Differentiated thyroid carcinoma : nuclear medicine studies

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Chapter 1

General introduction and aims of this thesis

Introduction

Differentiated thyroid carcinoma (DTC) is a rare disease with unique features. The central role of therapy with radioiodine (RaI)-131 (^{131}I) for instance is unique for DTC. Another special aspect is that despite the good prognosis, a substantial proportion of patients develop metastases, that are not life threatening but may impair quality of life considerably, a situation that is not often encountered in general oncology.

The focus of the present thesis is the therapy with ^{131}I, and long term follow-up of patients with DTC. Although many aspects of diagnosis, initial therapy and follow-up procedures have been covered in recently published guidelines and consensus papers (published by the American and European Thyroid Associations and by the Dutch CBO thyroid carcinoma consensus group (www.cbo.nl) [1;2], many questions with regard to the clinical approach to patients with DTC still remain to be answered. This thesis addresses some important clinical questions, related to the application of conventional (^{131}I) and experimental therapies with radionuclides in DTC.

Characterization of thyroid carcinomas

Human thyroid tumors are derived either from epithelial follicular cells or from parafollicular C-cells. Follicular cell-derived tumors represent a wide spectrum of lesions, ranging from benign adenomas to differentiated (follicular (FTC) and papillary (PTC) and undifferentiated (anaplastic) carcinomas.

Thyroid cancer, comprising less than 1% of all cancers in the Netherlands, has a good prognosis in general. In the Netherlands, the incidence of DTC is 2 per 100.000 inhabitants per year [3;4]. However, the prevalence of patients with DTC is relatively high due to the good prognosis (approximately 4000 patients in the Netherlands) [3]. In general, 80-90% of newly diagnosed thyroid carcinomas are differentiated tumors with a median age at diagnosis of 45 to 50 years [5]. These tumors are two to four times as frequent in women as in men.

DTC has a relatively favorable prognosis with a 10-yr survival of 70-95% (Table 1). This high survival rate is the result of the biological behavior of most of these tumors and the efficacy of primary therapy, consisting of surgery and RaI therapy. However, when distant metastases occur, the prognosis is worse as the results of RaI therapy, which is virtually the only curative treatment option, are moderate. Depending on the localization and size these metastases may affect quality of life for years.

Table 1. Overview of thyroid carcinomas [6;7].

Type of tumor	Frequency (%)	Age at diagnosis (yrs.)	Metastases	10-yr survival (%)
Papillary	65	5-70	Lymphatic	90-95
Follicular	20	30-70	Haematogenous	70-80
Medullary	5-10	5-70	Lymphatic	50-60
Anaplastic	5-10	>50	Both	<5

PTC mainly infiltrates diffusely into the thyroid gland and once they metastasize, it is generally to the locoregional lymph nodes. Pathological examination reveal papillary structures and in approximately 80% also follicles. Most of the PTC, are not encapsulated. FTC have almost always a tumor capsule and, in contrast to PTC, metastasize haematogeneously. A more aggressive variant of FTC is the so-called Hürthle-cell carcinoma, which has a poor capacity of RaI accumulation. Most DTC produce thyroglobulin (Tg).

The tumor-node-metastases (TNM) classification system is based primarily on pathologic findings and separates patients into four stages, with progressively poorer survival with increasing stage [8]. Recently, the 6th edition of the TNM system has become available [9]. The most important difference with the 5th edition is the fact that the dimension of T1 has been extended to 1.5 cm and that tumors with limited extrathyroidal extension are designated T3 instead of T4, which has implications for the prognosis of DTC [10]. Therefore, some experts

propagate to continue the use of the 5th edition. In the studies in this thesis the 5th edition of the TNM staging system is used [11].

