substitution reverses most cardiovascular alterations associated with hypothyroidism (227,230,231,237).

The consequences of acute hypothyroidism during thyroxine withdrawal on cardiac function have been investigated in only a few studies. The results of those studies have been inconclusive, varying from mainly decreased diastolic function to mainly altered systolic function (238-246). In these studies, without control groups, these parameters are measured by different techniques (echocardiography, radionuclide imaging), without blinding the observers with regards to treatment modalities. Therefore, we performed a prospective study in a homogeneous group of athyreotic DTC patients to assess the impact of overt hypothyroidism induced by short-term thyroxine withdrawal on cardiac function measured by a new sophisticated echocardiography technique: tissue Doppler imaging (TDI). Cardiac parameters of the patients are compared to a matched group of controls without cardiovascular co-morbidities **(Chapter 9)**.

4. Quality of life

Differentiated thyroid carcinoma is associated with an excellent medical prognosis, with 10-year survival rates reaching 90-95 %. The excellent prognosis and the moderate invasiveness of the initial therapy may implicate that quality of life in cured DTC patients may be relatively normal. On the other hand, the awareness of having a malignant disease and the TSH suppressive thyroxine replacement therapy may lead to a decreased quality of life (114,228,247). Only a few studies have evaluated quality of life in cured DTC patients (117,118,189,190,248). These studies are limited by small patient numbers (118,189), a limited number of quality of life parameters (117,248), and/or the absence of a healthy control group (117,189,190). Studies that focused on the relation between the level of TSH suppression and quality of life in DTC patients are inconclusive because of small patient numbers, selection of patients with symptoms of hyperthyroidism or selection of patients with a long duration of cure (100,228). For that reason, we investigated quality of life in a large cohort of cured DTC patients, compared to healthy controls matched for age, gender and socioeconomic status. In addition, determinants of quality of life, including TSH level were investigated **(Chapter 10)**.

IV. Outline of this thesis

In **Chapter 2** we evaluate the diagnostic value of the expression of retinoic acid receptors (RAR) and retinoid X receptors (RXR) expression for the differential diagnosis

of thyroid neoplasms. To improve especially the differentiation between benign and malignant thyroid tissues we defined optimal semi quantitative cut-off levels using ROC analysis and hierarchical cluster analysis.
In **Chapter 3** we describe a single arm phase II trial to determine the efficacy of sorafenib treatment in patients with iodine refractory metastatic DTC, focusing on the reinduction of RaI uptake and the efficacy in bone metastases.
Chapter 4 focuses on the observation of changes in thyroid hormone levels during treatment with sorafenib (described in chapter 3). We did this, in order to elucidate the mechanism behind the tyrosine kinase induced thyroid function alterations.

The remainder of this thesis describes the clinical consequences of exogenous subclinical hyperthyroidism during TSH suppressive therapy and of short term hypothyroidism during thyroxine withdrawal in order to study the metabolic effects of thyroid hormone.
Deiodinase type 2 catalyzes local T3 production in various tissues. Controversy exists about the functional implications of the D2-Thr92Ala polymorphism. In **Chapter 5**, we studied the association between the D2-Thr92Ala polymorphism and thyroid hormone levels and thyroxine dose in 154 patients treated for DTC and 141 patients substituted with T4 for Hashimoto thyroiditis.
It is suggested that every individual has a unique thyroid function setpoint, compatible with a genetic influence on the regulation of the pituitary-thyroid axis. **Chapter 6** studies the influence of polymorphisms in D1 and D2 on the setpoint of the hypothalamus-pituitary-thyroid axis.
Chapter 7 investigates the relationship between the D2-Thr92Ala polymorphism and bone mineral density and bone turnover parameters.
Controversy exists about whether high TSH or low FT4 influences bone metabolism in hypothyroidism. In **Chapter 8**, we describe a prospective study which investigates the effects of high TSH levels, either achieved by hypothyroidism or by recombinant human TSH on bone metabolism. Therefore we will be able to discriminate between potential effects mediated by decreased thyroid hormone levels *versus* those mediated by increased TSH.
In **Chapter 9**, we show the effects of short term overt hypothyroidism, 4 weeks after thyroxine withdrawal on cardiac function.
Chapter 10 describes quality of life in a large cohort of cured DTC patients compared to age, gender and socioeconomic status.

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