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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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Chapter 2

**Radioiodine-131 in differentiated thyroid cancer:
a retrospective analysis of an uptake-related ablation
strategy**

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Abstract

In our hospital, a 24-h radioiodine-131 (^{131}I) uptake-related ablation strategy is used in patients with differentiated thyroid cancer to destroy thyroid remnants after primary surgery. In this strategy, low doses of ^{131}I are used, but data in the literature on its efficacy are conflicting. Therefore, we performed the present study to evaluate the clinical outcome of this ablation strategy. In this study, patients (n=235) were selected who underwent thyroidectomy for differentiated thyroid cancer, followed by an ablative dose of ^{131}I. Approximately 6 months after ablation, treatment efficacy was evaluated using radioiodine scintigraphy and thyroglobulin (Tg) measurements. Successful ablation was defined as the absence of radioiodine uptake in the neck region (criterion 1). Tg values were determined 3-12 months after ablation (criterion 2). Based on criterion 1, unsuccessful ablation was found in 43.0% of cases. Pre-treatment uptake values were statistically significantly lower (p=0.003) in successfully ablated patients (mean 5.4%) than in unsuccessfully ablated patients (mean 8.2%). Based on criterion 2, unsuccessful ablation was found in 52.4% of patients. The uptake-related ablation strategy, using low doses of ^{131}I, shows a relatively high treatment failure rate. Based on these results it is suggested that a lower ablation failure rate could be achieved by applying higher ^{131}I doses in the ablation of thyroid remnants in differentiated thyroid carcinoma patients. In the case of lymph node metastases a further dose adjustment may be advisable.

Introduction

The therapy of choice in patients suffering from differentiated thyroid cancer, subdivided into papillary and follicular thyroid carcinoma, is (near-) total thyroidectomy. This is routinely followed by the administration of radioiodine-131 (^{131}I) to destroy any remaining benign or malignant thyroid tissue, so-called ablation. There are several reasons for routine ablation after surgery [1]: (a) to be able to detect a carcinoma recurrence by radioiodine scanning; (b) radioiodine can destroy microscopic foci of carcinoma in the thyroid remnant; (c) possible carcinoma outside the thyroid bed may be detected and treated by radioiodine; (d) to use thyroglobulin (Tg) as tumor marker of recurrent carcinoma all normal thyroid tissue has to be destroyed.

Iodine-131 has been used for many years to ablate thyroid remnants following thyroid surgery, but a single optimal dose has not yet been established [2]. According to Mazzaferri [3], more studies are required to establish the optimal dose necessary for ablation of the thyroid remnant. In this respect, data in the literature are inconsistent; some studies conclude that a dose of 1110 MBq of ^{131}I may be as effective as a high dose such as 3700 MBq [4-6], while other authors suggest that a higher dose of ^{131}I will improve the rate of successful remnant ablations [7-9].

In our hospital, relatively low doses of ^{131}I have been used for many years for ablation in patients without distant metastases. The applied ^{131}I dose, which was based on data in the literature [10-14], depends on the 24-h ^{131}I pre-treatment uptake value in the neck region and ranges from 1100 to 2800 MBq. To assess the outcome of this strategy and because of inconsistencies in the literature regarding the appropriate ablative dose of ^{131}I [4-9], we performed a retrospective study to evaluate the clinical outcome of this ablation strategy.

Materials and methods

Study population and equipment.

Patients were selected who received ablation treatment with ^{131}I at the Leiden University Medical Center (LUMC) between January 1986 and December 1999 (n=418), to destroy thyroid remnants after thyroidectomy for differentiated thyroid cancer. This period was selected as before 1986 standardised records regarding the applied dose of ^{131}I were not available. Furthermore, follow-up of at least 2 years was required.

Consecutive exclusion criteria were: first dose of ^{131}I before 1986 (n=37), a first dose of ^{131}I given in another hospital (n=15), radioiodine treatment more than 1 year after thyroidectomy (n=24), only hemi-thyroidectomy (n=6), ^{131}I doses not according to the standard protocol (n=64) and distant metastases (n=30). In ten cases, proper assessment for the presence of distant metastases by evaluating the post-ablative scintigram was not possible owing to scattered radiation on the post-ablative scintigram. In 11 patients, whole-body scintigraphy 3-10 days after ablation (post-ablative scintigram) was not performed. To assess whether these patients were free of distant metastases at the time of ablation, records of follow-up scintigrams and/or other data from the medical files were studied. Patients were excluded from analysis when these data revealed distant metastases (n=3) or when follow-up data were not available or incomplete (n=3). Histopathology in one of the 236 remaining patients revealed no malignancy in the thyroid gland, but only an ectopic localisation of thyroid carcinoma. This patient was also excluded. After withdrawal of 183 patients for the foregoing reasons, 235 patients were left for evaluation.

From the medical files, age, gender, histopathological data, treatment characteristics and laboratory data were recorded. Records of scintigrams were analysed and coded.

Tumor staging was scored according to the criteria of the TNM Atlas [15].

For all scintigrams, a Toshiba gamma camera (Tokyo, Japan) was used. A high-

energy collimator (matrix sizes of 256x1,024 and 256x256, window of 20% centered at 360 keV) for the ^{131}I scintigrams, a low-energy collimator (matrix sizes of 256x1,024 and 256x256, window of 20% centered at 159 keV) for the ^{123}I scintigrams was used. Anterior and posterior whole-body and planar views of the neck region were routinely obtained. For the whole-body scintigrams, scanning rates of 15 (^{131}I) and 10 cm/min (^{123}I) were used.

Radioiodine treatment.

The mean interval between thyroidectomy and the ablative dose was 7.0 weeks (standard deviation ±6.4 weeks). During this interval, no suppressive treatment with L-thyroxine was initiated. TSH values were measured at the time of ablation.

In patients treated from 1992, low-iodine diets were used approximately 4 days before the ablative dose was given. In patients 4 treated until 1992, low-iodine diets were not strictly applied according to the currently used protocol. The rationale of a low-iodine diet was to achieve a reduction in the iodide pool of the body, in order to achieve the highest possible entrance of ^{131}I ions into the thyroid remnant.

The 24-h ^{131}I pre-treatment uptake value in the neck region was measured using standard techniques (in %): 40 MBq of ^{131}I was given orally, followed by planar scintigraphy of the neck region 24 h later. A standard of 40 MBq ^{131}I that was calibrated on the day of admission and measured in a neck phantom after 24 h was used as a reference. Uptake of less than 5%, of between 5% and 10% and of more than 10% was followed by 2800, 1850 and 1100 MBq of ^{131}I in one dose, respectively. The rationale of this quantitative approach is to avoid unnecessary exposure [16] and local radioiodine side-effects [17;18]. In this regimen, no adjustments were made in the case of cervical lymph node metastases.

Documentation of treatment efficacy.

Treatment efficacy was evaluated approximately 6 months after ablation using low-dose radioiodine diagnostic whole-body scintigrams obtained 3 days after administration of ^{131}I or 24 h after administration of [123]I. For this purpose, hormonal supplementation was withdrawn. Records of these diagnostic radioiodine scintigrams were studied. The percentage of ^{131}I versus ^{123}I diagnostic scans was 87.6% versus 12.4%, respectively. For the ^{131}I scintigrams, doses of 40 (1.2%), 100 (7.6%) or 185 MBq (91.2%) were used. In patients who received a second therapeutic dose of [131]I (n=81), records of whole-body scintigrams obtained approximately 1 week after this second therapeutic dose (i.e. post-therapeutic scintigram) were also evaluated. In the case of a second therapeutic treatment with ^{131}I, the average dose was 6163 MBq (standard deviation ±449 MBq). Unsuccessful ablation of the thyroid remnant was defined as the visible presence of radioiodine uptake in the neck region on the diagnostic and/or post-therapeutic scintigram (criterion 1). Results of ablation are presented for the whole group, for patients without clinically lymph node metastases (N0) and for patients with histopathologically proven lymph node metastases (N1). Scintigrams obtained up to 2 years after ablation were included for analysis.

Available Tg values, determined 3-12 months after ablation, were also used to document ablation efficacy. Cut-off levels of ≤1μg/l (i.e. undetectable, criterion 2a) and ≤3 μg/l (criterion 2b) were applied. If anti-thyroglobulin antibodies (Tgab) were measurable, interference effects in the determination of Tg could be substantial [19]. As IRMA assays were used, these interference effects generally would have resulted in underestimation of the Tg value. Therefore, Tg values were excluded from analysis in the presence of measurable Tgab and a corresponding Tg value below the cut-off level.

Data collection and statistical analysis.

All collected data were put in a database using MS-Access97. For statistical analysis we used SPSS for Windows, version 10.0 and MS-Excel97. The quantitative data (continuous parameters) were analysed using Student's t test for normal distributed data or the Mann-Whitney U test for non-normal distributed data. For analysis of data on the nominal scale we used the Chi-squared test. Quantifiable data are given as minimal and maximal values as well as the mean ± standard deviation (SD). A statistically significant difference was considered when $p<0.05$.

Results

Study population

Papillary thyroid carcinoma was diagnosed in 184 patients, 38 men and 146 women (age at thyroidectomy 16.4-87.1 years; mean 42.1; SD ±14.2). Follicular thyroid carcinoma was diagnosed in 50 patients, 12 men and 38 women (age at thyroidectomy 14.8-85.5 years; mean 51.7; SD ±20.0). In one case, thyroid carcinoma was not otherwise specified (tcNOS) (Table 1).

At the histological study of the surgically excised material, lymph node metastases were diagnosed in 53 papillary thyroid carcinoma patients. In follicular thyroid carcinoma patients, no lymph node metastases were found (Table 1).

Table 1. Population characteristics including tumor and lymph node stage.

Differentiated thyroid carcinoma		No. of patients	No. of patients with lymph node metastases
Tumor stages in papillary thyroid cancer patients	T1	18	12
	T2	107	22
	T3	28	5
	T4	31	14
	Tx	0	0
	Total	**184**	**53**
Tumor stages in follicular thyroid cancer patients	T1	1	0
	T2	29	0
	T3	14	0
	T4	5	0
	Tx	1	0
	Total	**50**	**0**
Tumor stages in thyroid carcinoma not otherwise specified	T1	0	0
	T2	1	0
	T3	0	0
	T4	0	0
	Tx	0	0
	Total	**1**	**0**
Tumor stages: total numbers	T1	19	12
	T2	137	22
	T3	42	5
	T4	36	14
	Tx	1	0
	Total	**235**	**53**

Treatment efficacy (criterion 1)

In 200 patients, diagnostic and/or post-therapeutic scintigrams were available for evaluation. In the remaining 35 cases, scintigraphic follow-up was not performed for unknown reasons. There was no significant difference between the group of patients with (n=200) and without (n=35) scintigraphic follow-up with respect to age at thyroidectomy (p=0.249), sex (p=0.123), tumor stage (stages T1-T3 versus stage T4, p=0.906), lymph node stage (p=0.088) or pre-treatment uptake values (p=0.194). Therefore, we considered the outcome of ablation in the group of patients with follow-up scintigrams (n=200) as representative for the whole group of 235 patients.

In 86 cases (43.0%), radioiodine uptake was seen in the neck region on the diagnostic and/or post-therapeutic scintigram, implying unsuccessful ablation. In eight of these 86 cases, diagnostic scintigraphy revealed no evidence for a persistent thyroid remnant, while a subsequent post-therapeutic scintigram performed up to 2 years after ablation did indicate uptake.

Figure 1 demonstrates the percentage of unsuccessful ablations per histological type and tumor category without clinically lymph node metastases and with histopathologically proven lymph node metastases. No statistically significant differences could be found in ablation rates between papillary thyroid carcinoma and follicular thyroid carcinoma patients (p=0.738) or between tumor stages T1-T3 and tumor stage T4 (p=0.510).

In 59 of 151 clinically N0 patients (39.1%), ablation was unsuccessful, while in 27 of 49 patients (55.1%) with histopathologically proven lymph node metastases, ablation was unsuccessful. This difference in ablation rate was statistically significant (p=0.049).

As shown in Table 2, the frequency of unsuccessful ablations increased with rising 24-h ^{131}I pre-treatment uptake values: the uptake values were significantly lower (p=0.003) in successfully ablated patients (mean 5.4%; SD ±7.5%) than in unsuccessfully ablated patients (mean 8.2%; SD ±8.6%).

Table 2. Number of patients demonstrating uptake in the neck region on follow-up scintigraphy (criterion 1), in relation to the pre-treatment uptake values.

Pre-treatment uptake value (U)		No. of patients	Uptake in neck region on follow-up scintigraphy	
value	mean ±SD		No.	%
U ≤5	2.4 ±1.2	128	44	34.4*
5< U ≤10	7.7 ±1.4	31	17	54.8
U >10	21.9 ±8.5	33	20	60.6*
U unknown		8	5	62.5
Total		**200**	**86**	**43.0**

(* = statistically significant difference, p=0.006)
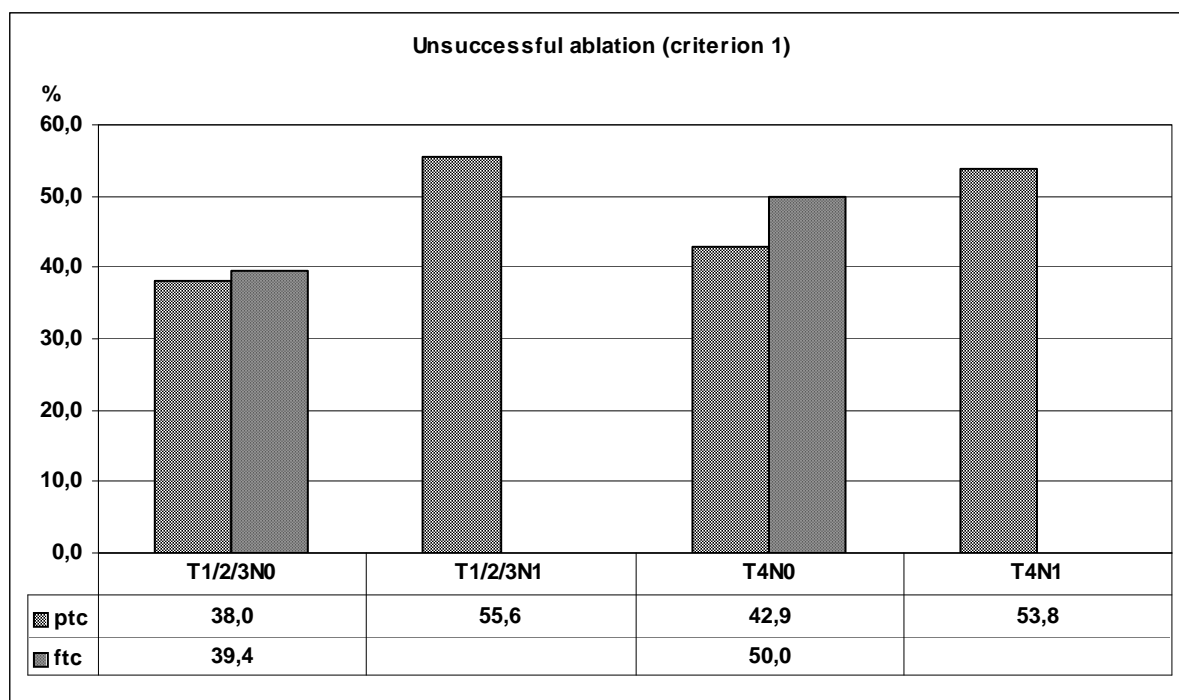
Figure 1. Percentage of unsuccessful ablations according to criterion 1 (radioiodine uptake in the neck region on follow-up scintigraphy). Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) patients. T1/2/3/N0: tumor stages T1, T2, T3 without clinically lymph node metastases; T1/2/3N1: tumor stages T1, T2, T3 with histopathologically proven lymph node metastases; T4N0: tumor stage T4 without clinically lymph node metastases; T4N1: tumor stage T4 with histopathologically proven lymph node metastases.

With respect to age, no statistically significant difference in ablation results was

found (p=0.197). A statistically significant difference (p=0.014) in ablation failure rate was found between males (58.7%) and females (38.3%). However, in our population there was a statistically significantly (p=0.001) higher prevalence of lymph node metastases in male patients (43.5%) than in female patients (18.8%).

No significant differences in treatment results (p=0.84) were found between patients treated until 1992 (low-iodine diets not strictly applied) and those treated after 1992 (low-iodine diets used 1 week before ablation).

Treatment efficacy (criterion 2)

With respect to Tg values, 191 and 187 evaluable cases were available for cut-off levels of ≤1 and ≤3 µg/l respectively. This difference in evaluable cases is caused by exclusion of values in the presence of measurable Tgab and a corresponding Tg value below the cut-off level. In 100 cases (52.4%) a Tg value >1 µg/l was present, implying unsuccessful ablation (criterion 2a). A Tg value >3 µg/l was present in 38 cases (20.3%) (criterion 2b). In Tables 3 and 4 a subdivision is given according to the pre-treatment uptake value.

Table 3. Number of patients with Tg values >1 µg/l (criterion 2a) determined 3-12 months after ablation, in relation to the pre-treatment uptake values.

Pre-treatment uptake value (U)	No. of evaluable cases	Tg >1 µg/l	
		No.	%
U ≤5	123	62	50.4*
5< U ≤10	31	16	51.6
U >10	30	15	50.0*
U unknown	7	7	100.0
Total	**191**	**100**	**52.4**

(* = No statistically significant difference, p=0.968)

Table 4. Number of patients with Tg values >3 µg/l (criterion 2b) determined 3-12 months after ablation, in relation to the pre-treatment uptake values.

Pre-treatment uptake value (U)	No. of evaluable cases	Tg >3 µg/l	
		No.	%
U ≤5	120	23	19.2*
5< U ≤10	30	4	13.3
U >10	30	9	30.0*
U unknown	7	2	28.6
Total	**187**	**38**	**20.3**

(* = No statistically significant difference, p=0.195)

TSH values

TSH values at the time of ablation ranged from 3.1 to 330.0 mU/l (mean 71.0; SD ±42.2). In 15 patients, a TSH value below 20 mU/l was found at the time of ablation. Nine of these 15 patients had a pre-treatment uptake value ≥10%, and in only one of these nine was ablation successful according to criterion 1. In this patient there were no signs of residual thyroid tissue.

Discussion

In the present study the clinical outcome of a 24-h ^{131}I uptake-related ablation strategy to destroy thyroid remnants after primary surgery for differentiated thyroid cancer was evaluated. In this strategy, rather low ablative doses of ^{131}I are used. Depending on the extent of the thyroid remnant, unsuccessful ablation was found in 34%-61% of cases, which is relatively high.

One criterion for successful ablation was the visible absence of radioiodine uptake in the neck region on follow-up scintigraphy, routinely performed 6 months after ablation. Furthermore, Tg values were evaluated and cut-off levels of ≤1 and ≤3 µg/l were applied. The rationale for using a low cut-off level of ≤ 1

µg/l, in our laboratory defined as undetectable, is that in the case of circulating Tg, residual normal thyroid or tumor cells are present [20]. A cut-off level ≤3µg/l was based on data published by Duren *et al*. [21] and Ozata *et al*. [20].

Samaan *et al*. [22] retrospectively analysed 1599 patients who were treated for well-differentiated thyroid carcinoma. There were 736 patients who received radioiodine and this group was compared with the 863 patients who did not receive radioiodine. The authors concluded that treatment with radioactive iodine improves diseasefree interval and survival. In an article by Mazzaferri [3] on a large follow-up study, similar conclusions were reported. However, the optimal dose to achieve total ablation after one dose of ^{131}I is still controversial. As already mentioned, some investigators conclude that a low dose, such as 1110 MBq, may be as effective as a high dose, such as 3700 MBq, in achieving ablation [4-6] while others suggest that increasing the dose will improve the rate of successful remnant ablation [7;8]. However, the above-mentioned studies included a small number of patients, ranging from 13 to 63. Roos and Smith [2] concluded that the issue of the appropriate dose of ^{131}I for ablation of thyroid remnants postoperatively still remains undetermined. In a meta-analysis including 11 studies and two additional cohorts of their own, Doi and Wood-house [9] compared the efficacy of remnant ablation following a single low dose (1074-1110 MBq) versus a single high dose (2775-3700 MBq). Their results demonstrate that a single high dose of ^{131}I is more efficient in ablating residual thyroid tissue than a low dose. However, ablation rates are also influenced by remnant size [9; 16; 23]. In general, irrespective of the dose, the more extensive surgery is performed, the more likely ablation will be successful [9]. Arslan *et al*. [24] found a statistically significantly lower remnant thyroid volume (calculated by ultrasonography) in patients in whom ablation was achieved compared with patients in whom ablation failed. In patients with total ablation, partial ablation and no ablation, Beierwaltes *et al*. [25] found average pre-

radioiodine treatment uptake of 5.22%, 9.91% and 13.11%, respectively. In the present study, we found statistically significantly lower pre-treatment uptake values in successfully ablated patients. This is in agreement with the above-mentioned studies. However, taking into account that better ablation results are achieved after more extensive surgery, Doi and Woodhouse [9] still concluded that the available data favor higher doses of [131]I (2775 - 3700 MBq) for remnant ablation.

In the study by Beierwaltes et al. [25], total ablation after thyroidectomy from the first dose of ^{131}I, not less than 3700 MBq, was achieved in 87% of 267 well-differentiated thyroid carcinoma patients with radioiodine uptake confined to the thyroid bed and an average pre-treatment percent uptake of 6.01%. Their results also demonstrated comparable ablation results when cervical lymph nodes were present (total ablation was achieved in 114 out of 129 patients after the first dose of more than 3700 MBq of ^{131}I). They treated patients with ^{131}I for ablation of remnants in the thyroid bed when there was significant 24-h ^{131}I uptake (generally >0.5%) after 74 MBq of [131]I. Within 1 year after ablation, they performed ^{131}I scintigraphy in the hypothyroid state. The thyroid remnant was judged to have been totally ablated when no residual uptake was seen in the thyroid bed and the measured percent uptake in the neck was <1%. De Klerk et al. [26] evaluated 93 differentiated thyroid carcinoma patients referred for their first ablative treatment after thyroidectomy. The patients were treated with 3700 MBq of ^{131}I in the absence of lymph node or distant metastases and 5550 MBq of ^{131}I in the presence of pre- or peri-operatively detected cervical lymph node metastases. Pre-ablative ^{131}I diagnostic scintigraphy was not performed. One year after ^{131}I ablation, a whole-body diagnostic [131]I (370 MBq) scintigram was performed after discontinuation of thyroid replacement therapy for 4-6 weeks. Their main criterion for successful ablation was the absence of visual ^{131}I residual neck uptake on diagnostic scintigraphy. This was achieved in 88% of the patients, with a mean uptake percentage in the neck of 0.23% (SD ±0.87%;

range 0.001-6.4%), measured 1 week after ablation. However, they reported a Tg value of <1 µg/l at 1-year follow-up in only 48% of the patients. We also found a discrepancy in ablation rate using criterion 1 (radioiodine uptake in the neck region) and criterion 2a (Tg value ≤1µg/l). This discrepancy amounted to 16% in patients with comparable pre-treatment uptake of ≤5%.

Factors that could have influenced the treatment results

Stunning effect. It has been shown that relatively low diagnostic doses of ^{131}I may lead to impaired ability of remnant thyroid tissue to concentrate the subsequent ablative dose of [131]I (so-called stunning effect) and thereby reduce therapeutic efficacy [27;28]. Muratet *et al.* [28] suggested that the threshold dose of ^{131}I above which the stunning phenomenon may have an adverse effect on treatment efficacy is between 37 and 111 MBq [131]I. In a study by Morris *et al.* [29], no significant difference was found in ablation rates between patients who received 111-185 MBq ^{131}I for diagnostic scanning before the ablative dose and patients who did not receive any ^{131}I before the initial treatment dose. Since in the present study a dose of 40 MBq was usually applied in the pre-ablative uptake measurements, we assume that the stunning phenomenon made at most a slight contribution to the ablation failure rate.