Initial therapy of DTC

In most patients with DTC, initial therapy consists of (near-) total thyroidectomy followed by ablation with ^{131}I for the thyroid remnants 4 to 6 weeks after surgery. The rationale for this strategy is to eliminate microscopic or gross residual tumor tissue in the thyroid remnant or outside the thyroid bed. Furthermore, ablation of the thyroid remnant increases the specificity of follow-up strategies for recurrent DTC. Once a complete ablation has been achieved, increasing Tg values and/or RaI uptake in the head and neck region or chest, two main sites for recurrences, are indicative for recurrent DTC. Although there is still some controversy about the extent of thyroid surgery, there are strong arguments in favor of total or near-total thyroidectomy (leaving only as limited thyroid tissue as is necessary to keep vital structures intact) in all patients [12]. Total or near-total thyroidectomy results in a lower recurrence rate than more limited thyroidectomy, because many papillary carcinomas are multifocal and bilateral [13;14]. Furthermore, total thyroidectomy facilitates total ablation with ^{131}I and reveals a higher specificity of Tg as a tumor marker. In low risk patients (those with T1N0M0 (5th Edition) papillary carcinomas, if unifocal), a hemi-thyroidectomy may be appropriate. A total thyroidectomy is indicated in tumor stages T2 and higher [15-17] The argument against total thyroidectomy is that it increases the risk of surgical complications such as recurrent laryngeal-nerve injury and hypoparathyroidism. However even with total thyroidectomy, some thyroid tissue may remain, as detected by pre-ablative scanning with ^{131}I.

Lymph node metastases are frequently found in patients (65%) with papillary carcinomas [5;15]. Among patients with follicular carcinomas, a small proportion of the patients (about 35%) have lymph node metastases. In some studies, the presence of lymph node metastases is considered as an independent

risk factor for recurrence of the tumor in both types thyroid carcinoma [17;18]. In another study, this was only found in patients with stages T3 and T4 papillary carcinoma [19]. However, modified lymph node dissection has not been shown to improve recurrence and survival rate [17;20], although this is debated by others [21]. Various forms of extended or radical surgery were related to better prognosis, but the results were not conclusive [17;18;22;23].

Although controversy exists about the routine application of ^{131}I for ablation of thyroid remnants, many clinics follow this procedure. There are several reasons for routine ablation after surgery [24]: (a) to enable detection of a carcinoma recurrence by RaI scanning; (b) RaI can destroy microscopic foci of carcinoma in the thyroid remnant; (c) possible carcinoma outside the thyroid bed may be detected and treated by RaI; (d) to improve the specificity of Tg as tumor marker of recurrent carcinoma all normal thyroid tissue has to be destroyed.

In patients with small (<1,5 cm) intrathyroidal tumors, the effect of thyroid ablation on recurrence and mortality rates is not clear [17;25]. In patients with tumor stages T2-4 without metastases, a favorable effect on recurrence appears to be present in a considerable number of publications, whereas a beneficial effect on survival is probably only been observed in patients with irradical surgery [17;18;22;26]. However, in a multivariate analysis in this group ^{131}I ablation therapy was a significant predictive factor for recurrence, but not for survival [22].

In addition, doubts have arisen about the safety of routine RaI ablation, and a recent paper suggested a relation between excess non-thyroidal malignancies and RaI [27;28]. This has led to a more careful positioning of RaI ablation in recent papers [2;29].

In conclusion, there is consensus about the efficacy of ^{131}I ablation therapy in patients with: (a) tumor stages T2-4; (b) evidence for remaining thyroid tumor remnants and (c) metastases [30;31].

Regarding the initial ablation strategies with ^{131}I, two general protocols are

commonly used in the Netherlands. The first one, the so-called uptake-related strategy (described in Chapter 2), is based on a 24-hour uptake measurement using a low activity of ^{131}I or Iodine-123 (^{123}I). The amount of RaI uptake measured in the neck region is categorized into three subgroups: >10%, 5-10% and <5% uptake resulting in ablation activities of 1100, 1850 and 2800 MBq of ^{131}I, respectively. As the uptake generally is supposed to represent the amount of thyroid tissue, it can be seen that in a larger remnant, a lower amount of activity is given. The rationale of this quantitative approach is to avoid unnecessary exposure [32] and locoregional side-effects, which may be caused when a high amount of activity is given in patients with large thyroid remnants [33;34]. In this regimen, no adjustments are made in the case of cervical lymph node metastases. The second ablation strategy, the so-called fixed-dose or tumor-related strategy (described in Chapter 3), is based on the initial tumor stage. A standard activity of 3700 MBq of ^{131}I is given in patients with T0-3, N0, M0 disease. In patients with T4 and/or N1 disease and in patients with M1 disease, activities of 5550 MBq and 7400 MBq are given respectively. This ablation strategy is irrespective of the 24-hour uptake measurement.

In most clinics a standard activity of 1200 to 4000 MBq of ^{131}I is given for thyroid ablation. A meta-analysis found that a single administration of about 1200 MBq failed to fully ablate the remnant (46%) more often than did 2800 to 3700 MBq (27%) [35;36].

The efficacy of ^{131}I therapy depends on the radiation dose delivered to the thyroid remnant or tumor [37]. The radiation dose is negatively affected by decreased uptake and the shorter effective half-life of ^{131}I in tumor tissue compared with normal thyroid tissue [38-40].

Strategies to increase RaI uptake include the establishment of high TSH values, either by thyroid hormone withdrawal or by therapy with recombinant human (rh) TSH [41;42]. Another method to increase ^{131}I uptake is to deplete the plasma inorganic iodine pool before ^{131}I therapy. Low plasma iodine

concentrations may increase the expression of the sodium iodine transporter which subsequently leads to increasing thyroid remnant RaI uptake [38;43;44]. Iodine depletion can be achieved by limiting iodide intake through a low-iodine diet (LID). The LID in our hospital involves 4 days of iodine restriction aiming at a maximum urinary excretion of 49 ug/day [45]. Many clinics now use a LID before thyroid ablation. Pluijmen *et al.* [46] concluded that LID during thyroid remnant ablation improves the efficacy of ablation.

Follow-up

In our institution, the efficacy of ablation therapy is evaluated after 6 months by RaI scintigraphy and Tg values after withdrawal of thyroxine treatment (during 4 weeks) or after intramuscular injection of rhTSH [42]. If any uptake is detected on the RaI total body scan (WBS) and/or serum Tg is detectable (i.e. above cut-off level) an additional treatment with ^{131}I is given. For routine diagnostic scans, 185 MBq ^{131}I is given followed by a WBS three days thereafter. Assuming an equivalent fractional uptake after the administration of a low diagnostic activity of ^{131}I, an uptake too low to be detected with 185 MBq may be detected after the administration of high therapeutic activities (6100 – 7400 MBq). This is the rationale for the administering of therapeutic activities in patients with elevated serum Tg concentrations, even if the results of diagnostic scanning are negative. The post-therapeutic WBS should be obtained four to seven days later [5].

If no uptake on WBS is detected and serum Tg is undetectable (i.e. below cut-off level), subsequent follow-up is based on Tg measurements during thyroxin therapy.

The goals of follow-up after initial therapy are to maintain an adequate thyroxine therapy and to detect and prevent persistent or recurrent thyroid carcinoma. Recurrences are usually detected during the early years of follow-up but may be detected later, even after more than 15 years after initial treatment.

The most important tools in follow-up protocols are serum measurements of Tg, diagnostic WBS and neck-ultrasound.