Low-iodine diet. For many years, low-iodine diets have been used to increase the ^{131}I dose delivered to the thyroid remnant [30;31]. The increase in thyroid ^{131}I uptake after a low-iodine diet theoretically implies that a low-iodine diet will increase the effectiveness of ablative doses [32]. Nevertheless, Morris *et al.* [32] did not find a significant difference in ablation rate between patients who followed a regular diet and patients who followed a low-iodine diet before ablation. Between 4 and 42 months after the ablative dose they determined success of ablation according to the visual absence of uptake in the thyroid bed and neck region on a low-dose ^{131}I diagnostic scintigram. However, significantly

more patients were treated with 3700 MBq of ^{131}I in the low-iodine diet group and significantly more with 5550 MBq in the group of patients who followed a regular diet. In our study, low-iodine diets were not strictly applied in patients who were treated until 1992. In this group of patients we did not make a distinction in the analysis of treatment results between low-iodine diet and normal diet patients. However, no significant differences in treatment results according to criterion 1 were found between patients in whom low-iodine diets were not strictly applied (treated until 1992) and patients in whom low-iodine diets were applied according to the currently used protocol (treated from1992). One reason for the lack of difference in treatment results between low-iodine diet patients and patients in whom low-iodine diets were not strictly applied could be the short duration of iodine abstinence. Probably the iodide pool had not been significantly reduced.

Discontinuation of thyroid hormone supplementation.

The follicular cells of the thyroid gland trap and concentrate iodide from the blood, which is achieved by an active, energy-dependent transport process across the basolateral plasma membrane of the thyrocytes. The sodium/iodide symporter (*NIS*) gene encodes the protein responsible for the transport process [33]. Because thyroid cancers or metastases from thyroid cancer accumulate iodine to a lesser degree than normal thyroid tissue, intensive TSH stimulation is required in patients with thyroid cancer before administration of ^{131}I in order to increase *NIS* expression and thus the ability of thyroid cancer tissue to take up ^{131}I [33]. To achieve intensive TSH stimulation, discontinuation of thyroid hormone supplementation is necessary. As expected, the TSH stimulation varied between patients, which theoretically could have had an impact on the success of ablation of the thyroid remnant.

In the present study we did not take into account the effect of TSH values on the ablation results. It is possible that ablation results could be affected in the

presence of an inadequate degree of hypothyroidism, for example a TSH value below 20 mU/l. As mentioned above, in 10 of 15 patients who had a TSH value below 20 mU/l at the time of ablation, treatment with ^{131}I was unsuccessful. In eight of these ten patients a pre-treatment uptake value of ≥10% was measured, probably indicating that a substantial amount of residual functioning thyroid tissue prevented sufficient TSH elevation.

Limitations of the study

In 35 patients scintigraphic follow-up was not performed, implying that presentation of treatment results for the whole patient group was not possible. No statistically significant differences in age, sex, tumor stage, lymph node stage or pre-treatment uptake values were found between the group of patients with (n=200) and the group without scintigraphic follow-up (n=35). We assumed that the similarity of the groups allowed inference of the same ablation results.

Scintigrams were not independently reviewed by one individual, causing an element of uncertainty. As we defined unsuccessful ablation as the presence of radioiodine uptake in the neck region, we did not distinguish between residual normal thyroid tissue in the thyroid bed, pyramidal lobe or thyroglossal duct region and residual functioning thyroid cancer in cervical lymph nodes.

Total ablation according to criterion 1 was considered as the absence of uptake in the neck region on follow-up scintigraphy. However, in our study population, follow-up scintigraphy indicated new uptake outside the neck region in two patients, likely corresponding to new distant metastases. Nevertheless, in the presented results these two patients were regarded as having had successful ablation of their thyroid remnant.

In this retrospective study, data regarding the remnant mass were not available. Consequently, we could not provide exact information about a possible relation between tumor dosimetry, which is based on uptake values and remnant masses,

and subsequent failure rates. In our opinion, in current practice it is not feasible to correctly assess the size of small remnants by means of imaging techniques. Studies on the use of ultrasonography for the estimation of thyroid masses have been performed in hyperthyroidism, i.e. in patients with a thyroid in situ. Data on its use and, especially, on its accuracy and reproducibility in thyroidectomy patients are scarce or even not available.

Conclusion

The uptake-related ablation strategy as described in the present study shows relatively high failure rates. As we excluded Tg values from analysis in the presence of detectable Tgab and a Tg value below the cut-off level, the given ablation failure rate according to criterion 2 could actually be even higher. Furthermore, as described in our results, low-dose radioiodine diagnostic whole-body scintigraphy may give a false-negative outcome.

Based on these results and on studies in the literature, it is suggested that a lower ablation failure rate could be achieved when higher ^{131}I doses are applied in the ablation of thyroid remnants in differentiated thyroid carcinoma patients. Because our results show high unsuccessful ablation rates in the group of patients with uptake values above 10% (statistically significantly higher compared with the group of patients with uptake values below or equal to 5%), surgical re-exploration for additional thyroid tissue removal may be suggested for this group of patients. However, further studies are required in which higher ablation doses are tested, even in the case of high uptake values.

We found statistically different ablation results between male and female patients and between patients without and with lymph node metastases. In a study by Arslan *et al*. [24], a significantly higher total ^{131}I dose was needed for successful ablation in males and in patients with a higher stage of disease. This is probably related to the fact that the less differentiated the tumor, the lower the uptake function and hence the need for a higher activity for the ablation of

possible malignant cells in the remnant. Therefore, in the case of lymph node metastases a further dose adjustment may be advisable.

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Chapter 3

The success rate of ^{131}I ablation in differentiated thyroid cancer: comparison of uptake-related and fixed-dose strategies

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Abstract

Introduction: The aim of the study was to compare the success rate of an uptake-related ablation protocol in which the dose depends on an ^{131}I 24-h neck uptake measurement and a fixed-dose ablation protocol in which the dose depends on tumor stage.

Methods: All differentiated thyroid carcinoma patients with M0 disease who had undergone (near-) total thyroidectomy followed by ^{131}I ablation were included. In the uptake-related ablation protocol, 1100 (uptake >10%), 1850 (uptake 5-10%) and 2800 MBq (uptake <5%) were used. In the fixed-dosage ablation strategy, 3700 (T1-3, N0 stage) and 5550 MBq (N1 and/or T4 stage) were applied. We used ^{131}I uptake on whole-body scintigraphy and thyroglobulin-off values to evaluate the ablation 6-12 months after treatment.

Results: In the uptake-related ablation protocol, 60 out of 139 (43%) patients were successfully treated versus 111 out of 199 for the fixed-dose ablation protocol (56%) (p=0.022). The differences were not statistically significant for patients with T4 (p=0.581) and/or N1 (p=0.08) disease or for patients with T4N1 tumor stage (p=0.937).

Conclusion:The fixed-dose ^{131}I ablation protocol is more effective in ablation of the thyroid remnant in differentiated thyroid carcinoma patients than an uptake-related ablation protocol. This difference is not observed in patients with a N1 and/or T4 tumor stage.

Introduction

The therapy of choice in patients suffering from differentiated thyroid cancer (DTC), subdivided into papillary and follicular thyroid carcinoma, is (near-) total thyroidectomy. This is routinely followed by the administration of radioiodine-131 (^{131}I) to destroy any remaining benign or malignant thyroid tissue, so-called ablation. There are several reasons for routine ablation after surgery [1;2]: a) to be able to detect a carcinoma recurrence by radioiodine scanning; b) radioiodine can destroy microscopic foci of carcinoma in the thyroid remnant; c) possible carcinoma outside the thyroid bed may be detected and treated by radioiodine and d) to use thyroglobulin (Tg) as tumor marker of recurrent carcinoma all normal thyroid tissue has to be destroyed. Although ^{131}I has been used for many years to ablate thyroid remnants following thyroid surgery, a single optimal ablation strategy is still not established. Reports on the amount of ^{131}I required to achieve successful ablation show a considerable range [3-7].

At the Leiden University Medical Center (LUMC) and the University Medical Center Utrecht (UMCU), two academic hospitals in the Netherlands, different ablation strategies have been used over the years. At the LUMC, a relatively low-dose uptake-related ablation strategy was applied until June 2002 [8], whereas in the UMCU a fixed-dose strategy with relatively high administered ^{131}I activities has been in use since January 1990 [9;10]. The aim of this study was to compare the success rates of ablation according to these two above-mentioned protocols.

Methods

Study population

Patients were selected who received ablation treatment with ^{131}I at the LUMC or UMCU from January 1990, as this date marks the start of the fixed-dose protocol in the UMCU. Both subgroups consisted of patients in whom surgery

has been performed in the University Medical Centres as well as in referring peripheral hospitals. All DTC patients with M0 disease who had undergone (near-) total thyroidectomy followed by ^{131}I ablation were included. Tumor staging was scored according to the criteria of the fifth TNM Atlas. In all patients with N1 disease, a neck dissection was performed in addition to a resection of the thyroid and prior to ablation. So, in patients with N1 disease, this stage was established before ablation. All patients with M1 disease were excluded to avoid a bias. M1 disease as exclusion criterion was based on post-ablation whole-body scans with high ^{131}I doses and radiological examinations, such as CT scanning and/or chest-X-rays, in patients with T4 and/or N1 disease. Finally, additional inclusion criteria were: a) ablation has been performed in accordance with either protocol and b) 6-12 months after ablation patients returned for follow-up studying consisting of Tg-off measurements and/or ^{131}I whole-body scintigraphy.

Uptake-related ablation protocol

This treatment strategy was used at the LUMC until June 2002. All patients had undergone (near-) total thyroidectomy, followed by ^{131}I ablation 4-6 weeks after surgery. During this interval, no suppressive treatment with L-thyroxine was initiated. Furthermore, low-iodine diets were prescribed to optimize the therapeutic outcome [11;12]. The 24-h pre-treatment radioiodine uptake percentage in the neck region was measured using standard techniques: 40 MBq of ^{131}I was given orally, followed by planar scintigraphy of the neck region 24 h later. A standard of 40 MBq ^{131}I that was calibrated on the day of admission and measured in a neck phantom after 24 h was used as a reference. An uptake of less than 5%, between 5 and 10%, and more than 10% was followed by 2800, 1850 and 1110 MBq of ^{131}I in one administration respectively. The rationale of this quantitative approach was to avoid unnecessary exposure [13] and local side effects from radioiodine [14;15]. In this regimen, no adjustments were made in

the case of cervical lymph node metastases.

Fixed-dose ablation protocol

This strategy was used in the UMCU from 1990 onwards. All patients had undergone (near-) total thyroidectomy, followed by ^{131}I ablation 4-6 weeks after surgery. A standard activity of 3700 MBq was administrated in cases without any (known) metastases. In case of pre- or peri-operatively detected lymph node involvement or T4 tumor stage, an activity of 5550 MBq was given. Between surgery and ablation patients did not receive L-thyroxine supplementation, and they had been instructed to keep a low-iodine diet for approximately 1 week [11;12]. No pre-ablative diagnostic scintigraphy was performed.

Follow-up strategy

Between 6 and 12 months after ^{131}I ablation, patients were evaluated by the measurement of Tg-off values, i.e. Tg values under thyrotrophin (TSH) stimulation. For this purpose, hormonal supplementation was withdrawn for 4 weeks, whereas in a minority of the UMCU cohort recombinant human TSH was applied. In the UMCU study group, all patients underwent ^{131}I whole body scintigraphy (WBS), whereas in the LUMC cohort ^{131}I WBS was performed in case of Tg <1 µg/l. In both hospitals, scintigraphy was performed at least 3 days after administration of [131]I. In case of increased Tg values or an abnormal WBS, additional treatment was given followed by WBS within 7 days after the administration of a therapeutic dose. Follow-up results 6-12 months after this treatment were not studied. Despite the increased use of ultrasonography in the follow-up of DTC patients, it was not routinely used in this study.

Laboratory analysis

From 1990, in both hospitals, various kits were used for the measurement of Tg and Tg antibodies. Test results for Tg cannot be considered reliable in the

presence of Tg antibodies [16;17]. As all assays were IRMA assays, the presence of Tg antibodies would have resulted in unreliable Tg values. Therefore, Tg values were excluded from analysis in the presence of measurable Tg antibodies and a corresponding Tg value below the cut-off level. As results of Tg measurements are not interchangeable between kits [18], Tg values in any patient were considered undetectable if they were below the lower detection limit of the kit used (i.e. cut-off level). Until 1997, serum Tg was measured using an IRMA, the Dynotest TG (Brahms Diagnostica GmBH, Berlin, Germany), with a detection limit of 1 µg/l. From 1997 onwards, the Dynotest TG-s (Brahms Diagnostica GmBH) was used, with a detection limit of 0.5 µg/l. Recurrent disease, however, was defined as Tg values >1µg/l. TSH values were measured by means of an immunofluorometric assay with the Delfia (Wallac, Turku, Finland) until 1997. Thereafter, an immunoluminometric assay was used with the Elecsys (Boehringer Mannheim). Serum Tg-antibodies were determined by the Ab-HTGK-3 IRMA test (DiaSorin Biomedics, Saluggia (VC) Italy).

Criteria for successful ablation

Ablation was considered successful if 6-12 months after ablation when patients fulfilled the following criteria: Tg-off values below the cut-off level of the assay used and negative ^{131}I whole-body scintigraphy.

Statistical analysis

For statistical analysis, we used SPSS version 12.0.1 for Windows (SPSS Inc., Chicago, Illinois, USA). The quantitative data (continuous parameters) were analysed using the Mann-Whitney *U*-test. For categorical data, the χ^2 -test was used. A statistically significant difference was considered when p<0.05.

Results

Study population

In this study, a total of 359 patients were included. According to the uptake-related and fixed-dose ablation protocols, 153 and 206 patients were treated respectively. In Table 1, the patient characteristics and results of tests for differences between the two groups are displayed. Papillary microcarcinomas were not observed in the groups studied. In the uptake-related protocol, 20% of patients were treated with 1110 MBq ^{131}I, 19% with 1850 MBq and 61% with 2800 MBq. The mean 24-h ^{131}I uptake value in this group was 6.86% (range: 0.03-12.0%). In the fixed-dose protocol, 69% of patients were treated with 3700 MBq ^{131}I and 31% with 5550 MBq. In this group, 24-h uptake values were not measured.

According to the evaluation with ^{131}I WBS as single tool (Table 2), 89 out of 153 (58%) patients had no iodine uptake in the neck at the first follow-up scintigraphy in the uptake-related ablation protocol. In 174 out of 206 patients (84%) treated according to the fixed-dose ablation, scintigraphy did not show radioiodine uptake in the neck. This difference was statistically significant (p<0.001). The scintigraphic ablation results in various subgroups as well as the differences between the protocols are displayed in Table 2, demonstrating significant differences between the different protocols in all subgroups with the exception of T4 tumor stages.

Regarding the combination of ^{131}I WBS and Tg measurement as evaluation tools, it was decided to exclude patients with Tg antibodies and a negative diagnostic ^{131}I WBS to avoid a bias leaving 338 patients available for analysis. Of those treated according to the uptake-related ablation protocol, 60 out of 139 (43%) patients were successfully treated. For patients treated according to the fixed-dose ablation protocol, 111 out of 199 (56%) patients had successful ablation. Again, this difference was statistically significant (p=0.022). The results of ablation in various subgroups and tests for differences between the

protocols are also displayed in Table 2. We found significant differences between the protocols for almost all subgroups defined. However, differences were not statistically significant for patients with papillary thyroid cancer (p=0.23) and for patients with N1 (p=0.08) and/or T4 (p=0.581) disease. In addition, 10 patients in the uptake-related dose group and 9 patients in the fixed-dose group had T4N1 disease (p=0.006). In both subgroups, only one patient had a successful ablation (p=0.937) revealing a high failure rate in these tumor stages. All patients with radioiodine uptake in the neck and/or elevated Tg values 6-12 months after ablation, the so-called failures, underwent subsequent treatment with a high therapeutic ^{131}I dose. The results of the post-therapy scans were not part of the present study, but all patients with uptake on the diagnostic follow-up WBS also demonstrated uptake on the post-therapy scan. The post-therapy scans of patients with increased Tg values were not evaluated.

Table 1. Differences in population characteristics for the ablation protocols studied.

	Uptake-related	Fixed-dose	p value
Total number of patients	153	206	
Mean age in years (range)	42.6 (15-87)	43.1 (19-82)	0.675
Gender			0.07
Male	33 (22%)	62 (30%)	
Female	120 (78%)	144 (70%)	
Histology			0.294
Papillary carcinoma	123 (80%)	156 (76%)	
Follicular carcinoma	30 (20%)	50 (24%)	
24-hr ^{131}I -uptake (range)	6.86% (0.03-12)	NA	
N-stage			0.008
N0	125 (82%)	140 (68%)	
N1	27 (18%)	66 (32%)	
NX	1 (<1)	0 (0)	
T-stage			0.005
T1-3	131 (86%)	194 (94%)	
T4	22 (14%)	12 (6%)	

N-stage, lymph node stage (N0, without clinically lymph node metastases; N1, with histopathologically proven lymph node metastases); T-stage, primary tumor stage; NA, not available.

Table 2. Successful ablation results in the entire population and various subgroups according to ^{131}I WBS and ^{131}I WBS with Tg measurements.

Group	[131]I Whole body scan			[131]I Whole body scan and Tg		
	Uptake-related (n=153) (%)	Fixed-dose (n=206) (%)	p value	Uptake-related (n=139) (%)	Fixed-dose (n=199) (%)	p value
All patients	89 (58)	174 (84)	<0.001	60 (43)	111 (56)	0.022
PTC	73 (59)	133 (85)	<0.001	47 (43)	75 (50)	0.230
FTC	16 (53)	41 (82)	0.006	13 (45)	36 (72)	0.016
N0	76 (61)	119 (85)	<0.001	55 (48)	86 (63)	0.017
N1	12 (44)	55 (83)	<0.001	5 (20)	25 (40)	0.080
T1-3N0	70 (62)	117 (85)	<0.001	53 (51)	86 (65)	0.034
T4	10 (45)	12 (75)	0.236	3 (15)	1 (8)	0.581

Twenty-one patients with positive Tg-antibodies were excluded in the evaluation using ^{131}I WBS and Tg measurements. PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; N, lymph node stage; T, tumor stage.

Discussion

In the present study, two fundamentally different ablation strategies were compared. The rationale of the quantitative uptake-related protocol was to avoid unnecessary exposure [13] and minimize local radioiodine side effects [14;15], whereas the fixed-dose ablation protocol was designed to maximize the chance of successful ablation after one administration of [131]I. The present study showed that the fixed-dose ablation protocol has a significantly higher rate of successful ablation compared with the uptake-related ablation strategy. However, of all subgroups, the fixed-dose ablation protocol failed to show a significant advantage in patients with extra thyroidal invasion of the primary tumor (T4 tumors) and/or lymph node involvement (N1 stage). In addition, the results also

demonstrate the low sensitivity of ^{131}I WBS in the follow-up of thyroid cancer patients compared with the Tg measurements. This finding is in agreement with the recommendation presented in the European guidelines indicating that for the control of successful ablation in low-risk patients Tg measurements are the first step in the follow-up and WBS is not recommended anymore.

Several studies have shown that higher administered ^{131}I activities lead to higher ablation rates, although estimations of the optimal activity vary between authors. A randomized trial reported by Bal *et al*. [19] revealed no differences in the rates of remnant ablation for activities over 925 MBq (25 mCi). With successful ablation defined as a follow-up scintigram of the neck with less than 0.2% uptake and Tg less than or equal to 10 µg/l, they achieved in 81.6% of the cases successful ablation with activities of 925 MBq or more after one administration. The absence of activity-related differences in success rates of ablation in the study by Bal *et al*. is in sharp contrast with the differences encountered in the present study between those treated with a lower activity (with a minimum of 1110 MBq) and a higher activity (minimum 3700 MBq). The findings of Bal *et al*. are also in contrast with the results described in their earlier study [5], in which an activity of 1850 MBq (50 mCi) or more performed significantly better than an activity of 1110 MBq.

Also in contrast to our results are the findings of Johansen *et al*. [4], who found a success rate of 81% after one administration of 1073 MBq and 84% after the first administration for those receiving 3700 MBq. However, they analyzed only 63 patients in total, whereas their reported success rates have been based on scintigrams performed 3-4 months after ablation. They also reported that the elevated Tg values in the ablated subjects were not statistically significant. However, their lower detection level for Tg was 5 µg/l, which is higher than our cut-off levels (0.2-1.0 µg/l). The comparable ablation results of 1073 and 3700 MBq could be caused by less sensitive follow-up (short follow-up period after ablation and higher cut-off levels for Tg).

An interesting comparison can be made with the uptake-related protocol published by Zidan *et al.* [20], who reported results of an uptake-related protocol with used activities varying from 3145 MBq (85 mCi) for the patients with lowest uptake to 1110 MBq (30 mCi) for those with the highest uptake. Despite the fact that their definition of a successful ablation was based solely on a diagnostic ^{131}I WBS, they reported a higher overall success rate of 94%. However, compared with the uptake-related protocol as described in the present study, Zidan *et al.* used higher ^{131}I activities (approximately 1100 MBq more) for uptake values between 6 and 15%.

In two recently published articles, systematic meta-analyses were presented on the ^{131}I activity for remnant ablation in patients with DTC. In the analysis by Hackshaw *et al.* [21], 41 case notes, 12 prospective cohorts and 6 randomized trials were used to compare the outcome in patients treated with 30 mCi with those treated with 100 mCi. The pooled ablation success rates in the observational studies were 10% lower using 30 mCi compared with the higher dose. The meta-analysis of the randomized trials revealed equivocal results. Despite these findings and because of the lack of randomized trials, these authors concluded that it is not possible to reliably determine whether ablation success rates using the low activity are similar to those using the high activity. This statement was in contrast with the analysis presented by Doi *et al.* [22]. In line with their previous report, they clearly stated that the available data continue to favor higher doses of radioiodine (ranging from 2775 to 3700 MBq) for remnant ablation, especially after near-total thyroidectomy. The use of high doses in these patients results in about one-third less risk of non-ablation than low doses. Our data support the use of higher doses in thyroid cancer.

Regarding the results in the present study and the data published in the literature, it is highly important to stress the difference between the ^{131}I activity administered and the absorbed dose of radiation in thyroid tissue. The absorbed dose causes the ablation effect. This dose depends on several factors, such as

uptake of ^{131}I and retention time in the remnants, the mass of the thyroid remnant, different TSH values, the initial activity given and patient's preparation. Despite the fact that a standard amount of radioactivity is used in the present study protocols, it may still result in different ablation doses.

In both academic hospitals, the aim of surgery is to do an optimal resection of malignant tissue, which is a combination of a (near-) total thyroidectomy combined with a neck dissection in case of lymph node metastases. In T4 tumors, there seems to be, however, a high chance of residual malignant cells in the thyroid remnants. In addition, a comparable phenomenon has been described for N1 disease, in which even after a modified neck dissection micrometastases in left lymph nodes cannot be excluded. In the literature, it has been described that thyroid carcinoma cells take up and process iodine less efficiently than normal thyroid cells due to a lower expression of the sodium-iodine symporter [23-25]. In a recently published study on prognostic parameters in thyroid cancer, both N1 and T4 tumor stages significantly correlated with a high chance of local tumor recurrences [26]. Consequently, minimal residual disease could be a thorough explanation for the fact that our study did not show a statistically significant difference in ablation results between the two protocols in case of T4 and/or N1 tumors. Even a mean activity of ^{131}I up to 5000 MBq as used in the fixed ablation dose, which is twice as much as applied in the uptake-related strategy, fails to achieve a complete response in 60 and 92% of the patients with N1 and T4 tumor stage respectively. In addition, in only 1 out of 10 and 9 patients with T4N1 disease in the uptake-related and fixed-dose strategies respectively, success was achieved. These findings are in agreement with data published by Rosaria *et al.* [27]. They studied 274 patients with DTC and found a clear relationship between ablation failures and the presence of metastases and tumors larger than 4 cm in diameter. However, also thyroid remnants with an uptake >5% resulted in a higher failure rate.

It has to be realized that two factors could have influenced the treatment results

in the present study. First, the two centres used different follow-up strategies. An endocrinologist of the LUMC performed the clinical follow-up of patients who underwent ablation in the LUMC. The clinical follow-up of a part of the UMCU patients is in their own (referring) hospitals by means of ^{131}I diagnostic scintigraphy and Tg measurements. This subgroup of UMCU patients only returns to the UMCU if additional radioiodine treatment is required (in case of unsuccessful ablation). This effectively may create a bias, as a number of patients with a successful ablation cannot be included in the present study. In this respect however, the missing data would have further increased the overall success rate in the fixed-dose group compared with the uptake-related protocol. Second, it has been shown that relatively low diagnostic activities of ^{131}I may lead to impaired ability of remnant thyroid tissue to concentrate the subsequent ablative dose of ^{131}I (so-called stunning effect) and thereby reduce therapeutic efficacy [28-31]. Although this phenomenon has been acknowledged for some time, the precise time interval and ^{131}I activity after which it occurs is still a subject to discussion. If an applied activity of 40 MBq causes a lower concentration of ^{131}I in the thyroid remnant, part of the effect seen in this study could have been attributed to the stunning effect with a probable bias against the uptake-related protocol. However, data on stunning effects caused by such low doses have not been reported yet.

In the present study, we evaluated patients at 6-12 months after ablation, demonstrating a significant difference in short-term outcome. However, data on long-term recurrence rates are currently not available. The number of studies evaluating differences in long-term outcome in patients treated with high or low ^{131}I doses is scarce. Data presented by Chow *et al.* clearly demonstrated the influence of radioiodine after surgery regarding the 5-, 10- and 15-year local relapse rate [32]. In patients not treated by radioiodine after surgery, the cumulative relapse rate after 15 years follow-up was 20.9% compared with 9.2% in patients treated with radioiodine. In this study, patients who were treated

received a mean dose of 3400 MBq at initial stage. It was shown by Verburg *et al.*, that a successful ablation itself seems to be a highly important prognostic factor for long-term outcome [33]. They found that of the patients with a successful ablation, 87% were still free of the disease after 10 years, whereas of the patients with an unsuccessful ablation, only 50% were free of disease (p<0.001). According to this finding, a higher recurrence rate may be expected during follow-up in the uptake-related protocol group compared with the group of patients treated according to the fixed-dose protocol. However, this statement is not supported by data recently published by Rosario *et al*. [34]. They treated 82 patients with 3700 MBq ^{131}I and 44 patients with 1100 MBq. At the end of a 5-year follow-up period, the recurrence rate was 3.6% in patients who had received the high dose and 3.4% in those treated with the low dose (p=NS). Criteria used for patient's selection and risk factors were unfortunately not reported, which may have caused a selection bias. Therefore, more randomized trials are required to assess the short- and long-term outcome in relation to the ablation dose used in DTC ablation.

Conclusion

The fixed-dose ablation protocol, using relatively higher ^{131}I activities, is generally more effective in thyroid remnant ablation than a 24-h ^{131}I uptake-related ablation protocol that uses relatively low activities. This difference, however, is not observed in patients with T4 and/or N1 tumor stages, which can be clarified by the presence of minimal residual malignant disease. The present study addressed the issue of ablation efficacy as judged by scintigraphy and Tg measurements after 6-12 months, whereas long-term outcome was not evaluated. Therefore, follow-up studies are necessary to solve whether this lack of difference between both algorithms results in poorer long-term outcome.

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Chapter 4

The success rate of ^{131}I ablation in thyroid cancer patients is significantly reduced after a diagnostic activity of 40 MBq ^{131}I

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Abstract

Objective: Dosimetry studies have shown that activities of ^{131}I as small as 10-20 MBq may cause a stunning effect. A result of this stunning effect may be a lower success rate of the ablative ^{131}I therapy for differentiated thyroid carcinoma (DTC). The aim of this study was to determine whether pre-therapeutic uptake measurement with 40 MBq ^{131}I causes a lower success rate of ablation.

Design: retrospective chart review study.

Patients, methods: In two hospitals the ablation protocols differed in one respect only: in the one hospital no diagnostic ^{131}I was applied before ablation (group 1, n=48), whereas in the other hospital a 24-h uptake-measurement with 40 MBq ^{131}I was performed (group 2, n=51). Included were all DTC patients without distant metastases who had undergone ^{131}I ablation between July 2002 and December 2005, and who had returned for ^{131}I follow-up. Successful ablation was defined as absence of pathological ^{131}I uptake on diagnostic whole-body scintigraphy and undetectable thyroglobulin-levels under TSH stimulation.

Results: Overall, ablation was successful in 31/48 patients (65%) in group 1 and in 17/51 patients (33%) in group 2 (p=0.002). Multivariate analysis showed that pre-therapeutic uptake measurement using 40 MBq ^{131}I was an independant determinant for success of ablation (p=0.002).

Conclusions: After applying a diagnostic activity of 40 MBq ^{131}I before ablation, the success rate of ablation is severely reduced. Consequently, the routine application of ^{131}I for diagnostic scintigraphy or uptake measurement prior to ^{131}I ablation is best avoided.

Introduction

The therapy of choice in patients suffering from differentiated thyroid carcinoma (DTC) is (near-) total thyroidectomy. To DTC patients except for those with a papillary carcinoma ≤1 cm in diameter it is recommended to subsequently administer a high activity of ^{131}I, with the intent to ablate remnant thyroid tissue [5]. There is still some discussion whether follicular thyroid carcinoma patients with a tumour diameter ≤1 cm should receive the ^{131}I ablation treatment [29,34].

In many centres this ^{131}I ablation is preceded by pre-therapeutic uptake measurement using a small activity of [131]I [41,42]. A potential disadvantage of this is the presumed stunning effect to thyroid remnants [16,35], i.e. a diminished uptake of ablative ^{131}I activity after the application of a diagnostic ^{131}I activity.

This stunning effect may be noticed either by a lower than expected ^{131}I uptake on a post-ablation scintigram, or as a higher failure rate of ablation. The precise definition of stunning in the context of ^{131}I ablation has not been established, with many authors only reporting a visual difference in ^{131}I uptake by the thyroid remnant and only few offering quantitative evidence. Whereas not all authors agree that this phenomenon occurs [22,25,36], it has been demonstrated by others in malignant [12,16,17,26,30] and benign thyroid disease [14].

Dosimetry studies have shown that activities of ^{131}I as small as 10-20 MBq may deliver a significant radiation dose to thyroid cells [16,23], suggesting that the stunning effect may be due to direct radiation damage to thyrocytes. This is also supported by a study from Postgard *et al*. which showed that absorbed radiation doses as little as 3 Gy already reduced iodine transport by 50% [33]. Evidence was presented of downregulation of the sodium iodine symporter expression in reaction to diagnostic activities [27], thus reducing the uptake of [131]I [19].

At the University Medical Center Utrecht (group 1) and at the Leiden University Medical Center (group 2), two academic hospitals with geographically partially

overlapping patient populations, comparable fixed activity ablation protocols were used since July 2002 [4]. However, there is one difference:

- Group 1: no pre-therapeutic uptake measurement is performed,
- Group 2: a pre-ablative 24-h uptake measurement is performed (40 MBq ^{131}I).

Our aim was to determine whether this pre-therapeutic procedure with 40 MBq ^{131}I causes a lower success rate of ablative ^{131}I therapy in post-operative DTC patients.

Patients, material, methods

Study population

All DTC patients after thyroidectomy and without distant metastases (known before initial treatment or demonstrated by post-ablation scintigraphy or computed tomography / magnetic resonance imaging studies during initial treatment), who received ^{131}I ablation treatment in one of our centres between July 2002 and December 2005, were included in a retrospective study. Further inclusion criteria were:

- ablation had been performed in accordance with the hospitals' protocols;
- 6-12 months after ablation, patients had returned for diagnostic scintigraphy or additional treatment with ^{131}I and for measurements of thyroglobulin (Tg) levels during TSH stimulation.

Pre-ablative 24-h ^{131}I uptake

In group 1 the ablative activity was administered without prior diagnostic scintigraphy. In group 2 pre-ablative 24-h ^{131}I uptake measurements were performed in order to assess the percentage of ^{131}I taken up by the thyroid remnant using standard techniques: a capsule with 40 MBq ^{131}I was given orally, followed by planar scintigraphy of the neck region 24 h later.

A standard of 40 MBq ^{131}I, calibrated on the day of administration and measured in a neck phantom after 24 h, was used as a reference. The ablative ^{131}I activity was administered on the day after the uptake measurement. Patients with a ^{131}I uptake >15% would have been referred to the surgical department for evaluation of additional surgical treatment, but this never occurred.

Fixed activity ablation protocol

A fixed activity ablation protocol was used in the University Medical Center Utrecht from January 1990 onward and at the Leiden University Medical Center from July 2002 onward. All patients underwent ^{131}I ablation 4-6 weeks after (near-) total thyroidectomy. Patients did not receive L-T4 medication between surgery and ablation. In both centres TSH-levels had to be equal to or greater than 30 mU/l before ablation could take place. Since the Netherlands is an iodine-sufficient country, in both centres patients had been instructed to keep a low-iodine diet for one week prior to ablation [8,32].

An activity of 3700 MBq ^{131}I was administered to patients without (known) metastases or 5550 MBq to patients with nodular involvement (detected pre- or peri-operatively). Node negative patients with extensive extrathyroidal tumour growth (n=8) or Hürthle carcinomas (n=6) also received 5550 MBq.

Follow-up, laboratory analyses

6-12 months after ablation, patients returned to their respective hospitals for follow-up. At the UMCU this was performed with rhTSH stimulation using 370 MBq of ^{131}I while at the LUMC levothyroxin was withdrawn for 4 weeks and 185 MBq of ^{131}I was given. In both centres TSH-levels were checked before administration of ^{131}I and had to be ≥30 mU/l. At this follow-up blood was drawn for the measurement of TSH-stimulated Tg-levels. Concurrently, scintigraphy with a large-field-of-view camera and high-energy collimators in

both centres was performed, acquiring a scan of the entire body and separate planar acquisitions of the cervical region.

In group 1 the BRAHMS Dynotest Tg-pluS kit for measurement of Tg-levels and levels of Tg-antibodies was used (BRAHMS Diagnostica GmbH, Berlin, Germany). The lower detection limit of this kit was 0.2 μg/l. In group 2 the BRAHMS Dynotest Tg-S kit for measurement of Tg-levels and levels of Tg-antibodies was used (BRAHMS Diagnostica GmbH, Berlin, Germany), with a lower detection limit of 0.5 μg/l.

In the presence of antibodies, test results for Tg are not reliable [21,39]. As the assays used in both hospitals were IRMA assays, interference from antibodies against Tg generally would have resulted in underestimation of Tg-levels. Hence, eight patients with Tg test results below the cut-off level and with negative whole body scintigraphy were excluded from analysis because Tg antibodies were present in their serum.

Successful ablation, statistics

As our primary definition, ablation was considered successful if 6-12 months after the initial ^{131}I therapy patients fulfilled all of the following criteria:

- no additional therapy of any kind for thyroid cancer between ^{131}I ablation and first TSH-stimulated follow-up;
- TSH-stimulated levels below the detection limit of the assay;
- absence of pathologic ^{131}I accumulations on whole-body scintigraphy, including absence of a visually discernable uptake focus in the thyroid bed as rated by the nuclear medicine physician at the time.

In literature further measures are advised if Tg-levels meet certain cut-off levels, usually 1 μg/l [28] or 2 μg/l [6]. In order to study the clinical relevance of our findings we also analysed the overall success rate of ablation using both these cut-off levels combined with the other two criteria mentioned.

For statistical analysis we used SPSS version 12.0 for Windows (SPSS inc., Chicago, Illinois, USA). Statistical significance was defined as p<0.05. The quantitative data (continuous parameters) were analysed using the Mann-Whitney *U* test. For categorical data the Chi-squared test was used. Multivariate analysis was performed using binary logistic regression with a forward selection method based on likelihood ratios.

Results

Study population, cut-off

The 48 patients in group 1 received ^{131}I ablation without a pre-ablative uptake measurement, whereas the 51 patients in group 2 first underwent a 24-h-^{131}I-uptake measurement. Patient characteristics for both groups as well as tests for differences between the two groups are given in table 1; none of these differences were statistically significant.

Tg-levels undetectable

Overall, ablation was successful in

- 31/48 patients (65%) in group 1, and
- 17/51 patients (33%) in group 2.

The difference is statistically significant (p=0.002). Table 2 displays the results of analyses of various subgroups. In most subgroups, there was a significant difference between group 1 and group 2 with regard to success of ablation. In some subgroups (e.g., male patients or patients with follicular thyroid carcinoma) for which the group size was insufficient to show a significant difference, the distribution of successful vs. unsuccessful ablation approximated that of the total group. Remarkable was the lack of a significant difference between group 1 and group 2 for those patients who received 5550 MBq ^{131}I.

In order to exclude tumour size affecting the results, we compared all node negative patients without extrathyroidal tumor invasion (T1-3N0M0 according

to the 5th edition of the TNM system) [38] from group 1 (n=30), as no uptake data were available, with only those patients (n=18) from group 2 with an uptake of <5 %, reflecting a smaller thyroid remnant. In this analysis too group 1 did significantly better (p=0.024). Also we compared 6 node negative patients with extrathyroidal tumour invasion from group 2 with an uptake percentage $\geq 8\%$ with 11 patients who showed an uptake ≤ 2 %, representing the highest and lowest uptake percentages, respectively. The difference between the two groups was not significant (p=0.62).

For each group we also compared the results of those patients receiving 3700 MBq with those receiving 5550 MBq. This resulted in p=0.047 for group 1, and p=0.83 for group 2.

Multivariate analysis showed that having received a diagnostic ^{131}I activity was the most significant factor influencing the chance of successful ablation (p=0.002). The only other significant influence was having extrathyroidal tumour growth (p=0.007).

Tg-levels <1 µg/l and <2 µg/l

Ablation was deemed successful by using as cut-off

- Tg-levels <*1* µg/l
  - 35/48 patients (73%) in group 1, and
  - 26/51 patients (51%) in group 2
- Tg-levels <2 µg/l
  - 37/48 patients (77%) in group 1, and
  - 27/51 patients (53%) in group 2

The differences are statistically significant: p=0.025(Tg <1 µg/l); p=0.012(Tg <2 µg/l).

Table 1. Baseline characteristics of patients treated without (group 1) and with (group 2) pre-ablative diagnostic ^{131}I scintigraphy and differences between the two protocols.

	Group 1		Group 2		p value
No. Patients	48		51		
Mean age in years (range)	45.2 (19-80)		43.8 (13-79)		0.57
Gender					0.98
Male	14	(29%)	15	(29%)	
Female	34	(71%)	36	(71%)	
Histology					0.40
Papillary carcinoma	40	(83%)	39	(76%)	
Follicular carcinoma	8	(17%)	12	(24%)	
Extrathyroidal invasion					0.57
Not present	44	(92%)	45	(88%)	
Present	4	(8%)	6	(12%)	
Lymph node metastases					0.10
Not present	30	(59%)	40	(78%)	
Present	18	(41%)	10	(20%)	
Unknown	0		1	(2%)	
Administered activity					0.40
3700 MBq	34	(71%)	32	(63%)	
5550 MBq	14	(29%)	19	(37%)	

Table 2. Comparisons the rates of successful ablation (defined as undetectable Tg-levels, no visible pathologic ^{131}I uptake and no intermittent further treatment) of various subgroups in group 1 and group 2.

	Group 1 successful ablation	Group 2 successful ablation	p value
Total group	31/48 (65%)	17/51 (33%)	0.002
Males	9/14 (64%)	5/15 (33%)	0.10
Females	22/34 (65%)	12/36 (33%)	0.009
Papillary carcinoma	25/40 (63%)	11/39 (28%)	0.002
Follicular carcinoma	6/8 (75%)	6/12 (50%)	0.26
No extra-thyroidal invasion and node negative	23/30 (77%)	15/37 (41%)	0.003
Extra-thyroidal tumor invasion and/or node positive	8/18 (44%)	2/13 (15%)	0.09
3700 MBq	25/34 (74%)	11/32 (34%)	0.001
5550 MBq	6/14 (43%)	6/19 (32%)	0.51

Discussion

Our study shows substantial differences in efficacy of ^{131}I ablation, correlated with pre-therapeutic administration of 40 MBq [131]I: the success rate of ablation in the group without pre-ablative scintigraphy is nearly twice that of the group who underwent pre-therapeutic ^{131}I uptake measurement.

Stunning remains controversial

Thyroid stunning remains a controversial issue. Jeevanram *et al*. [12] were the first to report a 25-75% decrease in uptake of therapeutic ^{131}I activities after diagnostic scanning with 111-185 MBq [131]I. Subsequently, several authors have

reported various degrees of stunning of thyroid remnants after the administration of ^{131}I activities ranging from 74 MBq [16], to 111 MBq [26], 185 MBq [11,17], and 370 MBq [30], all resulting in a less successful outcome than a control group that was scanned either with a much lower (37 MBq) [131]I activity [26], with [123]I [17,30], or without any pre-therapeutic ^{131}I before ablation [11].

In contrast, McDougall *et al*. [22] and Cholewinski *et al*. [2] reported no visually apparent stunning after diagnostic activities of 74 MBq and 185 MBq ^{131}I, respectively. However, in neither of the latter studies the success rates of ablation were reported. Dam *et al*. [3] reported that even though visually apparent stunning was encountered in a part of their patient population, there were no differences in the success rate of ablation between those who did and those who did not show stunning on pre- or post-ablation scintigraphy. Sisson *et al*. even argued that visually apparent stunning may not be attributed to a diagnostic activity, but rather to early effects from the subsequent ablation activity [37]. However they did not compare to patients who had not received diagnostic ^{131}I activities. Silberstein [36] reported no difference in ablation success rates between patients receiving 14.8 MBq of ^{123}I or 74 MBq of ^{131}I for pre-therapeutic uptake measurement.

The activity of 40 MBq ^{131}I used in the study presented here is lower than those reported in the literature. Thus far there was only scant evidence as to whether or not stunning may be caused by such low ^{131}I activities. Medvedec [23] performed a meta-analysis by fitting a regression model on results reported in four studies, and concluded that thyroid remnant stunning might already occur after administration of ^{131}I activities as low as 10-20 MBq.

Limitations

Whether there is a time point at which a pre-therapeutic diagnostic activity does not influence the outcome of the following ablative activity is questionable and should be subject to further study; few data exist in literature and in this study

success of ablation is already diminished even if the diagnostic activity is given only 24-h before the ablative dose.

The success of ablation treatment is influenced by the size of the thyroid remnant [18]. Even though it is possible that there were some patients in group 1 with a considerably larger thyroid remnant, patients from group 2 did significantly worse even when only the smallest remnants were selected.

Follow-up

There are differences in the follow-up regime between group 1 and 2; both the method of stimulation (rhTSH vs. withdrawal) and the activity used (370 vs. 185 MBq). Neither of these differences should significantly influence the results: it was shown that the activity used for follow-up does not influence the results [31], and a large international trial established that results after rhTSH-stimulated follow-up are equivalent to those after levothyroxin withdrawal [20,40].

From the results of this study it can be deducted that patients with a favourable prognosis suffer most from performing pre-therapeutic ^{131}I uptake measurement: patients receiving 3700 MBq (who have low-risk tumours) show a difference between group 1 and group 2, whereas those receiving 5550 MBq (which are patients with higher risk tumours) do not show such a difference. In addition it turns out that in group 1 there is a large difference in success of ablation between those receiving 3700 and 5550 MBq ^{131}I; this difference is absent in group 2.

Most subgroups showed significant differences between group 1 and group 2; in those subgroups that were too small to achieve a statistically significant difference (e.g., male patients, and patients with follicular carcinoma) we found differences between group 1 and group 2 proportional to those in the entire group.

In order to establish the clinical relevance we also analysed the differences in success rate using different cut-offs for Tg-levels that have been mentioned in literature. Even though the difference was less pronounced than with the stricter criterium of undetectable Tg-levels, we still found a considerable, statistically significant difference in success rate between group 1 and group 2. This indicates that at the first TSH-stimulated follow-up patients in group 2 considerably more often showed Tg-levels at such levels that additional diagnostic or therapeutic measures are indicated, and therefore poses a clinically relevant effect.

Other conditions being equal, it is highly likely that the lower success rate of ablation in group 2, which was seen especially in those with a favourable prognosis, was caused by stunning from the pre-therapeutic uptake measurement procedure with 40 MBq [131]I. Consequently, in order to maximize the success rate of ^{131}I ablation and minimize the number of required additional ^{131}I therapies, 24-h uptake measurements or diagnostic scintigraphy using ^{131}I is best avoided in patients with differentiated thyroid cancer.

Conclusion

Whether pre-ablative diagnostic scintigraphy should be performed is in discussion. Pre-ablation dosimetry, especially using [124]I, may for instance allow a precise determination of the absorbed dose per MBq [131]I [7,13]; which may in turn lead to a reduction in the activity of ^{131}I given, although individual dosimetry may become difficult in patients with a thyroid remnant mass <1 g [9]. Small amounts of ^{131}I before ^{131}I therapy may be useful in determining the largest activity that can be given without a risk for hematologic toxicity [15].

The local situation, legal requirements or the frequent occurrence of large thyroid remnants may also necessitate a pre-ablative uptake measurements. In such cases ^{123}I scintigraphy may also provide a valuable alternative; to date no evidence of stunning of thyroid remnants after ^{123}I has been reported [1,10,24].

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Chapter 5

A new functional parameter measured at the time of ablation that can be used to predict differentiated thyroid cancer recurrence during follow-up

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Abstract

Background: This study addresses the questions whether patients with a high risk for recurrent thyroid cancer can be identified at initial stage, i.e. at the time of ablation.

Methods: We evaluated tumor recurrence in consecutive patients treated for differentiated thyroid cancer (DTC). Prognostic factors were statistically analyzed. We defined prognostic parameters based on thyroglobulin (Tg) levels, 24-h ^{131}I uptake rates and TSH levels: (a) Tg/TSH, (b) Tg/24-h ^{131}I uptake value, and (c) Tg/(TSHx24-h ^{131}I uptake).

Results: We included 190 patients (50 male, 140 female; mean age 47 years) with DTC for analysis, 146 without distant metastases and 44 with M1 tumor stage at initial presentation. The mean period of follow-up was 10.4 years (SD± 3.7 years). In 18 out of the 146 DTC patients with M0 disease (12.4%), tumor recurrence was found during follow-up. Although tumor stage, age, and standard biochemical values significantly differ between patients with and without recurrent disease or between patients with M0 and M1 tumor stage, the newly defined parameter Tg/(TSHx24-h ^{131}I uptake) was the best independent significant prognostic parameter in the assessment whether patients will develop a tumor recurrence during follow-up or not.

Conclusion: High Tg/(TSHx24-h ^{131}I uptake) ratios justify an adjustment of the ^{131}I activity for ablation therapy. To assess the optimal cut-off level for a dose adjustment, however, further studies are required in more patients, but the initial results are encouraging with respect to improving outcome in DTC patients.

Introduction

Differentiated thyroid cancer (DTC) is a rather uncommon tumor with a high survival rate. The therapy of choice consists of (near-) total thyroidectomy followed by ablation with radioiodine-131 (^{131}I). This combined treatment schedule is a prerequisite for an optimal tumor destruction as well as for an optimal patient follow-up [1]. The currently used follow-up strategy is based on regular thyroglobulin (Tg) measurements under thyroid stimulating hormone (TSH) stimulation (Tg-off levels) either using thyroid hormone withdrawal or rhTSH and ^{131}I whole body scintigraphy (WBS). Later on, Tg levels without TSH stimulation may guide the clinician during the follow-up of DTC. The purpose of optimal follow-up protocols in thyroid carcinoma is the early detection of recurrent or metastatic thyroid cancer, as it has a great impact on morbidity and mortality. Indeed, patients with recurrent DTC have a less favorable prognosis than those with primary disease, as more than 50% of patients with a recurrence experience tumor-related mortality. One of the major issues in such cases is the fact that a tumor recurrence may loose the ^{131}I uptake capacity [2]. In this respect, it has been stated that high ablation doses may be recommended to decrease the risk not only for persistent thyroid remnants but also for tumor recurrence. The question, however, could be raised whether this should be applied in all DTC patients or in subgroups only [3-6]. Therefore, it would be helpful to have one single or a combination of prognostic parameters at initial stage that can be used to identify patients with a high risk for tumor recurrence during follow-up. Thyroglobulin measured at initial stage may be of prognostic value, but its value cannot be disconnected from the TSH stimulation and the amount of residual disease after surgery, expressed as the 24-h ^{131}I uptake value. In the present study, this value is a surrogate value for remnant size. Although ultrasonography or computed tomography (CT)-scanning of the head and neck region would give a better estimation of the residual thyroid volume after surgery than the uptake value, these imaging techniques are less

reliable shortly after surgery due to edema. Furthermore, contrast administration is required for optimal CT-scanning of the neck which interferes with subsequent ^{131}I therapy.