Tg is a glycoprotein that is produced only by normal or neoplastic thyroid follicular cells. It should not be detectable in patients who have undergone total thyroid ablation. The presence of thyroglobulin in such patients reveals the presence of persistent and/or recurrent disease. The type of analysis (RIA or immunometric assay) affects the interpretation of serum Tg values [47]. Tg auto-antibody (TgAb) interference, which can lead to under- or overestimation of the serum total Tg concentration, regardless to the type of method used [47-51] is the most serious specificity and sensitivity problem affecting serum Tg measurements. Auto-antibodies against Tg are present at high concentrations in sera from patients with autoimmune thyroid disorders (51-97%) and at low concentrations in healthy individuals [50]. The incidence of serum TgAbs in DTC is between 15 and 30%.

Therapy in metastatic disease

Distant metastases, usually in the lungs and bones, occur in 10 to 15% of the 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.

In case of residual disease or metastases, surgery can be attempted when the lesion is accessible. In other cases, ^{131}I therapy will be given in patients with metastases that take up RaI. The remission rate in pulmonary metastases treated with ^{131}I is ~50%, varying from 90% in patients with microscopic metastases to only 10% in macronodular disease [31;52;53]. The remission rates of bone metastases in the same studies are worse, varying between 7-20%. A major problem in this category of patients is the diminished or lost ability of thyroid cancer cells to accumulate RaI, indicated by a negative post-therapeutic WBS. In these cases the prognosis is poor, as alternative treatment options (external

radiotherapy or chemotherapy) have limited success [54]. Bone metastases may cause considerable pain and functional impairments. In addition, these bone metastases may become problematic, because these patients may still have a very long survival. Bone metastases may escape attention during WBS, as they may not accumulate RaI. Bone scintigraphy may show decreased or moderately increased uptake [55]. Bone metastases are often difficult to visualize on radiographs, at least in the initial stages.

The treatment of symptomatic bone metastases may be cumbersome, especially if the lesions do not accumulate ^{131}I. In such patients, external irradiation [31] or selective embolization of bone metastases [56-60] is needed. Palliative surgery can also be considered, when there are neurological complications. Surgery may also be useful to debulk large tumor masses.

Despite RaI, no conventional therapy is available in metastatic DTC where RaI uptake has been lost. Results of conventional chemotherapy are disappointing. The classical chemotherapeutic agent adriamycin (alone or combined with cisplatin and bleomycin) may induce temporary remissions or stationary disease in about 30-50% of the patients [54;61]. The same has been reported for paclitaxel [62]. However, most remissions last only a few months and at the cost of a considerable reduction in quality of life, thus leading to the recommendation that there is no place in principle for chemotherapy [1;63].

Therefore much attention is focused on experimental treatment options, which can be subdivided in redifferentiation therapy, novel agents such as tyrosine kinase inhibitors and experimental therapies with radiolabeled somatostatin analogues.

Redifferentiation

Epigenetic therapies

One of the mechanisms by which cells can block the expression of certain genes is by enzymes that methylate these genes or deacetylate the histones that

envelope a particular gene. In an in-vitro study in thyroid carcinoma, the demethylating agent 5-azacytidine led to re-induction of NIS expression, accompanied by RaI uptake in thyroid cancer cell lines [64]. In parallel, the histone deacetylase inhibitor Depsipeptide has been reported to reinduce NIS mRNA expression and RaI uptake in DTC [65;66], although toxicity may be a serious problem [67].

Retinoids

Retinoids are derivatives of vitamin A (*i.e.* retinol). Beneficial effects of retinoids have been reported in promyelocytic leukaemia and several types of carcinoma [68-70]. It has been suggested that retinoids have beneficial effects on iodide uptake in vitro and in humans. A limited number of human studies have been performed on the effects of retinoids on ^{131}I uptake with mixed results [71-75], all using the retinoic acid receptor (RAR) agonist 13-cis retinoic acid. Bexarotene (Targretin, Ligand Pharmaceuticals, San Diego) is a retinoid X receptor (RXR) agonist, which also induces RAR by transcriptional activation. [76]. A prospective controlled clinical trial to investigate the efficacy of this novel ligand Bexarotene in 12 patients with metastases of DTC and decreased or absent ^{131}I uptake showed that Bexarotene may partially restore ^{131}I uptake in some, but not all, metastases of DTC [77]. However, a clinical trial to study the effectiveness of high activities of ^{131}I together with Bexarotene in DTC patients demonstrated that this therapy did not result in restoration of susceptibility to RaI therapy [78].