In the present study, data from 190 patients with newly diagnosed DTC were analyzed in order to assess the prognostic value of commonly determined initial parameters in the prediction of a tumor recurrence during follow-up. Furthermore, we studied the prognostic value of three newly defined parameters which are based on Tg under endogenous TSH stimulation, TSH levels, and/or the 24-h ^{131}I uptake value, all measured at the time of ablation. With the results, we might be able to adjust the ^{131}I ablation activity to decrease the risk of a recurrence and to improve morbidity and mortality.

Material and methods

Study population

Data were collected from the records of consecutive patients with DTC who received ablation treatment with ^{131}I at the Leiden University Medical Center (LUMC) between January 1986 and December 1999. This included a total of 255 patients with pathologically verified DTC, i.e. either papillary, follicular, mixed papillary follicular, or follicular Hürthle carcinoma. For the current evaluation, a follow-up period of at least 1 year was required. Exclusion criteria were: missing biochemical parameters, the presence of Tg-antibodies (Tg-abs levels >50 µg/l), or TSH levels <20 U/l at the time of ablation (n=49), unknown uptake (n=17), and/or follow-up of <1 year (n=10). As a result, 65 patients were excluded, resulting in a total study population of 190 patients. Out of these 190 patients, 146 had no distant metastases, whereas 44 had metastases at the time of initial diagnosis.

Hospital records were reviewed and the following (prognostic) data were recorded: age, gender, histopathological data, treatment characteristics, and laboratory values. Records of scintigrams were analyzed and coded. Tumor

staging was scored according to the criteria of the fifth tumor node metastasis (TNM) Atlas. We defined three new parameters as follows: (i) Tg/24-h ^{131}I uptake, (ii) Tg/TSH, and (iii) Tg/(TSHx24-h ^{131}I uptake) (Tg is expressed in µg/l and TSH in U/l).

Radioiodine treatment

Therapy for DTC consists of (near-) total thyroidectomy, followed 4-6 weeks later by radioiodine ablation therapy. During this interval, no treatment with L-thyroxin was initiated in order to increase TSH levels. The 24-h ^{131}I pre-treatment uptake value in the neck region was measured using standard techniques: 40 MBq of ^{131}I was given orally, followed by planar scintigraphy of the neck region 24 h later. This uptake value is regarded as a surrogate value for remnant size in the present study. Although stunning may occur during diagnostic scanning with ^{131}I, a recent study by Dam *et al.* [7] demonstrated that treatment efficacy is not influenced by activities <185 MBq [7-9]. In addition, follow-up studies and subsequent treatment are used to achieve a complete ablation. In case of a possible stunning effect, ablation failures will be depicted 6 months after initial treatment (see evaluation of treatment efficacy).

A standard ^{131}I activity of approximately 2800 MBq was given orally 24 h after the uptake measurement and adjusted in case of large thyroid remnants. The rationale of this quantitative approach is to avoid unnecessary exposure and local radioiodine side effects. In this regimen, no adjustments were made in the case of cervical lymph node metastases. Treatment of patients with M1 tumor stage at initial presentation as well as subsequent treatment for either initial ablation failures or recurrent disease was done with 6100 MBq of [131]I. Seven days after each treatment, whole-body scans were made according to the protocol described below to assess loco-regional uptake and the presence of metastases.

Evaluation of treatment efficacy

Six months after the ablation therapy, L-thyroxin was withdrawn for at least 4 weeks. Subsequently, radioiodine diagnostic whole-body scintigrams were obtained 3 days after the administration of 185 MBq of ^{131}I or 24 h after the administration of 370 MBq ^{123}I. For all scintigrams, a Toshiba gamma camera (Tokyo, Japan) was used. A high-energy collimator (matrix sizes of 256 X 1024 and 256 X 256, window of 20% centered at 360 keV) for the ^{131}I WBS, a low-energy collimator (matrix sizes of 256 X 1024 and 256 X 256, window of 20% centered at 159 keV) for the ^{123}I WBS was used.

Anterior and posterior whole-body and planar views of the neck region were routinely obtained. For the whole-body scintigrams, scanning rates of 15 (^{131}I) and 10 cm/min (^{123}I) were used. In addition, Tg levels were determined at the time of the diagnostic whole-body scan to document the ablation efficacy. For successful ablation, a cut-off level of Tg of ≤1 μg/l was applied. Patients with an unsuccessful ablation, documented by scintigraphy and/or a Tg level >1 μg/l during TSH stimulation after 4 weeks of L-thyroxin withdrawal, received a second treatment with ^{131}I.

Recurrent disease was defined as increased Tg levels, abnormal WBS, or both but not within 2 years after ablation and following at least one diagnostic session with normal test results. Persistent disease or ablation failures were defined if one or both tests remained abnormal after ablation, irrespective of the time interval.

Analytical methods

Until 1997, serum Tg was measured using an IRMA, the Dynotest TG (Brahms Diagnostica GmBH, Germany), with a detection limit of 1 μg/l. From 1997 onwards the Dynotest TG-s (Brahms Diagnostica GmBH) was used, with a detection limit of 0.5 μg/l. Recurrent disease, however, was defined as Tg levels >1 μg/l. TSH levels were measured by means of an immunofluorometric assay

(IFMA) with the Delfia (Wallac, Turku, Finland) until 1997. Thereafter, an immunoluminometric assay (ILMA) was used with the Elecsys (Boehringer Mannheim, Germany). Serum Tg-abs were determined by the Ab-HTGK-3 IRMA test (DiaSorin Biomedics, Italy).

Data collection and statistical analysis

All collected data were put in a database using MS-Access 2000. Statistical analysis was performed with SPSS 11.5 for Windows (SPSS Corporation, Chicago, IL, USA) and MS-Excel 2000. The quantitative data were analyzed using Cross-tabs with χ^2, Student's *t*-test, Cox regression, Cox regression forward stepwise, and by calculating curve coordinates. The prognostic value of the patient characteristics was quantified with the hazard ratio and its 95% confidence level. Throughout, a p value of 0.05 or less was considered statistically significant. Finally, three subgroups were identified for statistical analysis: patients with initially M0 stage DTC, irrespective of recurrent disease during follow-up; patients with initially M1 stage DTC; and finally, patients with initially M0 stage disease, but with recurrent DTC during follow-up. For the generation of the probability plot and prognostic stratification, only patients with initially M0 disease were used, whereas their results were compared with patients with M1 disease to assess the overall value of the study results.

Results

In the present study, 190 patients (50 male, 140 female; mean age 47.1 years) with DTC were included for further analysis, 146 without distant metastases and 44 with M1 tumor stage at initial presentation. Papillary thyroid carcinoma, consisting of papillary and mixed papillary follicular, was diagnosed in 102 patients. Follicular thyroid carcinoma was diagnosed in 44 patients. In the present study, 49 patients had lymph node involvement at the time of thyroidectomy. The mean period of follow-up was 10.4 ±3.7 years. In 18 out of

the 146 DTC patients with M0 disease (12.4%), tumor recurrence was found during follow-up. A total of 14 patients died in the group without metastases, 6 from the differentiated thyroid carcinoma, whereas 8 died from other causes, such as second primary tumors.

Table 1 shows subgroup characteristics of patients with initially M0 stage (n=146) and patients with M1 stage (n=44) DTC as well as for patients with initially M0 stage without (n=128) and with (n=18) recurrent disease respectively. Significant differences were found between almost all parameters tested between patients with M0 and M1 initial tumor stage. For age, we found a cut-off level of 59 years between those with a high and low risk for recurrent disease. In patients with M0 disease, age at diagnosis (>59 years), T stage, N stage, and all newly defined parameters were significantly different between those with and without tumor recurrence during follow-up. For the risk of recurrent disease, Tg levels (p=0.027), N stage (p=0.038), and Tg/TSH (p=0.021) were significant correlates for tumor recurrence. In stepwise analysis, an increased ratio of Tg/(TSHx24-h ^{131}I uptake) was selected as the most reliable variable (p=0.001) for tumor recurrence (Figure 1), with a Hazard rate of 12.1 (95% CI: 6.61-22.13). Initial ablation failure was not found to be a significant indicator for tumor recurrence. The number of patients with initial ablation failure was not significantly different between the groups with and without recurrent disease (p=0.522).

To assess whether the parameters studied may be indicative for bulky disease, we compared the parameters of patients having initially M1 disease with those having initially M0 disease and tumor recurrence during follow-up. In this respect, age at diagnosis was significantly different between these subgroups (p=0.021; see Table 2). Finally, we combined patients with M1 with patients with recurrent disease into one group to determine the accuracy of Tg/(TSHx24-h ^{131}I uptake) in the assessment of bulky disease at the time of ablation.

The area under the receiver operating characteristic (ROC) curve was 0.800 (95% CI: 0.714-0.866).

Table 1. Differences between differentiated thyroid cancer patients with and without metastases and between patients with and without recurrent disease during follow-up.

	Patients with initially M0 (SD) (n=146)	Patients with initially M1 (SD) (n=44)	p value	M0 without RD (SD) (n=128)	M0 with RD (SD) (n=18)	p value
Gender: Male / Female	32 / 114	13 / 31	0.400	27 / 101	5 / 13	0.521
Age at diagnosis	42.6 (±14.87)	61.9 (±16.46)	0.001	41.5 (±14.02)	50.7 (±18.3)	0.013
Histology			0.007			0.700
Papillary carcinoma	120	27		104	16	
Follicular carcinoma	26	17		24	2	
T-stage			0.001			0.003
T1	7	1		5	2	
T2	89	16		85	4	
T3	25	5		20	5	
T4	25	22		18	7	
N-stage			0.001			0.001
N0	110	31		101	9	
N1	36	13		27	9	
TSH (U/l)	77 (±36)	62 (±17)	0.023	77 (±37)	78 (±34)	0.949
Tg (µg/l)	21 (±110)	1246 (±4066)	0.000	8 (±14)	120 (±321)	0.001
Uptake (%)	6.1 (±7.3)	6.7 (±7.8)	0.621	6.3 (±7.6)	4.7 (±5.3)	0.125
Tg/Uptake	3.9 (±9.2)	827.1 (±3312.3)	0.003	2.5 (±5.6)	15.3 (±19.9)	0.001
Tg/TSH	0.4 (±2.3)	51.2 (±207.9)	0.003	0.1 (±0.2)	2.7 (±6.6)	0.001
Tg/(TSHx24-h ^{131}I uptake)	0.07 (±0.19)	38.00 (±170.55)	0.007	0.04 (±0.07)	0.31 (±0.49)	0.001
Initial ablation failure *				43 (34%)	8 (44%)	0.522

RD, recurrent disease; T stage, tumor stage; N stage, node stage; TSH, thyroid stimulation hormone; Tg, thyroglobulin.
* Evaluation 6-12 months after the ^{131}I ablation therapy.
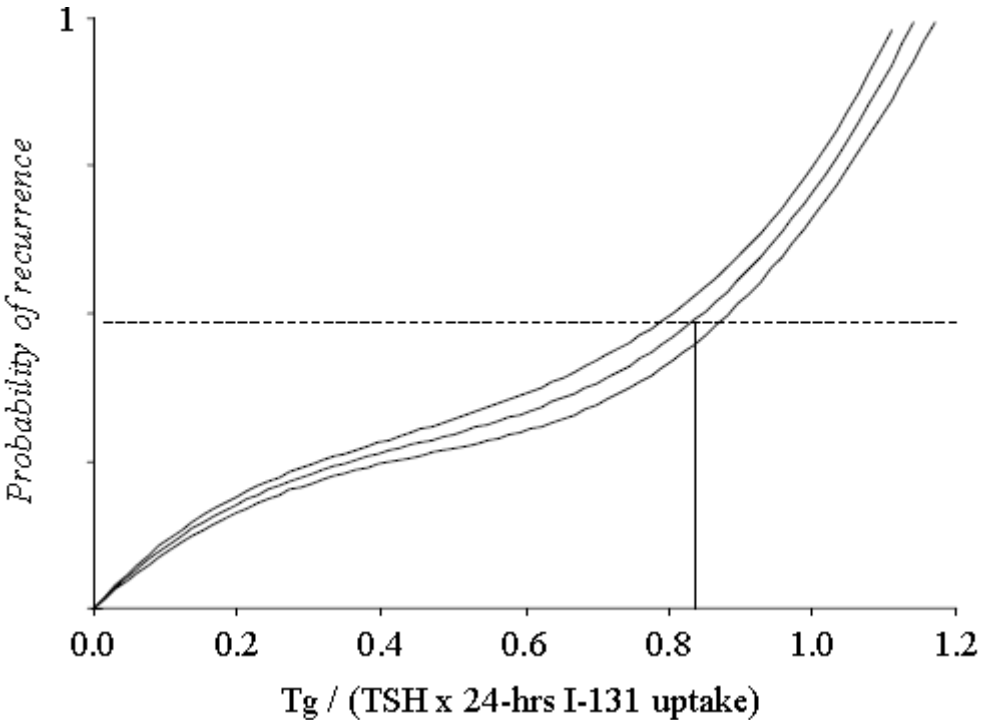
Figure 1. Probability plot of tumor recurrence with its 95% confidence interval in patients with initially MO tumor stage. Tg tryroglobulin; TSH, thyroid-stimulating hormone.

Table 2. Differences between differentiated thyroid cancer patients with initially distant metastases (M1) and with locoregional disease (M0) but a recurrence during follow-up.

	Patients with initially M1 (SD) (n=44)	Patients with initially M0 and RD (SD) (n=18)	p value
Gender: Male / Female	13 / 31	5 / 13	0.889
Age at diagnosis	62 ($\pm$16)	51 ($\pm$18)	0.021
Histology			0.061
Papillary carcinoma	27	16	
Follicular carcinoma	17	2	
T-stage			0.149
T1	1	2	
T2	16	4	
T3	5	5	
T4	22	7	
N-stage			0.217
N0	31	9	
N1	13	9	
TSH (U/l)	62 ($\pm$17)	78 ($\pm$34)	0.225
Tg (μg/l)	1246 ($\pm$4066)	120 ($\pm$321)	0.276
Uptake (%)	6.7 ($\pm$7.8)	4.7 ($\pm$5.3)	0.311
Tg/Uptake	827.1 ($\pm$3312.3)	15.3 ($\pm$20.0)	0.334
Tg/TSH	51.2 ($\pm$207.9)	2.7 ($\pm$6.6)	0.357
Tg/(TSH x 24-h ^{131}I uptake)	38.00 ($\pm$170.55)	0.31 ($\pm$0.49)	0.383

RD, recurrent disease; T stage, tumor stage; N stage, node stage; TSH, thyroid stimulating hormone; Tg, tryroglobulin.

Discussion

In the present study, we have assessed the value of clinical and biochemical parameters in prognostic stratification of patients with DTC at the time of ablation with radioiodine. Although T stage, N stage, age, and standard biochemical values at the time of diagnosis significantly differ between patients with and without recurrent disease or between patients with M0 and M1 tumor stage, we found a considerable overlap between these parameters to be of clinical value. Nevertheless, current study revealed the newly defined parameter Tg/(TSHx24-h ^{131}I uptake) determined at initial stage to be the strongest independent significant prognostic factor for tumor recurrence during follow-up. The Leiden University Medical Center is a reference center for patients with relatively complicated DTC, which is reflected in the high number of patients (n=44) with M1 disease at initial stage. In 12% of the patients with initially M0 disease tumor recurrence was seen during follow-up, which is in agreement with previous publications by others [10-12]. All patients had been treated by near-total thyroidectomy and subsequent ablation with radioiodine approximately 6 weeks after surgery. In a recent report [3], we have described that the use of rather low ablation doses results in failure rates up to 60% and, consequently, in a high number of additional treatments up to more than a year after initial operation. Although a relation between the initial treatment failure and recurrent disease was suggested, this could not be established in the present study, as differences in failure rates between patients with and without recurrent DTC were not statistically significant. This finding is in agreement with the data published by Falvo *et al*. [13].

In a recent report by Haigh *et al*. it was shown that survival of patients with DTC was not significantly influenced by the extent of initial thyroidectomy [14]. The authors found 10-year survival rates of 72 and 78% respectively for total and partial thyroidectomy. In contrast to these results, however, Cushing *et al*. [15] reported on the prognostic value of the extension of initial surgery. They

studied 333 patients with a mean age of 39.7 years and found that a total thyroidectomy revealed better results than a near-total or partial thyroidectomy. Regarding the number of patients with advanced disease at initial presentation in their study, it is not surprising that non-total thyroidectomy did not only result in a high frequency of large thyroid remnants, but also in a high number of patients with tumor remnants.

The fact that the presence of lymph node metastases is a predictive factor for recurrence, irrespective of initial surgery (partial or total thyroidectomy) [16], again underlines the issue that an optimal assessment and subsequent resection of the total tumor mass at initial stage is highly important for prognosis and survival. In addition, subsequent treatment with radioiodine, therefore, is almost a prerequisite for an optimal starting point, especially in extensive disease, as it destroys normal thyroid tissue as well as small tumor remnants. Indeed, Haq *et al.* [17] clearly showed the superior value of a combined therapeutic approach over surgery alone. Despite the low number of patients with recurrent disease in the present study, we found a significant difference in N stage between patients with and without recurrent disease (p=0.001).

Different staging classifications have been proposed over the past decades in hopes of a better identification of high risk patients, i.e. patients with bulky disease. In this respect, the TNM tumor staging system is still the most commonly used system. Although it can be used to differentiate low-risk from high-risk patients, it was found to be less valuable in identifying intermediate-risk groups [10;18]. The age for men, gender and histological subtype (AMES) classification, a system based on age, gender, and histological parameters, as well as the European Organization for Research and Treatment of Cancer (EORTC) classification were both tested in a prognostic study on 499 DTC patients by Jukkola *et al.* [10], revealing that these methods were not reproducible. Finally, the metastasis, age, completeness of resection, local invasion, tumor size (MACIS) scoring classification, which is based on age,

tumor size, incomplete surgery, extra-thyroidal invasion, and distant metastases, was found to leave the definition of the intermediate and high risk groups too wide. Consequently, most of the staging classifications are found to have more or less practical limitations.

One of the most well-known prognostic parameters is age at the time of diagnosis. In this respect, we observed not only a significant difference between patients with M0 disease (42.6 years) and those with M1 disease (61.9 years; p=0.001), but also between M0 tumor stage patients with (50.7 years) and without (41.5 years; p=0.013) recurrent disease. Falvo *et al*. [13] performed a study on biologically aggressiveness of DTC in elderly patients, in which an age exceeding 70 years represented the most unfavorable prognosis. Haq *et al*. [17] reported a comparable age of 70 years and older in relation to a poor outcome. Both Volante *et al*. [19] and Siironen *et al*. [20] described an age of >45 years in close relation to an aggressive tumor behavior. Based on the present data, however, it can be concluded that age at initial diagnosis is indicative for tumor extension, but it is not an independent prognostic parameter that can be used to identify patients with a high risk for tumor recurrence. Indeed, regarding age, the overlap between the subgroups defined is too much to be useful in clinical practice.

As tumor extension at initial presentation is highly important for the assessment of prognosis and clinical outcome, it would be helpful to have a test that better reflects tumor burden than current staging and imaging techniques. In one of the most interesting publications on this subject, a clear relation between tumor burden and thyroglobulin levels was described [21]. The authors reported not only that the number of metastatic lesions was linked with serum Tg/TSH levels, but also their total volume. The diagnostic value of Tg was confirmed and established in subsequent reports and it was demonstrated that the value of stimulated Tg levels, i.e. levels measured after hormonal withdrawal, clearly identifies persistent or recurrent disease. In a study by Giovanella *et al*. [11],

post-surgery Tg levels above 4.5 µg/l identified 94% of patients with metastasis, which, according to the authors, could be taken into account in treatment planning. Bernier *et al*. showed that Tg levels measured at the time of ablation and 5 days later expressed as TgD5/TgD0 ratio were highly suggestive for treatment failure [22]. The larger the ratio, the better the final outcome. In other studies, Tg levels measured at 3 or 6 months after ablation were found to be strongly correlated with metastatic disease and the authors concluded that levels measured at these time intervals are indicative for an intensive follow-up scheme or additional treatment [23;24]. Others have shown that the best positive predictive value for the detection of a local recurrence is brought by the slope of the Tg levels [25;26]. Finally, Kim *et al*. [27] showed that Tg levels measured at the time of immediate postoperative ^{131}I remnant ablation correlated well with serum Tg levels at the time of diagnostic whole-body scanning during follow-up. High Tg levels were indicative for tumor persistence or recurrence of disease in the earliest postoperative period.

Under normal circumstances, i.e. in normal thyroid tissue, an optimal re-uptake and storage mechanism should prevent leakage of Tg into the bloodstream. In clinical practice, however, it has been found that this physiologic mechanism is not fulfilling this task completely with measurable Tg levels as a consequence in patients with normal function of the thyroid gland. Increased Tg production and a distortion of the physiological process, as seen in infection and malignancy, results in a misbalance and in increased serum Tg levels compared with normal circumstances, a phenomenon that is enhanced by TSH stimulation. Indeed, from data in literature, it is known that Tg measurements after hormonal withdrawal have a higher accuracy than Tg-on levels in the detection of malignancy. In this respect, a TSH stimulation >20 U/l is regarded as prerequisite for an optimal Tg measurement. In general, patients who are admitted for ablation with radioiodine have normal thyroid tissue remnants in the neck region. Despite the optimal TSH stimulation at that time to facilitate an

optimal ^{131}I uptake, Tg levels should be relatively low in the case of a normal function of the remnant, as the re-uptake and storage mechanisms are intact. On the other hand, the levels may be significantly increased in remnants harboring malignant cells. In the present study, we have evaluated whether an increased Tg level is caused by a large nearly stimulated thyroid remnant or a small remnant with stimulated thyroid cancer cells. For this purpose, we have normalized the Tg levels for both the amount of functional thyroid tissue, expressed in a 24-h uptake value, and the amount of TSH stimulation. Although we used a low dose ^{131}I 24-h uptake scan before therapy, it has become more and more common practice to perform a post-therapy scan with uptake measurements over the neck region. In this respect, one of the major issues for discussion is the possible stunning effect that may occur even when using activities of ^{131}I in the range of 40 MBq [7-9]. Since therapeutic activities of ^{131}I are nowadays more based on tumor stage instead of uptake values, post-treatment uptake values may be advised for prognostic stratification to avoid stunning effects by pre-treatment scans.

We found significant differences in Tg levels at initial presentation between patients with (mean level, 8 μg/l) and without (mean level, 120 μg/l) recurrent disease during follow-up, whereas TSH stimulation and 24-h uptake values were not different. In the univariate analysis, T and N stage were significantly different between the two groups, but, using the stepwise forward multivariate analysis, Tg/(TSHx24-h uptake) remained the most significant independent parameter, irrespective of N and T stage. Moreover, except from age, we did not find significant differences in all parameters tested between patients with initially M1 disease and patients with M0 stage demonstrating recurrent disease during follow-up. Even the newly defined parameters that were based on Tg levels did not show any significance anymore, suggesting that high values indicate bulky DTC. Consequently, patients with M0 stage and high Tg/(TSHx24-h uptake) ratios at initial presentation should be regarded as

patients with initially M1 disease and therefore be treated with higher ^{131}I doses. In addition, a close clinical follow-up scheme is recommended for these patients. Finally, it has to be realized that at severe malignancy the Tg production may be low and not high as found in the present study, which may cause a false negative effect on this new parameter. In such cases, radioiodine uptake is often also severely diminished, as the expression of the sodium-iodine symporter is commonly the first factor being affected in a dedifferentiation process of thyroid cancer. This condition, however, is very rare at initial presentation, whereas such features are more common in anaplastic tumors, which were excluded in the present study.