Neovascularization

Molecular pathways involved in neovascularization have been demonstrated in thyroid carcinoma [79]. The cascade of approaches to target tumor-induced neovascularization has led to a number of promising compounds that are now being tested in clinical trials in prevalent tumors. Reports have been published on beneficial effects of anti-VEGF receptor antibodies in thyroid carcinoma cell-

lines [80] and endostatin in animal experiments [81]. A recently published clinical trial, including thyroid carcinoma patients was also successful [82]. Some compounds belonging to the class of tyrosine kinase inhibitors (see below) also inhibit angiogenesis by inhibiting VEGF production and/or activation of the VEGF receptor.

Tyrosine kinase inhibitors

Another intriguing development is the advent of tyrosine kinase inhibitors. The development of imatinib mesylate (Gleevec) is prototypical for the innovative design of modern drugs with the molecular pathogenic defect as a starting point. Following imatinib, other small molecules have been developed, aimed at other tyrosine kinase activated pathways such as the epithelial growth factor receptor (EGFR) activated pathway [83;84]. Activation of tyrosine kinase pathways is relevant for thyroid carcinoma. Several studies have been published reporting successful treatment with the tyrosine kinase inhibitors aimed at RET, vascular endothelial growth factor (VEGF) or the EGFR [85-87]. Recently, 2 studies have been published in which multiple target tyrosine kinase inhibitors were used [88] and sorafenib [89]. Both studies reported a promising response rate in metastatic DTC patients.

Radiolabeled somatostatin analogues

Another therapeutic modality in patients with ^{131}I non-responsive multiple metastases is the treatment with radiolabeled somatostatin analogues. In chapter 8 a study with high activities of ^{111}In-DTPA-octreotide is described. The therapeutic effect of ^{111}In-DTPA-octreotide on DTC metastases is based on the internalization of the radiolabeled octreotide through somatostatin receptors which are found in both papillary and follicular thyroid cancer [90]. Once in the cell, short-range Auger electrons emitted by the ^{111}In will cause DNA damage. The diagnostic value of ^{111}In-octreotide in thyroid cancer has already been

confirmed [91-94]. More recent reports have focused on somatostatin analogues labeled with β-particle-emitting radionuclides [95;96].

Aims of this thesis

Although many aspects of diagnosis, initial therapy and follow-up procedures have been covered in recently published guidelines and consensus papers, this thesis addresses some important clinical questions, related to the application of conventional (^{131}I) and experimental therapies with radionuclides in DTC. In this thesis, specific questions we focussed on are:

a) What is the short-term outcome of an uptake-related ablation strategy in differentiated thyroid cancer ? **(chapter 2)**
b) What is the difference in outcome between an uptake-related strategy and a fixed-dose strategy in thyroid remnant ablation? **(chapter 3)**
c) Is there a relation between the ablation failure and a pre-ablation 24-hour ^{131}I uptake measurement in DTC? **(chapter 4)**
d) Is it possible to predict the outcome of the uptake-related ablation strategy in differentiated thyroid cancer at the time of initial diagnosis? **(chapter 5)**
e) Is there a relation between the incidence of second primary tumors in thyroid cancer patients and treatment with RaI in the cohort studied? **(chapter 6)**
f) Is there a place for ^{111}In-DTPA-octreotide scintigraphy for the detection of non-functioning metastases from DTC during follow-up? **(chapter 7)**
g) Once the diagnostic value of ^{111}In-DTPA-octreotide scintigraphy has been established, is there also a role for this radiopharmaceutical in the treatment of RaI non-responsive thyroid cancer? **(chapter 8)**

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