Conclusion

In the present study, we have evaluated the prognostic value of clinical and biochemical parameters measured at the time of ablation for DTC. Based on these values, we have defined a new parameter, Tg/(TSHx24-h uptake), which was hypothesized to be a better prognostic indicator for the presence of malignant cells after total or near-total thyroidectomy for DTC. Although T stage, N stage, age at the time of diagnosis, and standard biochemical values significantly differ between patients with and without recurrent disease or between patients with M0 and M1 tumor stage, the newly defined parameter was the best independent significant prognostic parameter in the assessment whether patients will develop a tumor recurrence during follow-up or not. From the present data, it can be concluded that high ratios justify an adjustment of the ^{131}I doses as ablation dose and a close clinical follow-up.

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Chapter 6

The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer

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Abstract

Objective: The aim of the present study is to assess the prevalence of second primary tumors in patients treated for thyroid cancer. Furthermore, we wanted to assess the standardized risk rates for all second primary tumors, but especially for breast cancer, as data in the literature indicate an excessive risk in differentiated thyroid cancer (DTC) patients for this tumor.

Materials and methods: We included consecutive patients, who received ablation treatment with ^{131}I at the Leiden University Medical Center between January 1985 and December 1999 (n=282). The mean period of follow-up was 10.6±4.1 years.

Results: Thirty-five of the 282 patients (12.4%) had a second primary tumor (SPT), either preceding or following the diagnosis of thyroid cancer. Five other patients had three primary tumors, including DTC. As a result, 40 additional tumors were found in this group, revealing an overall prevalence of 14.2%. Twenty tumors (7.1%) preceded the thyroid cancer with a mean interval of 5.7 years (range: 0.5-22.0 years), whereas 20 tumors (7.1%) occurred after this tumor with a mean interval of 6.7 years (range: 1.0-15.0 years). In 13 female patients, breast cancer was found as SPT. The standardized incidence rate (SIR) for all cancers after the diagnosis of DTC in this study population was not increased (1.13; confidence interval (CI): 0.68-1.69). However, we found an increased SIR of 2.26 (CI: 1.60-3.03) for all cancers either following or preceding DTC, which is mainly caused by a SIR of 3.95 (CI: 2.06-6.45) for breast cancer.

Conclusion: Patients with DTC have an overall increased standardized incidence rate for second primary tumors, but not for second primary tumors following ^{131}I therapy. These findings suggest a common etiologic and/or genetic mechanism instead of a causal relation.

Introduction

Differentiated thyroid cancer (DTC) is the most frequent endocrine gland malignancy accounting for approximately 0.5-1.5% of all malignancies. The overall survival rate is high and currently even close to 99% in papillary carcinomas [10;22]. The standard treatment for DTC is a (near-) total thyroidectomy followed by ablation therapy using high doses of radioiodine-131 (^{131}I), except in small papillary thyroid cancer or minimal invasive follicular carcinomas. Although many reports have focused on the relationship between ^{131}I administration and the occurrence of second primary tumors, some studies found [e.g. 19] a relationship between ^{131}I administration and the occurrence of bone and soft tissue, colorectal and salivary gland cancers. Other studies reported an overall increased incidence of breast and kidney cancer among women treated for thyroid cancer, but this was not related to the exposure of ^{131}I [6;20;23].

The aim of the present study is to assess the prevalence of second primary tumors in patients treated for thyroid cancer using an uptake-related ablation strategy. Furthermore, we wanted to assess the standardized risk rates for all second primary tumors, but especially for breast cancer, as data in literature indicate an excessive risk in DTC patients for this tumor.

Materials and methods

We included consecutive patients, who received ablation treatment with ^{131}I at the Leiden University Medical Center (LUMC) between January 1985 and December 1999 (n=282) for DTC. This period was selected, as since 1985 standardized ablation doses were given. The mean period of follow-up was 10.6 ±4.1 years. From the medical files, age, gender, histopathological data, ablation dose, and subsequent ^{131}I treatments were recorded. Furthermore, data with respect to second primary tumors were gained, including site and interval.

In addition, malignancies preceding the diagnosis of DTC were recorded.

However, *in situ* and basal cell carcinomas were excluded. All information with respect to malignancies was obtained from the medical records as well as from the central hospital registration system for malignancies. This oncology documentation system, the ONCDOC, gathers information about tumors, follow- up, recurrences, second primaries, therapeutic interventions, survival, etc. To define the extent of thyroid carcinomas, the sixth edition of the tumor, node, metastasis (TNM) staging was used.

The ratio of the observed (O) numbers to the expected E) number (i.e. the standardized incidence ratio; SIR) was computed using cancer incidence data from the general population. These specific incidence rates were derived from the Dutch national cancer registry (www.ikcnet.nl) by gender, 5- and 15-year age groups and were multiplied by the accumulated person-years in the study cohort to estimate the expected number of cancer cases.

Radioiodine treatment

The mean interval between a thyroidectomy and the ablative treatment in the present population was 5.4 ±4.0 weeks. During this interval, patients did not receive any thyroid hormone supplementation with the aim of increasing the thyroid-stimulating hormone levels. All patients treated from 1992 were put on a low-iodine diet that started 4 days prior to ablation to facilitate an optimal uptake of ^{131}I in the thyroid remnant. Before 1992, low-iodine diets were not routinely prescribed [15].

The ablation dose of ^{131}I was determined by the 24-h ^{131}I pre-treatment uptake value in the neck region. Therefore, patients received 40 MBq of ^{131}I orally, which was followed by planar scintigraphy of the neck region 24 h later. Uptake values less than 5%, between 5 and 10%, and values more than 10% were followed by 2800, 1850, and 1100 MBq of ^{131}I in one dose respectively. The rationale of this uptake-related approach is to avoid unnecessary exposure and local radioiodine side effects [25].

Results

Clinical characteristics

Overall, we treated 282 patients, 219 female, and 63 male (age 47.5 ±17.5 years). During long-term follow-up, 64 patients died. The mean period of follow-up was 10.6 ±4.1 years. Tumor characteristics are presented in Table 1, demonstrating that T2, N0 tumor stage and papillary thyroid cancer were most frequently observed.

The mean 24-h ^{131}I uptake was 6.3 ±7.7%. The mean ablation dose given was 2616 ±1103 MBq of ^{131}I, whereas the overall cumulative dose given ranged from 1100 MBq up to 49 GBq (mean: 7657 MBq) of ^{131}I.

Table 1. Tumor and treatment characteristics.

Characteristics	Results (n=282)
Histology	
Papillary carcinoma	156
Follicular carcinoma	51
Follicular variant of papillary carcinoma	57
Hürthle cell carcinoma	17
Not further specified	1
T-stage	
1	20
2	153
3	45
4	61
X	3
N-stage	
0	209
1	70
X	3
M-stage	
0	232
1	50
24 hr ^{131}I Uptake (%)	6.3 ($\pm$7.7)
Mean ^{131}I ablation dose (MBq) (SD)	2616 ($\pm$1103)
Mean cumulative ^{131}I treatment dose (MBq) (range)	7657 (1100 – 49000)

T-stage, tumor stage; N-stage, node stage; M-stage, metastasis stage.

Additional tumors

Overall, 35 patients (12.4%) had a second primary tumor either preceding or following the thyroid cancer (Table 2). Five other patients had three primary tumors, including DTC, according to the medical files. As a result, in 40 patients additional tumors were found in this group, revealing an overall prevalence of 14.2%: 20 tumors (7.1%) preceded the thyroid cancer with a mean interval of 5.7 years (range: 0.5-22.0 years) and 20 tumors (7.1%) occurred after this tumor with a mean interval of 6.7 years (range: 1.0-15.0 years). In 13 out of 219 female patients (5.9%), breast cancer was documented. Regarding the mean period of follow-up of 10.6 years, we found an overall prevalence of 0.67% of second primaries per year following DTC and 0.5% per year when excluding breast cancer. Finally, the total follow-up years, defined as the mean period of follow-up times the number of patients studied, was 2989 years. Regarding this parameter, it resulted in an overall prevalence for second primaries following DTC of 0.0024 and 0.0018% per person follow-up year with and without breast cancer respectively.

In Table 3, the standardized incidence ratios are described. The SIR of second primary tumor (SPT), following treatment of thyroid cancer was not increased (1.13; 95% CI: 0.68-1.69). However, the SIR of all SPT, i.e. including all cancers occurring before as well after the diagnosis of DTC, was increased (2.26; 95% confidence interval (CI): 1.60-3.03). This was mainly due to an increased incidence of breast cancer (SIR 3.29; 95% CI: 2.06-6.45).

Table 2. Locations of second primary tumors in differentiated thyroid cancer (DTC) patients.

Tumors preceding DTC	n	Mean cumulative ^{131}I activity (MBq)	Mean Interval (yrs) (range)	Tumors following DTC	n	Mean cumulative ^{131}I activity (MBq)	Mean Interval (yrs) (range)
Melanoma	2	22400	13 (4 – 22)	Melanoma	1	1850	1
Breast	8	4900	4.3 (2 – 10)	Breast	5	9000	6.6 (2 – 11)
Colon	2	9100	3.3 (0.5 – 6)	Cervix uteri	2	5050	4 (1 – 7)
Lung	2	8400	2.3 (0.5 – 4)	Ovary	2	2400	8.5 (2 – 15)
Adrenal	1	8900	15	Endometrium	1	16512	7
Salivary gland	1	2800	17	Pancreas	2	2800	7 (3 – 11)
Grawitztumor	1	7400	7	Bladder	1	2800	3
Stomach	1	24735	2	Lung	1	2800	14
Prostate	1	26740	2	Prostate	1	9400	1
Lymphoma	1	15725	0.5	Hepatocellular	1	15400	2
				Grawitz	1	21100	14
				Leukaemia	1	2800	8
				Lymphoma	1	2800	12
Overall	**20**		**5.7 (0.5 - 22)**	**Overall**	**20**		**6.7 (1 – 15)**

Table 3. Ratio of observed to expected second primary tumors (SPT) following differentiated thyroid cancer (DTC) and both preceding and following differentiated DTC.

Site of SPT	SPT following DTC				All SPT prior to and/or following DTC			
	O_i	E_i	SIR	95% CI	O_i	E_i	SIR	95% CI
Head and neck	-	1.16	-	-	1	1.16	0.86	0.01 – 3.45
Lung	1	6.47	0.15	0.01 – 0.62	3	6.47	0.46	0.08 – 1.15
Breast	5	3.29	1.52	0.46 – 3.18	13	3.29	3.95	2.06 – 6.45
Digestive tract	3	9.12	0.33	0.06 – 0.82	6	9.12	0.66	0.23 – 1.30
Female genitourinary tract	7	4.35	1.61	0.62 – 3.06	9	4.35	2.07	0.92 – 3.68
Prostate	1	1.59	0.63	0.01 – 2.52	2	1.59	1.26	0.11 – 3.67
Melanoma	1	1.05	0.95	0.01 – 3.81	3	1.05	2.86	0.51 – 7.11
Others	2	-	-	-	3	-	-	-
Total	**20**	**17.70**	**1.13**	**0.68 – 1.69**	**40**	**17.70**	**2.26**	**1.60 – 3.03**

O_i, observed number of second primary tumors; E_i, expected number of second primary tumors; SIR, standardized incidence ratio; 95% CI, 95% confidence interval.

Discussion

Patients with DTC have a very good prognosis, which is achieved by surgery and postoperative ablation with ^{131}I therapy. Our data indicate that this treatment is not associated with increased incidence of malignancies following treatment of DTC. However, the data indicate that there is an increased incidence of second primary tumors in thyroid cancer patients if we consider their lifetime risks for cancer, especially of breast cancer.

Regarding the incidence and prevalence of SPT in general, an 1/3 rule has been hypothesized, which means that approximately 33% of the patients with a malignancy will develop an SPT, 33% of these patients with an SPT a third malignancy, and so on [17]. A well-described phenomenon, in this respect, is the field cancerization concept, which states that organ systems exposed to the same carcinogenic agents have a greater chance of transforming into a malignancy. One of the most striking examples of this concept is the combination of head and neck cancer with lung malignancies [8]. Another explanation for SPT may be the presence of a genetic base for multiorgan cancer [7]. These authors studied a multiorgan cancer susceptibility gene, the CHEK2 protein, in 4008 cancer cases and 4000 controls. This CHEK2 protein participates in the DNA damage response in many cell types. The missense variant I157T was associated with an increased risk of breast cancer, colon cancer, kidney cancer, prostate cancer, and thyroid carcinoma. Therefore, the authors concluded that cancers associated with mutations of the CHEK2 gene might be much greater than previously thought.

In some studies, an increased incidence of breast carcinoma has been suggested in women with thyroid carcinoma. Vassilopoulou-Sellin *et al*. [24] published one of the first studies on this, including 41686 patients with breast carcinoma and 3662 with thyroid carcinoma, which were retrospectively analyzed. Among 18931 women with a diagnosis of breast carcinoma, 11 developed DTC more than 2 years after the initial diagnosis of breast cancer. The observed incidence

of DTC was not different from that in a similar group of women without breast cancer. Among 1013 women with a diagnosis of thyroid carcinoma, 24 developed breast cancer more than 2 years after the primary tumor. In that group, the observed incidence of breast cancer in women of age 40-49 years was significantly higher than the expected incidence for women in the same age group. However, in a study by Sadetzki et al. [20], opposite results were observed. This group found an overall significant elevated risk for DTC following breast cancer in 49 207 female studied. The observed number of cases of DTC after breast cancer was 59, revealing a standardized incidence ratio of 1.34 (95% CI: 1.03-1.72), as the expected number of cases was 43. This ratio was 1.07 for breast cancer following DTC. In addition, the authors concluded that considering the long latency required for carcinogenesis and the excess risk of SPT soon after the index tumor argues against the hypothesis of primary tumor treatment as initiator. The authors suggested that early exposure to common risk factors or genetic susceptibility for both malignancies to be plausible. Cengiz et al. [6] observed an increased frequency of thyroid pathology in breast cancer patients compared with controls, but it has to be realized that the high percentage of thyroid disorders in that study might be related to the fact that Turkey is an endemic region for thyroid diseases. In a study by Simon et al. [23], only women with a history of thyroid cancer were found to have an increased risk, but this was restricted to parous women. The overall odds ratio in this respect was 3.5 (95% CI: 1.5-8.1). However, they concluded that, despite the increased incidence, there was no association between thyroid cancer treatment and the risk on breast cancer. Finally, Pal et al. [14] performed a study on double primary cancers of the breast and thyroid in women and assessed a molecular and genetic base.

Their data did not support the hypothesis that a significant proportion of double primary cancers are due to hereditary factors. In the present study, we found a standardized incidence ratio of 1.52 (95% CI: 0.46-3.18) for breast cancer

comparable with the data published by Berthe *et al*. [4]. Moreover, an increased overall incidence (the SIR increases up to 3.95 (95% CI: 2.06-6.45) for breast cancer in thyroid cancer patients was observed, when taking also the tumors preceding DTC into account. Based on data in literature, it is highly unlikely that ionizing radiation is involved in the genesis of breast cancer in DTC patients. Genetic predisposition and probably environmental factors seem to be a better explanation for the coincidence, as at least half of the breast tumors appear before treatment with ^{131}I for DTC.

A relation between the total dose of ^{131}I and SPT has been reported for solid cancers and leukemias with increasing cumulative activity of the dose administered [19]. The question remains whether this is related to the administration of ^{131}I solely or also to an increased organ sensitivity for carcinogens in general. Hemminki *et al*. [11] described an increased risk of cancer by site and histopathology, in which familial risks with SIRs over 4.0 were found for ovary cancer, thyroid cancer, and clear cell carcinoma. For this purpose, they used a nationwide Swedish Family cancer database on 10.2 million individuals and 1 million tumors to calculate SIRs for familial cancers. Their results called for a closer description of tumor-susceptibility genes. It was the group of Fisher, who firstly studied the expression of five gene family members in relation to different cancers [9]. It is beyond the scope of this article to report on these findings in detail, but an important finding was the observation of significantly elevated expression levels of osteopontin in cancer of the breast, ovary, uterus, and thyroid compared with normal tissue levels. In this study, the relative mRNA expression units quantified using ImageQuant for normal tissue and these tumor subtypes were as follows: 18000 and 54000 respectively, for normal breast tissue and breast cancer: 14000 and 70000 respectively, for normal tissue of the uterus and cancer of the uterus: 20000 and 126000 respectively, for normal ovary tissue and ovary cancer: 4000 and 16000 respectively, for thyroid tissue and thyroid cancer. Especially, the relation

between these glycoproteins and matrix metalloproteinases, critical for the development of wound healing and cancer progression, is suggestive for a common genetic base. Ronckers *et al.* recently published a large report on thyroid cancer and multiple primary tumors [18]. They studied the risk of thyroid cancer after an earlier primary cancer, as well as the risk of developing multiple cancers after an earlier thyroid cancer in the US, using the cancer registry program of more than 2 million patients. They observed an absolute excess risk for all cancers following DTC of 7.64, which is mainly based on an increased risk for female breast, prostate, and kidney cancer. Breast cancer contributed 36% of all second cancers after DTC. Patients <40 years of age at diagnosis of DTC had a 39% increased risk of a second cancer, whereas for older patients this was 6%. On the other hand, breast cancer patients had a 1.3-fold risk of developing DTC. Several other cancer sites showed significantly increased risks in both directions, including salivary glands, prostate, breast, kidney, scrotum, brain, and leukemia. Although ^{131}I therapy may play a role in the induction of some of these tumors, the high incidence of tumors preceding DTC suggest etiologic similarities. Finally, Adjadj *et al.* [1] reported comparable results obtained from 2365 women who were treated for thyroid carcinoma. In this series, 48 women developed subsequent breast carcinoma, revealing an overall SIR of 1.3, but even up to 2.5 for patients treated at an age ranging from 4 to 30 years. The authors did not find a correlation between the high SIR and radiation treatment with ^{131}I, but the co-occurrence may be related to a genetic deregulation, as the H23 gene, which is overexpressed in both DTC and breast cancer. It is still not clear why the gene coding for H23 antigen mRNA is overexpressed in these cancers. As one of its forms is probably a transmembrane receptor-like protein, it may be an element of signal transduction and, therefore, reflect an involvement in cell growth [26;27].

Recent reports have focused on malignancies within the scope of certain cancer syndromes. Mutations in MLH1 and MSH2, genes coding for mismatch repair

enzymes that are involved in the repair of DNA replication errors, are associated not only with an increased risk of hereditary nonpolyposis colorectal cancer, but also with other malignancies, such as cancer of the stomach, urinary tract, and thyroid. [5;12;13]. It may be an explanation for some of the present findings related to thyroid cancer. However, a correlation between MSH2 mutations and breast cancer as SPT in thyroid cancer patients, or vice versa, has never been described. Another gene that is associated with cancer syndromes is the PTEN gene, which is located on chromosome 10q23. This phosphatase suppressor tumor gene downregulates cell survival through apoptosis and/or G1 cell cycle arrest. It is characterized by an increased risk of benign and malignant tumors of the breast, thyroid, and endothelium [2;3;16]. Consequently, these studies stress the need to better screen for clonal PTEN rearrangements and gene mutations, especially in DTC patients presenting with second primaries of the breast.

Recently, Sandeep *et al*. published a large multinational record linkage study on second primary cancers in thyroid cancer patients [21]. The study was conducted at 13 population-based cancer registries in Europe, Canada, Australia, and Singapore and included a cohort of 39002 patients with primary thyroid cancer. During an observation period of 356035 person-year, 2821 second primary tumors were observed resulting in an overall SIR of 1.31 (CI: 1.26-1.36). Remarkable increased incidence rates were found for cancer of the oral cavity (SIR: 1.43), small intestine (SIR: 2.11), bone (SIR: 3.62), soft tissue sarcoma (SIR: 3.63), kidney (SIR: 2.33), endocrine glands (SIR: 6.75), lymphoma (SIR: 1.68), and leukemias (SIR: 2.26). The SIR for breast cancer was 1.31, which is definitely lower than present findings. However, this discrepancy can be fully ascribed to the differences in number of patients studied and in period of follow-up. The group of Sandeep *et al*. also found and increased incidence of second primary thyroid cancer after cancers of the lung, larynx, esophagus, and salivary gland. Although a relation between initial treatment, such as radiotherapy, for the index tumor and subsequent thyroid cancer may be suggested, the short

interval and age of initial treatment do not support this hypothesis. Nevertheless, we fully ascribe their conclusion that clinicians should maintain a high index of suspicion, both for second primaries following treatment for thyroid cancer and for cancer of the thyroid as SPT.

A limitation of our study is the small number of patients included in the database. Patients who received ablation treatment with ^{131}I at the LUMC between January 1985 and December 1999 were selected for analysis. The mean period of follow-up is more than 10 years, which gives a good estimate of the relative risk and its relation to the induction of SPT. In most other series on this subject, the interval between therapy and the occurrence of a therapy-related SPT is up to 5 years.

In conclusion, we studied the incidence of second primary tumors in relation to DTC and found an overall increased SIR for all cancers, but especially for breast cancer. Despite the relatively small number of patients studied, the present results are highly suggestive for a common etiologic and/or genetic mechanism. In this respect, further study is required, but in agreement with recently published data by others, close clinical follow-up of thyroid cancer patients may be recommended for the early diagnosis of second primary tumors.

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Chapter 7

Indium-111 octreotide scintigraphy for the detection of non-functioning metastases from differentiated thyroid cancer: diagnostic and prognostic value

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Abstract.

In this prospective study, we evaluated the diagnostic and prognostic value of ^{111}In-octreotide scintigraphy (SRS) in papillary and follicular thyroid carcinoma (DTC) with increasing thyroglobulin (Tg) levels but no response to treatment with [131]I. Twenty-three consecutive patients (13 female, 10 male; mean age 55 years, range 13-81 years) with progressive DTC were selected for the study. All patients had non-functioning metastases, defined by no or slight uptake of ^{131}I in metastases. Diagnosis of tumor progression was based on rising Tg levels during follow-up and was confirmed by radiological examination. Uptake on SRS was scored from 0 to 4. Data on initial tumor stage, histology, age, gender, Tg levels, TSH levels, ^{131}I treatment doses, intervals and survival were gathered. Seven patients died during follow-up. The overall sensitivity for the detection of metastases was 74%. The sensitivity was better in patients in whom ^{131}I whole-body scintigraphy did not show any abnormal uptake (82%;14/17) than in patients with faint ^{131}I uptake (50%; 3/6). The 10-year survival rate was significantly different between patients with an uptake score of 0 or 1 (100%) and those with an uptake score of 2, 3 or 4 (33%) (p=0.001). Gender, log Tg and uptake on SRS significantly correlated with survival, but in stepwise analysis, ^{111}In-octreotide uptake was selected as the most prognostic independent variable (hazard rate 6.25, p=0.006). We conclude that ^{111}In-octreotide scintigraphy is a valuable clinical tool for the detection of non-functioning DTC metastases. The uptake seems to correlate with prognosis and survival.

Introduction

The prognosis of well-differentiated thyroid cancer is very good, with a 10-year survival rate ranging from 85% to 93% [1-3]. In a minority of patients, however, a variable degree of dedifferentiation may occur, accounting for a poorer outcome. This dedifferentiation is seen in approximately 50% of patients with distant metastases [4;5]. In such cases, tumor cells lose their radioiodine (^{131}I) uptake capability, which is usually associated with an increased growth rate and a larger tumor load [6]. As a consequence, whole-body scintigraphy (WBS) with ^{131}I will yield false negative results, whereas in most cases rising thyroglobulin (Tg) levels will be measured during follow-up. For optimal follow-up and accurate Tg quantification in such cases, TSH stimulation is required, which can be achieved by either discontinuation of hormonal replacement or recombinant TSH administration. Radiological techniques such as ultrasonography of the head and neck region, chest X-rays or CT scanning are valuable techniques to assess tumor recurrence or progression. However, small lesions with diameters of less than 1 cm may be missed [7-9]. Positron emission tomography (PET) using fluorodeoxyglucose (FDG) can be used to demonstrate tumor recurrence or small lesions in the head and neck region. However, tumors in the chest with a diameter of less than 1 cm may also be missed by this technique [7;10;11]. In addition, systemic treatment options for patients with multiple metastases are scarce and therefore alternative techniques are required which give the option of visualising but also treating patients with iodine-negative differentiated thyroid cancer (DTC) metastases [12;13].

Somatostatin receptor scintigraphy (SRS) has established its diagnostic value in tumors and metastases which express somatostatin receptors (SSTR), such as neuroendocrine tumors [14-16]. In recent reports, high expression of SSTR5 was described in papillary thyroid cancer, which offers an opportunity to visualise such tumors with octreotide [17;18].

In the present prospective study, we evaluated the diagnostic value of ^{111}In-

octreotide in differentiated thyroid carcinoma with increasing Tg levels but no response to treatment with [131]I. Furthermore, we studied the prognostic value of ^{111}In-octreotide scintigraphy in different subgroups.

Materials and methods

Patients. Twenty-three consecutive patients (13 female, 10 male) (mean age 55 years, range 13-81 years) with progressive, ^{131}I non-responsive DTC were selected for this study. All patients had non-functioning metastases, as defined by increased Tg levels and no or slightly elevated ^{131}I uptake on post-treatment whole-body scans. Slightly elevated uptake was defined as uptake that could hardly be distinguished from background activity. Diagnosis of tumor progression was based on rising Tg levels and was confirmed by radiological examination. The mean interval between the last treatment with ^{131}I and scintigraphy with ^{111}In-octreotide was 15 months (SD ±7 months). The mean interval between scintigraphy with ^{111}In-octreotide and initial diagnosis was 4 years. All patients were on hormonal replacement therapy at the time of scintigraphy and had relatively low Tg and TSH levels. In some patients with disease progression, chemotherapy (generally a combination of adriamycin, cisplatinum and/or bleomycin) was administered in an attempt to palliate the condition. Data on initial tumor stage, histology, age, gender, Tg levels, TSH levels, ^{131}I treatment doses, intervals and survival were gathered. The initial (clinical) N stage was based on physical examination, ultrasonography of the neck and close clinical follow-up for 1 year (N0). A modified neck dissection was performed in patients with clinically palpable lymph nodes or enlarged nodes detected by ultrasonography. N1 stage at the time of diagnosis was confirmed by histological examination of the neck dissection specimen. The initial M stage was based on post-treatment WBS (after ablation with a high dose of ^{131}I) as well as follow-up ^{131}I WBS up to 1 year after initial treatment. Radiological examination (CT scan, chest X-ray or MRI) was used to confirm

the presence of distant metastases (M1) in cases of abnormal uptake outside the head and neck region. Patients with persistent elevated Tg levels 12 months after ablation without abnormal uptake on ^{131}I WBS were scored as having NxMx tumor stage, as locoregional or distant micrometastases cannot be excluded in such cases.

[131]*I whole-body scintigraphy.* WBS was performed 7 days after the oral administration of 7400 MBq of [131]I (Mallinckrodt BV, Petten, The Netherlands). The run speed of the dual-head gamma camera (Toshiba GCA 7200, equipped with a high-energy collimator) was 15 cm per minute (matrix size 256x256). WBS was followed by anterior and posterior planar images of the head and neck and chest region (matrix size 256x256, preset time 10 min).

Somatostatin receptor scintigraphy. SRS was performed 4 and 24 h after the injection of 200 MBq of ^{111}In-octreotide (Mallinckrodt, Inc, St. Louis, Minnesota). The run speed was 10 cm per minute (Toshiba, GCA 7200, dual-head gamma camera equipped with a medium-energy collimator) (matrix size 256x1,024). As this is the minimum speed of the camera system used, singlephoton emission computerised tomography of the head and neck region and chest was additionally performed (matrix size 128x128) with a 6° step angle and a 1-min step time. Images were reconstructed with a Butterworth pre-processing filter (8 order, 0.12 subset) and filtered back-projection.

Analysis. Two experienced observers visually analysed all images. The uptake was scored according to the criteria described by Krenning *et al.*, ranging from 0 (=no uptake) to 4 (=intense uptake) [15]. All sites visualised on SRS and confirmed by radiological examination were recorded. In addition, sites that were seen on CT, MRI and/or ultrasonography, but missed on SRS, were record-ed separately. Due to the fact that FDG-PET was not available to exclude smaller lesions than can be detected with radiological techniques, we decided to calculate the results on a patient basis and not based on the number of lesions.

Quantitative variables were summarised with their mean, standard deviation and

range. Tg levels appeared to have a very skewed distribution and therefore their median value and range were reported. In subsequent analysis, log Tg was used. The comparison between the parameters studied was made using Student's *t* tests, Mann-Whitney *U* tests or Chi-square tests. Actuarial survival curves were calculated according to the Kaplan-Meier technique. Multivariate analysis with respect to survival was performed with the Cox regression model (stepwise forward). Throughout, a p value of 0.05 or less was considered statistically significant.

Results

In 11 out of 23 patients, distant metastases were already present at the initial stage, i.e. at the time of diagnosis of thyroid cancer, while in five patients, lymph node metastases were present at that time. Furthermore, in 15 patients the initial primary tumor (T) stage was T3 or T4, indicating advanced disease at the time of initial presentation. In ten patients, Tg levels and ^{131}I WBS both normalised as early as 6 months after ablation, which led us to stage these tumors as N0M0. Thirteen patients had papillary thyroid cancer and eight patients had follicular cancer. Finally, two patients had Hürthle cell carcinoma (Table 1). Seven patients died during follow-up.

The uptake scored on the ^{111}In-octreotide scans was as follows: 0, n=6; 1, n=8; 2, n=3; 3, n=3 and 4, n=3. The overall sensitivity for the detection of metastases on a patient basis was 74%. The sensitivity was better in patients in whom ^{131}I WBS did not show any abnormal uptake (82%; 14/17) than in patients with slight uptake (50%; 3/6). As can be seen from Table 1, the most common sites containing metastases that were missed were the chest (n=8), spine (n=1) or head and neck region (n=2). In Figure 1, appearances in four patients exemplifying the four uptake scores are shown.

Using Cox regression analysis, log Tg (p=0.001), uptake (p<0.001) and gender (p=0.03) were selected as prognostic variable for survival. However, in stepwise

analysis, ^{111}In-octreotide uptake was selected as the most prognostic variable for survival (hazard rate: 6.25; p=0.006). To increase the number of patients per subgroup, they were clustered: group 1 had an uptake score of 0 or 1 (no or slight uptake), whereas group 2 had an uptake score of 2, 3 or 4 (moderate to intense uptake). Gender, tumor stage (TNM), histology and the intervals between SRS and initial diagnosis as well as SRS and ^{131}I WBS were comparable in the two groups (Table 2). The mean age was significantly lower in group 1, but this was due to patient number 15, who was 13 years old. Excluding her from the analysis, age was no longer significantly different (p=0.07). Tg levels were significantly different in the two subgroups. Although a correlation between Tg levels and uptake scores was expected, the Spearman's ρ was 0.67. Some of the patients with rather low Tg levels (patients 2 and 3) had high uptake scores, whereas some patients with high Tg levels, such as patients 9 and 19, had low uptake scores. The 10-year survival rate was significantly different between the groups, being 100% in group 1 and 33% in group 2 (p<0.001) (Figure 2).
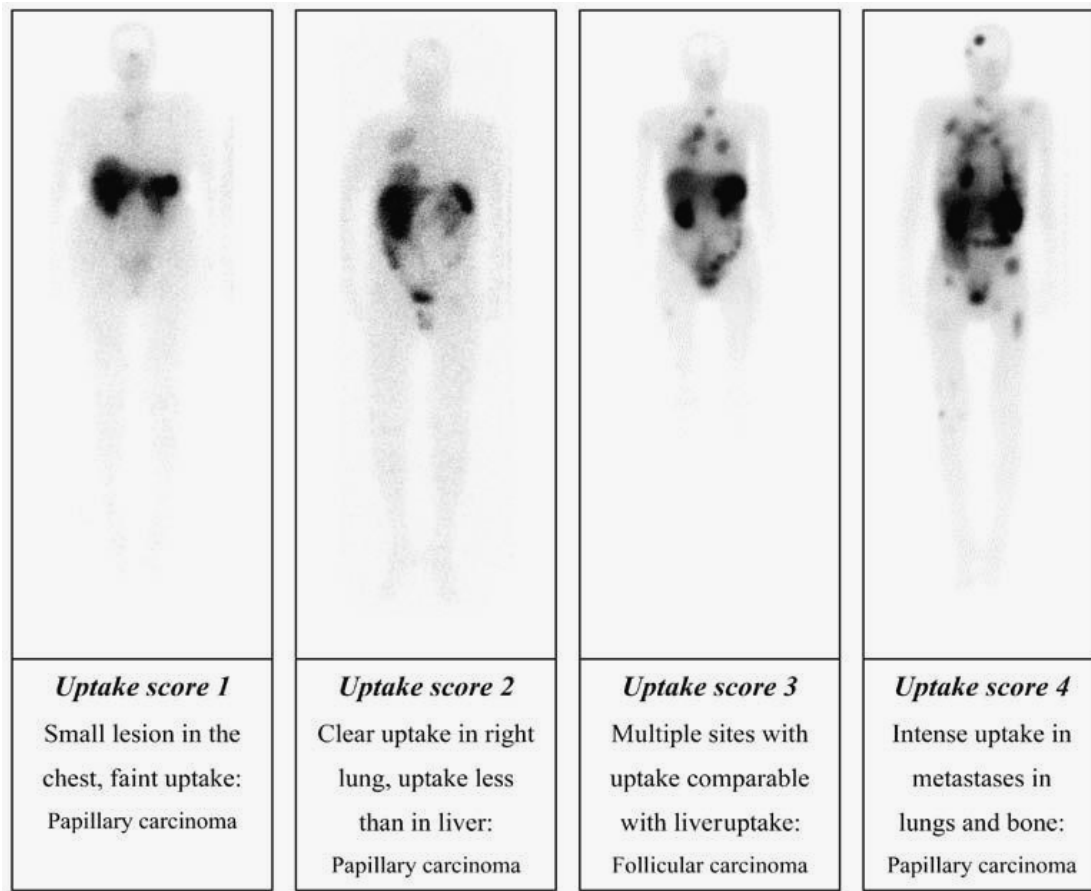
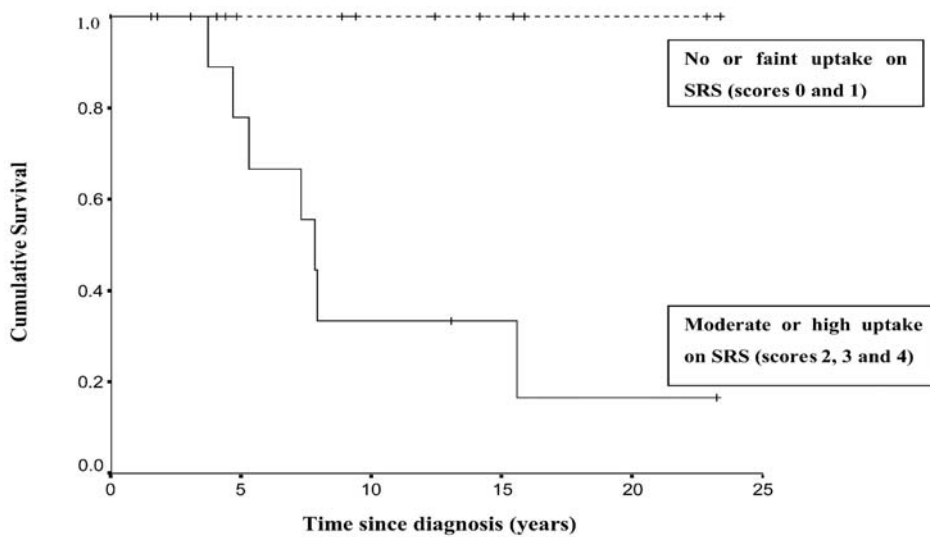**Figure 1.** Uptake scores on ^{111}In-octreotide scintigraphy.

Figure 2. Kaplan-Meier curves for patients with different uptake scores on ^{111}In-octreotide scintigraphy.

Table 1. Patient characteristics and diagnostic results in patients with differentiated thyroid cancer.

No	Age (yrs)	Gender	Histology	Tumor stage at initial diagnosis	Interval between last ^{131}I WBS and SRS (mo)	Cumulative ^{131}I dose (GBq)	TSH at time of SRS (mU/l)	Tg-on at time of SRS (µg/l)	SRS uptake score	Site of metastases seen on SRS	Sites missed on SRS
1	68	M	PTC	T2N0M0	7	19.4	0.022	28809	3	B, Li, LR	Lu
2	81	M	FTC	T4N0M0	9	8.9	1.370	364	4	B, Lu	-
3	67	M	PTC	T4N0M1	2	27.2	0.694	967	3	B, Lu, C	Spine
4	66	M	FTC	T2N0M1	11	36.4	0.005	26700	3	B, Lu	-
5	55	M	PTC	T3N0M0	45	27.6	8.140	380	2	B, Lu	-
6	44	F	FTC	T4N4M1	2	34.8	0.039	4000	1	B, Lu, Li	-
7	67	F	PTC	T2N0M1	2	36.5	0.005	586000	4	B, Lu, Br	-
8	55	F	PTC	T3N1M0	11	38.7	0.032	350	0	-	Lu, LR
9	75	F	FTC	T2N0M0	8	45.4	0.283	14430	2	Lu	-
10	67	F	PTC	T4N1Mx	2	33.8	0.008	95	1	Lu	Med
11	53	F	FTC	T3N0M0	85	36.5	0.005	73	2	Lu, Med	-
12	69	F	PTC	T4N0M1	5	30.7	0.459	1069	1	B, Lu	-

13	68	F	H	T2N0M0	-	21.1	0.005	62	0	-	Lu
14	34	F	FTC	T4N0M1	5	12.0	0.065	2101	1	Lu, Med	-
15	13	F	PTC	T4N1M1	6	20.3	13.2	70	0	-	Lu, Med
16	55	F	PTC	T2N0M1	7	36.7	0.007	108	1	Lu	-
17	55	M	H	T3N0M0	90	NA	12.5	174100	4	B, Lu	-
18	43	F	PTC	T1N1M1	5	6.1	0.793	310	1	Li, Lu, B	-
19	41	F	PTC	T4N0M1	2	20.7	0.358	2900	0	-	Lu
20	52	M	FTC	T4N0M1	2	30.5	0.005	640	1	Lu	-
21	26	M	PTC	T4N0M0	16	15.4	16.3	22.9	0	-	LR
22	70	M	FTC	T2N0M0	12	32.1	0.006	16.6	0	-	Lu
23	74	M	PTC	T4N0M0	4	16.5	0.015	0.8*	1	Lu, Med, LR	-

M , male; F, female; FTC, follicular carcinoma; PTC, papillary carcinoma; H, Hürthle cell carcinoma;
TSH, thyroid-stimulating hormone; Tg, thyroglobulin; SRS, somatostatin receptor scintigraphy;
Lu, lungs; Li, liver; Med, mediastinum; B, bones; C, cutaneous; LR, loco-regional recurrence; Br, brain
* Tg antibody positive.

Table 2. Comparison of population characteristics in the groups of patients with an uptake score of 0 or 1 (group 1: no or slight uptake) or an uptake score of 2, 3 or 4 (group 2: moderate to intense uptake).

	No or slight octreotide uptake (score 0 or 1)	Moderate to intense octreotide uptake (score 2, 3 or 4)	p value
Age (years): mean (SD)	51 (±18)	68 (±9)	0.04
Gender: (female): n (total)	10 / 14	3 / 9	0.10
Interval between diagnosis and scintigraphy (months): mean (SD)	8.3 (±6.9)	8.7 (±6.4)	0.97
Follow-up since diagnosis (years): mean (SD)	8.6 (±7.1)	8.4 (±6.0)	0.97
Cumulative ^{131}I dose (GBq): mean (SD)	24.9 (±10.2)	29.9 (±10.8)	0.27
Log Tg levels (μg/L): median (range)	5.7 (2.83 – 8.29)	9.5 (4.29 – 13.28)	0.02
Tumor stage (n)			
T-stage			0.12
1	1	0	
2	3	4	
3	1	3	
4	9	2	
N-stage			0.12
0	9	9	
1	5	0	
M-stage			0.27
0	6	6	
1	8	3	
Histology			0.65
Papillary	9	4	
Follicular	4	4	
Hürthlecell	1	1	
Died: n (total number)	0 (14)	7 (9)	<0.001

Discussion

In this study, we evaluated the diagnostic and prognostic value of SRS with ^{111}In-octreotide in progressive papillary and follicular thyroid cancer. The overall sensitivity for the detection of metastases on a patient basis was 74%, but the highest diagnostic yield was seen in patients with metastases that had completely lost the capacity to take up [131]I. Furthermore, it was found that the ^{111}In-octreotide uptake correlated significantly with survival.

Overall prognosis and survival in DTC

Up to 20% of the patients with DTC have a local recurrence or regional metastases [5;6]. Some of these relapses are due to an incomplete initial treatment, whereas in others relapse is indicative of an aggressive tumor. Some parameters have prognostic value, such as younger age, T4 tumors and certain histological subtypes. In the present study, 19 out of 23 patients had T3 or T4 tumor stage and/or distant metastases indicating an initial bulky tumor stage.

DTC usually demonstrates a concordance between the ^{131}I uptake and serum Tg levels and in these cases prognosis is good. On the other hand, patients with recurrent disease that does not concentrate ^{131}I were found to have more invasive cancers and to have a poorer outcome. In these patients, the reported 2-, 5- and 10-year survival rates are 55%, 16% and 11%, respectively, compared to 91%, 77% and 62%, respectively, in patients with ^{131}I uptake [19;20]. The presence of metastases in distant organs other than lungs, such as bones, brain or liver, is an important unfavorable prognostic variable. In a study by Casara *et al.* including 134 patients with lung metastases, it was shown that the 5- and 10- year survival rates were 69% and 62%, respectively, for patients with only lung metastases compared to 36% and 10%, respectively, for those with multiple metastases [1]. In this study, T and N stages and gender were not significantly related to prognosis. Comparable results were found in patients with bone metastases of DTC [21]. Again, the reported median survival was significantly different

between patients with functioning metastases (4.6 years) and those with non-functioning metastases (2.4 years). It has to be realised that in approximately 65% of patients with non-functioning metastases the disease is limited to the neck and/or mediastinum. In these patients, the only effective treatment is radical surgery, which results in a complete remission in almost 50% of cases. Such results confirm the necessity for early detection of recurrent DTC, and also show the need to assess whether it is limited to one organ system or not. Therefore, it would be helpful to have a diagnostic and prognostic tool in patients with non-functioning metastases that identifies patients in whom a more aggressive treatment is required to stabilise disease [12].

Somatostatin receptor expression in thyroid cancer

In a study by Ain *et al.*, it was shown that normal thyroid tissue shows high expression of SSTR3 and 5 and weak expression of SSTR1 and 2 [22]. With respect to thyroid cancer tissue, the expression of SSTR2 was only found in Hürthle cell carcinomas. In papillary and follicular tumors, high expression of SSTR3, 4 and 5 was seen. As ^{111}In-octreotide in general binds to SSTR2, 3 and 5, it can be concluded that, even though the binding to SSTR3 and 5 is less optimal than that to SSTR2, non-functioning thyroid tumors may be visualised using this radiopharmaceutical. In 1996, Baudin *et al.* were the first to report on octreotide scintigraphy in DTC in clinical practice [23]. An overall sensitivity of 80% was described, irrespective of the ^{131}I WBS result. In more recent reports by Postema *et al.* and Gorges *et al.*, comparable results (75% and 74%, respectively) were found [16;24]. In these studies, a correlation was found between the sensitivity and the Tg levels. Finally, Haslinghuis *et al.* reported that thyroxin withdrawal seems to increase the diagnostic yield of ^{111}In-octreotide scintigraphy from 67% to 85% in DTC [25]. Our results are in agreement with the data found in literature, but we did not discontinue hormonal replacement. In a majority of the patients SRS may guide the clinician to alternative treatment

options, such as surgery in the presence of locoregional disease or chemotherapy in cases of extensive disease. In this respect, however, it is important to note that false positive imaging with ^{111}In-octreotide may also occur, especially in the region at risk. For example, focally increased uptake in the mediastinum or head and neck region can be caused by an infection. More diffuse uptake in this region can be seen after surgery, external radiation therapy or in the lungs after chemotherapy.

Prognostic stratification and nuclear medicine techniques

In this study we have shown that patients with non-functioning DTC with moderate to high ^{111}In-octreotide uptake (scores 2, 3 and 4) have a significantly poorer outcome than patients with no or slight uptake. Although the number of patients studied is limited, the results suggest more aggressive tumor behaviour in cases of SSTR-positive DTC. In the present study we were not able to correctly assess the tumor mass or tumor volume in each patient. Nuclear medicine techniques in general cannot be used to assess such a parameter. More-over, as stated in the introduction, radiological techniques such as ultrasonography of the head and neck region, chest-X rays or CT scanning are valuable in assessing tumor recurrence or progression and tumor mass. However, small lesions with diameters of less than 1 cm may be missed [8;9]. In addition, lymph node enlargement may be caused by infection as well as by tumor. Therefore, assessment of tumor mass is highly difficult. In this respect, some reports have focussed on the correlations between Tg levels, tumor mass and prognosis [26-28]. Tg measurement is a highly specific and sensitive test for the follow-up of thyroid cancer. During hormonal treatment, serum Tg is elevated in most patients with large metastases and is lower or even unde-tectable in patients with small metastases. After withdrawal of hormonal replacement, the serum Tg level increases or becomes detectable in the majority of the patients [4;5]. In some of the reports on Tg, a relationship has been

suggested to exist between serum Tg level and tumor burden. In a more recent report by Bachelot *et al.*, it was shown that the number of metastatic lymph nodes and their total surface or volume were significantly associated with serum Tg/TSH ratios [29]. In this selected group of patients, lymph node metastases in the head and neck region were the only source of serum Tg, resulting in an accurate evaluation. In their study, it was shown that this relation was not altered by possible confounding factors such as the clinical characteristics, histology and previous treatment modalities. On the other hand, it was shown that undetectable or very low Tg levels cannot be used as a reliable criterion for minimal tumor burden in patients who have been treated with ^{131}I. As shown in the study by Bachelot *et al.*, even patients with Tg levels <1 ng/ml had tumor volumes up to 7178 mm^3. Such values were also observed in patients with Tg levels between 1 and 10 ng/ml and patients with Tg levels >10 ng/ml.

In the present study, Tg levels were used as an indication for tumor mass. As probably was to be expected, we found a significant difference in mean Tg levels between groups 1 and 2, suggesting a difference in tumor mass between the selected groups. In some of the patients in group 1, however, high Tg levels were found which did not result in an uptake score of 2, 3 or 4, and conversely, some patients with a high uptake score had low Tg levels. Although significant, the Spearman's correlation coefficient of 0.67 was rather weak. Despite the fact that the number of patients studied is probably too small, the findings suggest that tumor mass is not the only parameter responsible for the difference in clinical outcome identified in the present study. One has to realise, however, that the rather weak correlation might be due to the use of Tg-on levels, i.e. Tg levels in the absence of TSH stimulation. Therefore, further studies have already been initiated to assess the prognostic value of SRS in patients in whom TSH stimulation is achieved via recombinant human TSH administration.

Regarding the different radiopharmaceuticals used over recent years in patients with non-functioning DTC, ^{201}Tl has been most extensively employed in follow-

up [30-32]. In this respect, it seems to be of predictive value: a high uptake is correlated with a poor prognostic outcome [33]. More recent reports have focussed on the diagnostic value of ^{99m}Tc-methoxyisobutylisonitrile (MIBI) [34-37]. Data on the prognostic value of ^{99m}Tc-MIBI in thyroid cancer are not available.

Data on the use of FDG-PET in thyroid cancer are increasing [38]. Feine *et al.* showed that FDG uptake seems to be an indicator of poor functional differentiation and possibly higher malignancy grades in thyroid cancer [11]. In a report by Sarlis *et al.*, ^{111}In-octreotide scintigraphy was compared with FDG PET in 21 patients with progressive DTC [39]. The sensitivity of SRS and FDG PET were 49.5% and 67.7%, respectively. Importantly, SRS detected five unexpected lesions, which were negative on FDG PET imaging. This finding underlines the unpredictability of the metabolic profile and receptor expression in metastatic lesions. The value of such conflicting results is still not clear, but these data confirm the necessity of multi-modality imaging to assess tumor burden.

Nevertheless, in the present study we have shown that scintigraphy with ^{111}In-octreotide is a valuable diagnostic tool in non-functioning DTC. The long-standing expression of SSRT, even in cases of dedifferentiation in DTC as shown in the present study, may also form the basis for treatment with somatostatin analogues. In this respect, a cytostatic, anti-angiogenetic effect of octreotide has already been suggested. In the first preclinical in vitro studies by Ain *et al*. [40], dose-dependent growth inhibition in a papillary carcinoma line (NPA87) was observed though stimulation of growth was seen in a follicular cancer cell line (RO87-M-1). In a study by Hoelting *et al*. [41], conflicting results were found in the treatment of three different follicular thyroid cancer cell lines. In vitro studies revealed a biphasic effect, with enhanced growth at low cold octreotide concentrations, but an inhibiting effect at high concentrations. In their studies in nude mice, however, there was no effect on the growth of these cells. In contrast to these findings in animal studies, Robbins

et al. demonstrated a reduction in thyroid tumor volumes in two patients who had been treated with 3- to 4-month courses of octreotide [42]. Their results were observed on follow-up FDG-PET studies in a patient with thyroid cancer that was unresponsive to ^{131}I treatment and in another patient with thyroid cancer without ^{131}I uptake on WBS. These findings were in contrast to a previous study described by Zlock *et al*. in which subjects were monitored while receiving relatively high doses (4 mg daily) of octreotide subcutaneously for up to 12 months [43]. Octreotide as a single agent did not significantly decrease tumor markers (e.g. Tg, calcitonin, carcinoembryonic antigen). The carcinomas progressed during treatment, as evidenced by an increase in the size and/or number of metastatic lesions. Finally, other reports have focussed on the enhancement of the anti-neoplastic effects of tamoxifen and doxorubicin by octreotide [44-46]. Despite the fact that these results were observed in breast cancer and pancreatic tumor cell lines, it is suggested that octreotide may also increase the therapeutic effectiveness in thyroid cancer treatment with adriamycin. These results, however, need to be confirmed in large-scale clinical trials.

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Chapter 8

Six month follow-up after ^{111}In-DTPA-octreotide therapy in patients with progressive radioiodine non-responsive thyroid cancer

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Abstract

Background and aim ^{111}In-DTPA-octreotide is internalized by thyroid and neuroendocrine cancer cells via somatostatin receptor subtypes and can cause DNA damage by the emission of conversion and Auger electrons. The aim of the study was to determine the effect of ^{111}In-DTPA-octreotide therapy in patients with progressive radioiodine non-responsive thyroid cancer in relation to ^{111}In-DTPA-octreotide uptake by tumor localizations assessed on pre-treatment diagnostic octreotide scans.

Methods Eleven consecutive patients, selected on positive pretreatment diagnostic scans, were treated with fixed doses of approx. 7400 MBq of ^{111}In-DTPA-octreotide with an interval of 2-3 weeks between the doses. In one patient, the dose was adjusted because of sickle-cell disease. To assess the effects during treatment with ^{111}In-DTPA-octreotide thyroglobulin levels were gathered from 2 years before treatment, during treatment and up to 1 year after treatment. A computed tomography scan was performed 3 months after the last treatment.

Results Two patients died during and shortly after the treatment course. Death was due to a sepsis and an insulin overdose, respectively. In 44% of the patients, stable disease was achieved up to 6 months after the first treatment according to both criteria. All four had relative low pretreatment thyroglobulin levels (mean level 275 µg/l), representing limited metastasized disease. In two patients biochemical stable disease was observed, whereas computed tomography showed tumor progression.

Conclusion Treatment with high doses of ^{111}In-DTPA-octreotide in differentiated thyroid cancer results in a stable disease in a subgroup of patients. Our results suggest that a low pre-treatment thyroglobulin level, representing a small tumor load, may be a selection criterion for treatment.

Introduction

Follicular and papillary thyroid cancer, so-called differentiated thyroid cancer (DTC), is an uncommon tumor, representing approximately 3% of all neoplasms. The incidence of DTC is 5-10/ 100000 per year and the overall prognosis is good with 10 year survival rates between 92-98% [1;2]. The initial treatment consists of surgery, which is followed by ablation with [131]I. To assess tumor recurrence and/or metastases, plasma thyroglobulin (Tg) and ^{131}I whole body scintigraphy (WBS) are well-established techniques [3;4]. Recurrences and/or metastases can be treated with repeat surgery, ^{131}I treatment and/or radiotherapy. However, a number of patients show disease progression, assessed either radiological or by increasing Tg levels, under ^{131}I treatment or have WBS scans with no ^{131}I uptake. Many reports have focused on the value of fluorodeoxyglucose positron emission tomography (FDG PET) for the detection of metastatic disease in these patients [5-7]. Iodine negative locoregional disease detected by FDG PET can be treated with surgery or external irradiation, but, despite an improved locoregional control, it does not affect the overall survival [8;9]. Irrespective of the good diagnostic accuracy, there are currently no well-established treatment options for patients with ^{131}I non-responsive multiple metastases. In such cases, 5 year survival rates decline to 60-82% [10;11]. Recent reports have focused on redifferentiation of thyroid cancer by means of retinoic acid stimulation. Despite promising results in *in vivo* studies, *in vitro* studies revealed disappointing results [8;12].

As response to chemotherapy and radiotherapy is variable, more effective treatment modalities are needed. It has been proposed that endocrine and neuroendocrine tumors may be treated with a high dose of radiolabeled ^{111}In-octreotide (^{111}In-DTPA-octreotide). Octreotide is a somatostatin analogue with affinity for specific somatostatin receptor subtypes. There are five different subtypes (SST 1-5) of the somatostatin receptor. In a study by Forsell-Aronsson

et al. [13], a high expression of SST 1, 3, 4 and 5 was found in both papillary thyroid cancer and follicular thyroid adenoma. Medullary thyroid cancer cells showed expression of all subtypes, whereas neuroendocrine tumors express SST 1 and 2 and to a lesser extent SST 5 [14]. The somatostatin analogue octreotide shows high affinity for subtype 2, average affinity for subtypes 3 and 5, and no affinity for SSTs 1 and 4 [15;16]. The expected effect of ^{111}In-DTPA-octreotide on tumor tissue is based on the internalization of the radiolabeled octreotide through these somatostatin receptors. 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 in some small case series [17-20].

The aim of this study was to observe the effect of high doses of ^{111}In-DTPA-octreotide therapy in patients with disseminated and progressive radioiodine non-responsive thyroid cancer.

Patients, materials and methods

Patients

Eleven consecutive patients (seven women and four men; mean age, 63 years, range 44-69) with progressive disseminated thyroid cancer not responding to ^{131}I treatment were included from 1 February 2000 to 1 December 2001. All patients had multiple sites of uptake of ^{111}In-octreotide, an exclusion criterion for surgery.

Tumor progression before entering this study was based on rising Tg levels (Figure 1) and confirmed by radiological evaluation. To assess the effects during treatment with ^{111}In-DTPA-octreotide Tg levels were gathered from 2 years before, during and up to 1 year after treatment. Exclusion criteria were a life expectancy <6 months, kidney and liver dysfunction other than caused by metastases and no visible ^{111}In-octreotide uptake in metastases. The medical ethics committee of our institution approved therapy and all patients gave

informed consent.

Baseline characteristics

To assess the octreotide uptake, baseline scans were performed using 220 MBq of ^{111}In-DTPA-octreotide. Whole body scintigraphy (run speed 10 cm/min) and single photon emission computed tomography (SPECT) of the chest and head and neck region were performed at 4 and 24 h p.i. using a dual-head gamma camera (Toshiba GCA 7200, Japan). The SPECT images (matrix size 128 x 128; with a 6° step angle and a 1 min step time) were reconstructed using filtered back-projection and a Butterworth pre-processing filter (8 order, 0.12 subset). These scans were used to exclude patients with no ^{111}In-DTPA-octreotide uptake from treatment. In this respect, scoring of tumor radioactivity was done visually according to the criteria described by Krenning *et al*. ranging from 0 to 4 [16].

All patients underwent a baseline radiological evaluation (computed tomography (CT) or magnetic resonance imaging (MRI) approximately a month before or immediately after the first therapeutic octreotide dose to determine baseline tumor size and extent and number of metastases. A complete biochemical and haematological screening was done for all patients as well as the measurement of Tg-on and thyroid stimulating hormone (TSH) levels.

^{111}In-DTPA-octreotide therapy

In this protocol we intended to treat patients with a standard activity of approximately 7400 MBq ^{111}In-DTPA-octreotide per injection. A complete treatment course was defined as four administrations with an interval between two administrations ranging from 2 to 3 weeks. The treatment dose was adjusted or postponed in case of side effects, as trombocytopenia.

Follow-up

On days 0, 3, 7, 14 and 21 after each ^{111}In-DTPA-octreotide administration a complete biochemical and haematological screening, including tumor markers and tumor marker antibodies, were performed. In addition, whole body scintigraphy was performed on days 3 and 7 (run speed 20 cm/min) to measure the uptake in at least two metastases during treatment using the procedure described previously [21]. Tg levels were also measured 3 and 9 months after the final ^{111}In-DTPA-octreotide administration, which is approximately 6 and 12 months, respectively, after the first administration. Furthermore, 3 months after the last treatment a CT scan was performed.

Treatment evaluation

Three criteria were used for evaluation: criterion number 1 was a radiographic (CT or MRI) response in which images prior to and 6 months after the first administration were compared. Radiological stable disease was defined as an equalization in tumor size and in number/extent of metastases. Any increase in tumor size or number of metastases was defined as progression. Criteria 2a and 2b were tumor marker response assessed at 3 and 6 months, respectively, after the first administration.
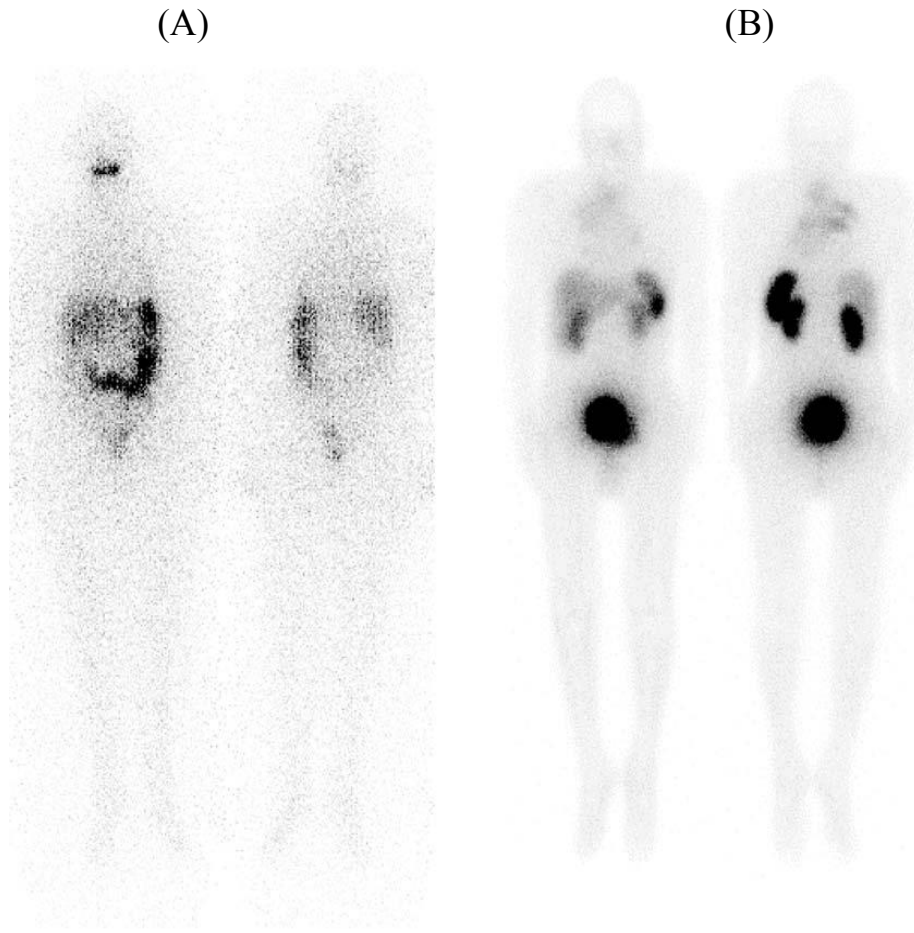
(A)   (B)

Figure 1. Post-treatment ^{131}I whole body scintigraphy (8000MBq) (A) in a 57-year-old man with a history of a T3N0M1 follicular thyroid carcinoma and an increasing thyroglobulin (Tg) level showed a normal, physiological distribution. The accumulation in the pelvic region is physiological excretion into the bladder and rectum. Whole body scintigraphy after the injection of 8000 MBq of ^{111}In-DTPA-octreotide (B) revealed metastases in the chest and thoracic spine.

Results

Baseline characteristics and follow-up

The patients' characteristics are summarized in Table 1. Patient nr 7 received 3700 MBq [^{111}In-DTPA]-octreotide at the third administration because of a low platelet count. Due to this adjustment, the total dose administered to this patient was 27.5 GBq. Neither clinical nor haematological side effects were observed in the other patients. Patient nr 9 had sickle-cell disease and, therefore, received 3700 MBq per session up to a total amount of 14.3 GBq. Overall, the total amount of [^{111}In-DTPA]-octreotide administered ranged from 14.3 to 33.1 GBq.

Figure 1 demonstrates a typical example of an ^{131}I negative whole body scan after the treatment with 7400 MBq of ^{131}I and multiple metastases in the chest and spine on the whole body scan after the administration of 7400 MBq of ^{111}In-DTPA-octreotide.

During the 1 year follow-up three patients died. Patient nr 5 died of an insulin overdose at 28 days of follow-up. He had completed the whole treatment course with ^{111}In-DTPA-octreotide. Patient nr 6 died of a non-tumor related sepsis 6 days after the second ^{111}In-DTPA-octreotide dose. Since the start of ^{111}In-DTPA-octreotide therapy he had been showing a decrease in tumor marker production. Neither patient nr 5 nor nr 6 had had a follow-up CT scan at time of death. Patient nr 2 died 2 months after the last treatment course due to tumor progression causing pleural effusion and emboli seen on CT performed the day before she died. Shortly before she died, which is 5 months after the first treatment, a complete biochemical and radiological evaluation was performed. Although the 6 month follow-up was not completed, we decided to use these data for further evaluation. Finally, in none of the patients was there a significant difference measured in tumor uptake between the first and last treatment measured on days 3 and 7.

Effect of [^{111}In-DTPA]-octreotide therapy
Effect related to Tg levels at 3 and 6 months follow-up
Four patients with initial Tg levels <1000 μg/l demonstrated biochemical stable disease at 6 months after the start of the treatment course. This effect was already observed 3 months after the first administration. An effect of increased TSH levels during follow-up compared to the initial levels was excluded (Tables 1 and 2). Three out of five patients with rather high Tg levels had a further increase, which was already observed at the 3 month time interval.

In Figure 2, Tg levels are presented from before, during and up to 1 year after

treatment. Because of the very skewed distribution, log Tg levels are reported. Due to the lack of follow-up in patients 5 and 6, the Tg curves are not shown.

Table 1. Patient characteristics.

Nr	Age	Sex	Tumor	TNM	Prior treatment	Last treatment and interval	Initial TSH (mU/l)	Initial Tg levels (µg/l)	Sites of metastases at start of ^{111}In-octreotide therapy
1	57	M	FTC	T3N0M1	surg, ^{131}I, RT, emb	RT / 491	<0.005	980	lung, bone, LN
2	67	F	PTC	T2N1M1	surg, [131]I	[131]I / 108	0.010	772000	lung, brain, LN
3	69	F	PTC	T4N1M1	surg, [131]I	[131]I / 193	0.796	1275	lung, LN
4	65	F	FTC	T2N0M1	surg, [131]I	[131]I / 291	<0.020	42610	lung, pleura
5	67	M	FTC	T2N0M1	surg, ^{131}I, RT, emb	RT / 133	<0.005	27000	bone
6	67	M	PTC	T4N0M1	surg, ^{131}I, emb	emb / 28	0.040	1367	lung, bone, skin
7	68	M	PTC	TxN1M1	surg, ^{131}I, RT	RT / 176	0.022	28809	liver, lung, LN
8	55	F	PTC	T4N1M1	surg, [131]I	[131]I / 323	0.009	101	lung, LN
9	44	F	FTC	T4N1M1	surg, chemo, ^{131}I, RT, emb	[131]I / 130	<0.005	5277	liver, lung, bone, mediastinum, LN
10	67	F	PTC	T4N1M1	surg, ^{131}I, RT	[131]I / 172	<0.005	104	lung, LN
11	53	F	FTC	T3N1M1	surg, [131]I	[131]I / 2650	<0.005	78	lung, LN

FTC, follicular thyroid cancer; PTC, papillary thyroid cancer; surg, surgery; chemo, chemotherapy;
emb, embolization; RT, radiotherapy; ^{131}I, radioiodine treatment; LN, lymph nodes.

Table 2. Results of treatment with high doses ^{111}In-Octreotide.

nr.	Octreotide uptake	Number of doses	Cumulative ^{131}I dose (MBq)[***]	TSH* (mU/l)	Tg* (μg/l)	Biochemical response at 3 months*	Biochemical response at 6 months**	Radiological response
1	2	4	32333	0.238	744	S	S	S
2	3	4	30582	0.137	749000	S	S†	P†
3	1	4	30279	0.395	3900	P	P	P
4	1	4	31776	<0.005	60400	P	P	P
5	2	4	32349	0.019	24300	S	NA	NA
6	1	2	16828	NA	NA	NA	NA	NA
7	3	4	27551	<0.005	37150	S	S	P
8	1	4	31996	0.017	113	S	S	S
9	1	4	14308	<0.005	9711	P	P	P
10	1	4	32210	0.015	168	S	S	S
11	2	4	31748	<0.005	76	S	S	S

*Results 3 months after the first ^{111}In-octreotide therapy; **results 6 months after the first ^{111}In-octreotide therapy; ***before ^{111}In-octreotide therapy. †Results 5 months after the first therapy: these data were obtained shortly before she died. NA, not available; P, progression; S, stabilization.
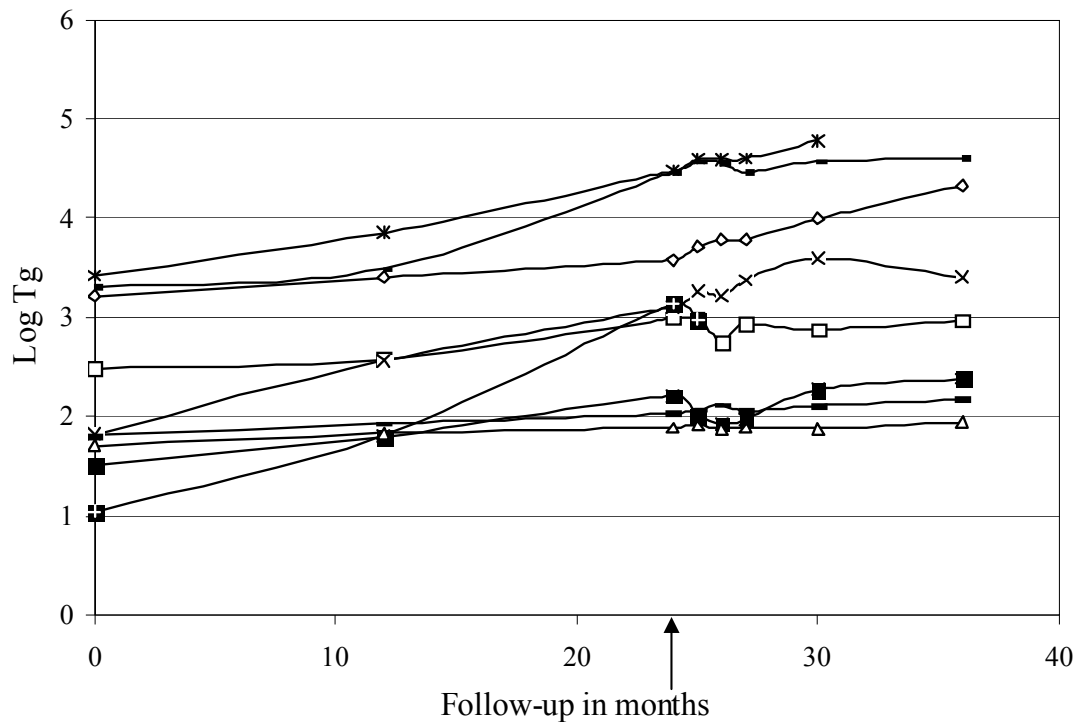
Figure 2. Tg levels from 2 years before up to 1 year after treatment with high activity ^{111}In-octreotide. The arrow indicates the start of the treatment course with high doses of ^{111}In-octreotide. Because of the skewed distribution of the Tg levels, log Tg levels were used. Symbols represent the nine surviving patients in the study.

Therapeutic effect based on follow-up CT and Tg levels at 6 months

No patient had a tumor reduction on CTscan. However, in four of the patients studied stable disease was seen on CT. These patients had also stable tumor markers (mean Tg level 275µg/l; range 76-744µg/l). Five patients had radiological progression after ^{111}In-DTPA-octreotide therapy, of which three also had tumor marker progression. One of these three patients, nr 9, had received an adjusted dose because of sicklecell disease. The mean Tg level in this group was 180432 µg/l (range, 3900-749000 µg/l). From these data it is concluded that, in small tumors, expressed by rather low Tg levels, an antiproliferative effect was observed. In two out of these five patients, dissociation was observed between biochemical and radiological response criteria, suggesting a metabolic but no anti-proliferative effect.

The number of patients was too limited to draw any conclusion with respect to the uptake score and the therapeutic effect.

Discussion

The purpose of this study was to determine the effect of treatment with high, fixed doses of ^{111}In-octreotide in patients with progressive iodine non-responsive thyroid cancer. Two patients died during follow-up, which was due to a sepsis in one and an insulin overdose in the other. Only patients with rather low Tg levels (<1000 µg/l) demonstrated both a biochemical and radiological stable disease, which reflects the response of small tumors to such large treatment doses as used in the present study.

Prognosis and survival

Thyroid cancer is often a slow growing tumor with a very good long-term survival. Of the patients diagnosed with differentiated thyroid cancer, 5-20% will develop a local or regional recurrence or metastatic disease [2]. Therapy is still the same as that for initial disease: surgery and ^{131}I treatment. More recent reports have focused on the value of external beam radiotherapy in the management of locoregional advanced thyroid cancer. In four of the recently published studies [8;12;22-24], it was shown that radiotherapy indeed significantly improved locoregional control in patients with pT4 tumors or lymph node involvement. In the study by Ford *et al*., even a possible dose response was found with a local recurrence rate of 63% and 18% for doses <50Gy and >54Gy, respectively [23]. However, in two studies it was shown that, despite a better local control by a combination of surgery and external irradiation, this strategy did not improve survival in patients with locally advanced disease. In these case series, locoregional radiotherapy revealed 5 and 10 year survival rates of 96%, whereas the results for patients without radiotherapy were 94% and 89%, respectively [8;24].

In the presence of extensive metastasized disease the overall 5 year survival rates declines to 60-82%. In case of ^{131}I uptake in metastases, the reported 2, 5 and 10 year survival rates are 91%, 77% and 62%, respectively. In contrast,

however, the survival rates are 55%, 16% and 11%, respectively, in the case of metastatic disease that lost its capability of ^{131}I uptake [25;26]. Patients with radioiodine non-responsive progressive disease can be treated with radiotherapy for recurrent neck disease or chemotherapy (adriamycin) for widely metastatic disease. Adriamycin, however, reveals a partial response in only 30-40% of patients [10], but these studies were performed in selected patient groups. These results support the necessity for early detection and treatment of recurrent thyroid cancer that does not concentrate radioiodine.

Somatostatin receptor therapy

The use of unlabeled somatostatin in the treatment of neuroendocrine tumors is well established and is based on its inhibitory effect on hormone production and its antagonistic effect with regard to tumor growth factors. Somatostatin binds to a family of G-protein-coupled receptors [14]. There are five subtypes (SST 1-5) and somatostatin binds to all five. However, due to its short half-life (approx. 3 min) and its diversity of action, somatostatin is relatively unsuitable for treatment purposes. Somatostatin analogues more resistant to enzymatic degradation, like octreotide, have been manufactured. Octreotide has a high affinity for receptor subtype 2, average affinity for SSTs 3 and 5, and no affinity for SSTs 1 and 4. The diagnostic and therapeutic efficacy of octreotide is based on the binding with SSTs 2, 3 and 5. Data with respect to the diagnosis and treatment of follicular and papillary thyroid cancer with somatostatin analogues, however, are still limited.

Non-medullary differentiated thyroid cancer cells show expression of SSTs 1, 3, 4 and 5. Octreotide can target thyroid tumors through somatostatin receptor subtypes 3 and 5. In this respect, non-radiolabeled somatostatin analogues, like octreotide, have proven to be effective in tumor growth reduction. In preclinical *in vitro* studies by Ain *et al*. [27], a dose dependent growth inhibition in papillary carcinoma lines (NPA87) was observed though stimulation of growth

was seen in follicular cancer cell lines (RO87-M-1). The authors concluded that it might be due to differential stimulation and regulation of distinct somatostatin receptors. In a study by Hoelting *et al.*, *in vitro* experiments in follicular cancer cell lines showed comparable results [28]. They found a biphasic effect, enhancing growth at low concentrations (1-10 nmol/ml), but inhibiting it at high concentrations (100 nmol/ml to 1 μmol/ml). Also a dose dependent biphasic effect on the invasion of the cancer cells, inhibiting all cell lines tested at high concentration. However, during a 3 week treatment period, octreotide had no antiproliferative effect on the growth of the cancer cell lines in nude mice. In humans, tumor reduction rates of approximately 10% have been reported in gastrointestinal tumors [29]. Data with respect to the treatment of differentiated thyroid cancer patients are still limited to case reports. Zlock *et al.* treated five patients with octreotide for 2 to 14 months [30]. All patients had lung metastases and they were considered to be untreatable by surgery or radioiodine. Despite doses up to 1 mg tid or qid, all patients had progressive disease. Finally, Robbins *et al.* [31] described the treatment of two patients with widely metastatic papillary thyroid cancer. In these patients, baseline metabolic activity and threedimensional volume of the lesions were determined by FDG PET. After 3 or 4 months of octreotide therapy, repeat FDG PET scans showed a reduction in tumor volume and decreases in the metabolic activity. Whether this reduced activity inhibits the progression of poorly differentiated thyroid carcinomas could not be concluded from this report.

A relative new application, especially in case of DTC, is the use of octreotide labeled with [111]In. Its therapeutic effect is based on the toxicity of short range Auger electrons, emitted by ^{111}In, on cellular DNA. Due to the short particle range of Auger electrons, success depends on the amount of radioligand that can be concentrated into the cell and this depends on the rate of internalization, degradation and recycling of the ligand and the receptor expression. Internalization is receptor mediated and temperature dependent [14]. Of the

receptor subtypes, SST 3 is the most efficient at internalization while SST 1 does not. Reubi *et al.* [32;33] have evaluated the affinity of various radiolabeled somatostatin analogues for the different somatostatin receptor subtypes. They found that although radiolabeling with ^{111}In decreased the affinity of octreotide to somatostatin receptors by 10-fold, its affinity to these was still significant. So, ^{111}In-octreotide still can be sufficiently internalized by tumor cells expressing SST 3.

Most of the reports with regard to the therapeutic value of ^{111}In-DTPA-octreotide are related to neuroendocrine tumors. In a review by McCarthy [16;34], results of five institutions, a total of 85 patients with metastatic neuroendocrine tumors, are described. Response included radiographic, biochemical and/or improvement in Karnofsky performance status, which revealed an overall response rate between 62% and 69%. ^{111}In-DTPA-octreotide doses ranged from 4 to 11.1 GBq per course and were given in two to eight courses with an interval of 3-4 weeks per course. Krenning *et al.* (included in the above review), reported that the effectiveness of ^{111}In-DTPA-octreotide therapy seems to be related to the amount of ^{111}In-DTPA-octreotide uptake by the tumor. Response was 86% in patients with high uptake (=intense), 67% in patients with average uptake (=higher than liver) and 50% in patients with low uptake (=lower than/equal to liver). In contrast to this, in our patient population the response to ^{111}In-DTPA-octreotide therapy was observed in patients with rather low uptake scores (scores 1 and 2). The number of patients studied, however, is too small to draw a definite conclusion.

Thyroglobulin levels and treatment effect

Caillou *et al*. [35] as well as Lazar *et al*. [36] investigated the expression of thyroid-tissue specific genes in normal thyroid tissue and in thyroid carcinoma tissue. Correlation was found between the expression of the hNIS gene (human sodium/iodine symporter gene) and the ability of the tumor to concentrate iodine. Expression of the Tg gene in thyroid cancer cells, though 2-fold to 300-fold less than in normal tissue, remained well preserved in later tumor stages, being absent only in undifferentiated cancer cells [37]. Whether this dissociation between tumor marker production and tumor growth, as observed in two patients in the present study, can be clarified by a further positive selection of poorly differentiated cancer cells is not clear yet. If this is the case, labelling octreotide with a beta emitter could increase the effectiveness of radiolabeled octreotide therapy. However, results of somatostatin receptor scintigraphy (SRS) reported by Baudin *et al*. [17] do not support this theory. Although not fully elucidated, an anti-metabolic effect is more likely in the present cases. This effect also has been observed in neuroendocrine tumors, which causes a relief in symptoms caused by increased hormone production [38-41].

Radiolabeled octreotide therapy in thyroid cancer and future prospects

This is one of the scarce studies in which the therapeutic value of ^{111}In-DTPA-octreotide in patients with progressive radioiodine non-responsive non-medullary thyroid cancer is evaluated. Our results are comparable to those observed in neuroendocrine tumors reported by other institutions, though dosage and frequency of ^{111}In-octreotide therapy vary. Krenning *et al.* [16] reported on the effect of ^{111}In-octreotide in a patient with papillary thyroid cancer and a complete follow-up who showed disease stabilization. This patient received a total cumulative dose of at least 20 GBq and had grade 2 uptake. Our study population included 11 patients with non-medullary thyroid cancer with uptake scores ranging from 1 to 3. In four treatments per patient a cumulative dose of

approximately 30 GBq ^{111}In-DTPA-octreotide was given. The treatment scheme used in the present study was based on data in literature in which a cumulative dose of at least 20 GBq is recommended. Furthermore, major side effects with single doses up to 14 GBq and cumulative doses up to 75 GBq have not been reported [38-41].

More recent reports have focused on somatostatin analogues labeled with ^{90}Y, a beta particle emitter. In contrast to the short range of the Auger electrons, the radiation emitted from ^{90}Y can extend over several cell diameters. In the theory, it can destroy both somatostatin receptor positive and receptor negative tumor cells. Görges *et al*. [18] has reported on three patients treated with a different radiolabeled somatostatin analogue, ^{90}Y-DOTATOC. One patient had two treatments with a cumulative dose of 4400 MBq, the second had one dose of 1700 MBq and the last patient had four doses with a cumulative dose of 9620 MBq. In all three patients radiographic progression could not be stopped, whereas only one patient had decreasing tumor marker production. Otte *et al.* [42] have reported on results with ^{90}Y-DOTATOC in 29 patients with advanced neuroendocrine tumors who had no other treatment options. These patients were treated with four or more doses of ^{90}Y-DOTATOC, with a cumulative dose of around 6000 MBq/m^2. Twenty patients showed disease stabilization, two showed tumor reduction of more than 50%, four showed a reduction of the tumor mass of less than 50% and three showed tumor progression. Paganelli *et al.* [43] reported results for 30 patients with somatostatin receptor positive tumors treated with ^{90}Y-DOTA-D-Phe^1-Tyr^3-octreotide. Cumulative dosage was between 3 GBq and 8 GBq, given in three courses over a period of 6 months. The patient population included 23 carcinoid tumors and three medullary thyroid cancers. Complete or partial reduction of the tumor mass occurred in 23% of patients, 64% had stable disease and 13% progressive disease. In a more recent report by Waldherr *et al*. [44], the value of ^{90}Y labeled octreotide (DOTATOC)

in differentiated thyroid cancer was described. Twenty patients with therapy resistant thyroid cancer were treated with a dose in the range of 1700 MBq/m^2 to 7400 MBq/m^2 ^{90}Y-DOTATOC, administered in one to four injections at intervals of 6 weeks. Stable disease was achieved in 35% of the patients, whereas progressive disease was found in 65%. They suggested that more significant tumor responses in thyroid cancer may be obtained with radiopeptides, which more selective bind to SSTs 3 and 5, both receptors expressed by thyroid cancer cells.

Throughout the last decade several somatostatin analogues, such as lanreotide and depreotide [45-47], have been introduced on the basis of their recognition for SSTs 3 and 5. Preclinical data and clinical studies confirm their potential use in diagnosis as well as in therapy of cancer patients. The possible antiproliferative effects of these radiolabeled somatostatin analogues may lead to a new treatment option in differentiated thyroid carcinoma metastases that do not respond to treatment with high doses of [131]I. Based on the present results it may be concluded that diagnostic ^{111}In-octreotide scintigraphy revealing uptake scores ranging from 1 to 4 and measurement of low Tg levels representing a small tumor load can be used as selection criteria for treatment. More studies are required to assess the value of treatment with ^{111}In-octreotide in differentiated thyroid cancer. In this respect, however, it is highly important to evaluate and discuss the issue of stabilization of Tg levels in patients with radiologically confirmed tumor progression. Therefore, further study is required.

Finally, more recent reports have focused on the use of retinoic acids, as proliferation inhibiting and differentiation inducing effects in thyroid cancer [48;49]. These acids exert their effects via receptors. It has been shown that retinoic acids in various thyroid cell lines regulate NIS expression. In particular, the messenger RNA encoding the NIS is upregulated by the retinoic acid stimulation. In former clinical pilot studies, 40-50% of the patients with poorly

differentiated thyroid carcinomas lacking iodine uptake responded to treatment to retinoic acids with an increase of iodine uptake [50-52]. In theory, this redifferentiation process of advanced thyroid carcinomas by stimulating the hNIS expression makes tumors accessible for radioiodine therapy again. In a more recent clinical study, however, it could not be confirmed. Grûning *et al.* [12], studied 25 patients who were treated with retinoic acids at 1 mg/kg for 3 months followed by [131]I. In two out of 14 patients with raised Tg levels but no ^{131}I uptake, a slightly improved uptake was seen. In three out of 11 patients with slight uptake a dosimetrically relevant improvement of uptake was seen. Of these five responders (20%), two were completely free of symptoms, one showed stable disease and two patients worsened. Retinoic acid gave improvement of ^{131}I uptake in metastases with low radioiodine uptake, but it did not appear to induce uptake in ^{131}I negative metastases. Consequently, despite the mild and reversible side effects, its therapeutic use as a single agent in the patients reported in the present study is debatable. A possible enhancement of the antiproliferative effect of retinoic acid by phenylacetate is still under study. In a report by Eigelberger *et al.* [53], it was shown that retinoic acid and phenylacetate alone inhibited growth in a follicular cell line to 16% and 35%, respectively, compared with controls, whereas the combination of the two inhibited growth to 60%. This effect is probably due to an upregulation of the retinoic acid receptor by phenylacetate. Although an improvement of ^{131}I uptake in iodine negative metastases due to this synergistic effect might be expected, its role in clinical practice is still unclear and needs further study.

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Chapter 9

Summary and Discussion

The therapy of choice in patients suffering from differentiated thyroid cancer (DTC), subdivided into papillary and follicular thyroid carcinoma, is (near-)total thyroidectomy. This is routinely followed by the administration of radioiodine (RaI)-131 (^{131}I) to destroy any remaining benign or malignant thyroid tissue, so-called ablation.

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 has addressed some important clinical questions, related to the application of conventional (^{131}I) and experimental therapies with radionuclides in DTC.

Iodine-131 has been used for many years to ablate thyroid remnants following thyroid surgery, but a single optimal activity has not yet been established. In this respect, data in the literature are inconsistent; some studies conclude that an activity of 1110 MBq of ^{131}I may be as effective as a high activity such as 3700 MBq, whereas other authors suggest that a higher activity of ^{131}I will improve the rate of successful remnant ablations. Two protocols are commonly used in the Netherlands: the uptake-related ablation strategy in which relatively low activities of ^{131}I are used and the fixed-dose or tumor-related ablation strategy in which higher ablation activities are used.

The main aim of this thesis was to study the short-term and long-term outcome parameters in DTC according to the uptake-related ablation protocol and to compare the success rates of both ablation strategies. Furthermore, we investigated whether there was a relation between ablation failure and pre-ablation 24-hour uptake measurement of ^{131}I (by the so-called stunning effect). By assessing the prevalence of second primary tumors in patients treated for thyroid cancer we wanted to confirm that ^{131}I can be used safely regarding long-

term effects. Finally, we focused on ^{111}In-DTPA-octreotide scintigraphy and therapy as an alternative tool in progressive radioiodine non-responsive thyroid cancer.

In **chapter 2** the efficacy of the uptake-related ablation strategy was studied. In this strategy relatively low activities of ^{131}I are used. The applied activity depends on the measurement of ^{131}I 24-hour neck uptake. In the uptake-related ablation protocol, activities of 1100 MBq (uptake >10%), 1850 MBq (uptake 5-10%) and 2800 MBq (uptake <5%) were used. In this study, 235 patients were selected who had been treated by thyroidectomy for DTC, followed by ^{131}I ablation. Approximately 6 months after ablation, treatment efficacy was evaluated using radioiodine scintigraphy and thyroglobulin (Tg) measurements. Successful ablation was defined by two criterions: the absence of radioiodine uptake in the neck region (criterion 1) and based on Tg serum values measured during TSH stimulation (Tg-off) determined 3–12 months after ablation (criterion 2). Based on criterion 1, unsuccessful ablation was found in 43% of cases. Based on criterion 2, unsuccessful ablation was found in 52% of patients. These data showed a relatively high treatment failure rate of the uptake-related ablation strategy. Based on these results we suggested that a lower ablation failure rate could be achieved by applying higher ^{131}I activities in the ablation of thyroid remnants in DTC patients. Furthermore, in the case of lymph node metastases a further adjustment of the applied activity may be recommended.

In **chapter 3** we compared the success rate of the above-mentioned uptake-related ablation protocol with the success rate of a fixed-dose ablation protocol in which the applied activity depends on tumor stage. In a fixed-dose ablation protocol relatively higher activities of ^{131}I are used, compared to the uptake-related ablation protocol. All differentiated thyroid carcinoma patients with M0 disease who had undergone (near-)total thyroidectomy followed by ^{131}I ablation,

were included. The activities in the uptake-related ablation protocol are mentioned above. In the fixed-dose ablation strategy, activities of 3700 MBq (T1-3, N0 stage) and 5550 MBq (N1 and/or T4 stage) were applied. Two criteria were used to assess successful ablation: (1) no ^{131}I uptake in the neck, and (2) negative ^{131}I whole-body scintigraphy (WBS) combined with Tg-off values below cut-off level of the assay used. According to criterion 1 the uptake-related ablation protocol was successful in 89 out of 153 patients (58%), compared to 174 out of 206 patients (84%) treated according to the fixed-dose ablation protocol (p<0.001). According to criterion 2 the uptake-related ablation protocol was successful in 60 out of 139 patients (43%) versus 111 out of 199 patients (56%) for the fixed-dose ablation protocol (p=0.022). From these data, we concluded that the fixed-dose ^{131}I ablation protocol is more effective in ablation of the thyroid remnant in DTC patients than an uptake-related ablation protocol.

In **chapter 4** we focused on the so-called stunning effect. Dosimetric studies have shown that activities of ^{131}I as low as 10-20 MBq may deliver a significant dosage to thyroid cells and may cause a stunning effect. A result of this stunning effect may be a lowered success rate of the ablative ^{131}I therapy. The aim of the study described in chapter 4 was to determine whether pre-therapeutic uptake measurement with 40 MBq ^{131}I causes a lower success rate of ablation. We compared the success rate of ablation in two hospitals in which the ablation protocols differed in one respect only: in one hospital no pre-therapeutic ^{131}I was applied (group 1), whereas in the other hospital ablation was preceded by a 24-hour uptake-measurement with 40 MBq [131]I (group 2). Data from both groups were reviewed retrospectively. All T0-4, N0-1, M0 patients who had undergone ^{131}I ablation between July 2002 and December 2005, and who had returned for ^{131}I follow-up, were included. Ablation was considered successful in the case of absence of pathological ^{131}I uptake on WBS combined with a TSH-stimulated Tg value below cut-off level of the assay used. A total of 99 patients were

included (48 in group 1 and 51 in group 2). Overall, ablation was successful in 31/48 patients (65%) in group 1 and in 17/51 patients (33%) in group 2 (p=0.002). We concluded that after applying a diagnostic activity of 40 MBq ^{131}I before ablation, the success rate of ablation is severely reduced. Consequently, the routine application of ^{131}I for diagnostic scintigraphy or uptake measurement prior to ^{131}I ablation is best avoided.

In **chapter 5** we tried to identify patients with a high risk for recurrent thyroid cancer at initial stage, i.e. at the time of ablation. Therefore, we evaluated tumor recurrence in consecutive patients treated for DTC. Well known prognostic factors were statistically analyzed. In addition we defined prognostic parameters based on Tg values, 24-hour ^{131}I uptake rates and TSH values: (a) Tg/TSH, (b) Tg/24-hour ^{131}I uptake rate, and (c) Tg/(TSHx24-h ^{131}I uptake). We included 190 patients (50 male, 140 female; mean age 47 years) with DTC for analysis, 146 without distant metastases and 44 with M1 tumor stage at initial presentation. The mean period of follow-up was 10.4 years (SD ±3.7 years). In 18 out of the 146 DTC patients with M0 disease (12.4%), tumor recurrence was found during follow-up. Although tumor stage, age, and standard biochemical values significantly differ between patients with and without recurrent disease or between patients with M0 and M1 tumor stage, the newly defined parameter Tg/(TSHx24-h ^{131}I uptake) was the best independent significant prognostic parameter in the assessment whether patients will develop a tumor recurrence during follow-up or not. We concluded that high Tg/(TSHx24-h ^{131}I uptake) ratios justify an adjustment of the ^{131}I activity for ablation therapy. To assess the optimal cut-off level for an adjustment of the ^{131}I activity, however, further studies are required in more patients.

The aim of the study described **in chapter 6** was to assess the prevalence of second primary tumors in patients treated for thyroid cancer. Furthermore, we

assessed the standardized risk rates for all second primary tumors, but especially for breast cancer, as data in the literature indicate an excessive risk in DTC patients for this tumor. Patients who received ablation treatment with ^{131}I at the Leiden University Medical Center between January 1985 and December 1999 (n=282) were included in the study. The mean period of follow-up was 10.6±4.1 years. Thirty-five of the 282 patients (12.4%) had a second primary tumor (SPT), either preceding or following the diagnosis of thyroid cancer. Five other patients had three primary tumors, including DTC. As a result, 40 additional tumors were found in this group, revealing an overall prevalence of 14.2%. Twenty tumors (7.1%) preceded the thyroid cancer with a mean interval of 5.7 years (range: 0.5–22.0 years), whereas 20 tumors (7.1%) occurred after this tumor with a mean interval of 6.7 years (range: 1.0–15.0 years). In 13 female patients, breast cancer was found as SPT. The standardized incidence rate (SIR) for all cancers after the diagnosis of DTC in this study population was not increased (1.13; confidence interval (CI): 0.68–1.69). However, we found an increased SIR of 2.26 (CI: 1.60–3.03) for all cancers either following or preceding DTC, which is mainly caused by a SIR of 3.95 (CI: 2.06–6.45) for breast cancer. We concluded that patients with DTC have an overall increased SIR for second primary tumors (especially for breast cancer) but not for second primary tumors following ^{131}I therapy. These findings suggest a common etiologic and/or genetic mechanism instead of a causal relation.

We realize that these findings are in contrast to other publications [3;4]. This has led to a more careful positioning of RaI ablation in recent papers [2;5] where harmful effects of RaI have been suggested.

In the last two chapters we focused on the minority of DTC patients in whom dedifferentiation of the tumor occurred, accounting for a poorer outcome. This dedifferentiation is seen in approximately 50% of patients with distant metastases. In such cases, tumor cells lose their ^{131}I uptake capability, which is

usually associated with an increased growth rate and a larger tumor load. As a consequence, WBS with ^{131}I will yield false negative results, whereas in most cases rising Tg values will be measured during follow-up.

In **chapter 7** we evaluated the diagnostic and prognostic value of ^{111}In-DTPA-octreotide scintigraphy in papillary and follicular thyroid carcinoma with increasing Tg values, but no response to treatment with [131]I. Twenty-three consecutive patients (13 female, 10 male; mean age 55 years, range 13–81 years) with progressive DTC were selected. All patients had non-functioning metastases, defined by no or slight uptake of ^{131}I in metastases. Diagnosis of tumor progression was based on rising Tg values during follow-up and was confirmed by radiological examination. Uptake on octreotide scintigraphy was scored from 0 to 4. Seven patients died during follow-up. The overall sensitivity for the detection of metastases was 74%. The sensitivity was higher in patients in whom ^{131}I WBS did not show any abnormal uptake (82%; 14/17) than in patients with low ^{131}I uptake (50%; 3/6). The 10-year survival rate was significantly different between patients with an uptake score of 0 or 1 (100%) and those with an uptake score of 2, 3 or 4 (33%) (p=0.001). Gender, log Tg and uptake on octreotide scintigraphy significantly correlated with survival, but in stepwise analysis, ^{111}In-DTPA-octreotide uptake was selected as the most prognostic independent variable (hazard rate 6.25, p=0.006). Therefore, we concluded that ^{111}In-DTPA-octreotide scintigraphy is a valuable clinical tool for the detection of non-functioning DTC metastases. The uptake seems to correlate with prognosis and survival.

The aim of the study described in **chapter 8** was to determine the effect of ^{111}In-DTPA-octreotide therapy in patients with progressive radioiodine non-responsive thyroid cancer in relation to ^{111}In-DTPA-octreotide uptake by tumor localizations assessed on pre-treatment diagnostic octreotide scans. Via

somatostatin receptor subtypes, ^{111}In-DTPA-octreotide is internalized by thyroid and neuroendocrine cancer cells and can cause DNA damage by the emission of conversion and Auger electrons. Eleven consecutive patients, selected on positive pre-treatment diagnostic scans, were treated with fixed activities of approximately 7400 MBq of ^{111}In-DTPA-octreotide with an interval of 2–3 weeks between the administrations. In one patient, the applied activity was adjusted because of sickle-cell disease. To assess the effects during treatment with ^{111}In-DTPA-octreotide Tg values were collected from 2 years before treatment, during treatment and up to 1 year after treatment. A computed tomography scan was performed 3 months after the last treatment. Two patients died during and shortly after the treatment course. Their death cause was unrelated to the treatment. In 44% of the patients, stable disease was achieved up to 6 months after the first treatment according to both criteria (results of radiographic studies and Tg values). All four had relative low pre-treatment Tg values (mean value 275 μg/l), representing limited metastasized disease. In two patients biochemical stable disease was observed, whereas computed tomography showed tumor progression. We concluded that treatment with high activities of ^{111}In-DTPA-octreotide in metastatic DTC results in stable disease in a subgroup of patients. Our results suggest that a low pre-treatment Tg value, representing a small tumor load, may be a selection criterion for treatment.

Overall conclusions:

- An uptake-related ablation strategy results in a relatively high treatment failure rate, which is significantly lower when higher ablation activities according to a fixed-dose strategy are used.

- Pre-therapeutic uptake measurement using 40 MBq ^{131}I reduces the success of ablation and, therefore, the routine application of ^{131}I for diagnostic scintigraphy or uptake measurement prior to ^{131}I ablation should be avoided.

- High Tg/(TSHx24-h ^{131}I uptake) ratios justify an adjustment of the ^{131}I activity for ablation therapy, because this is the best independent significant prognostic parameter in the assessment whether patients will develop a tumor recurrence during follow-up or not.

- DTC patients have an overall increased standardized incidence rate for second primary tumors (especially for breast cancer), but not for second primary tumors following ^{131}I therapy, although this remains a subject of debate.

- Scintigraphy using ^{111}In-DTPA-octreotide is a valuable clinical tool for the detection of non-functioning DTC metastases and uptake of this radiopharmaceutical seems to correlate with prognosis and survival.

- Treatment with high activities of ^{111}In-DTPA-octreotide in DTC patients with non-functioning metastases results in a stable disease in a subgroup of patients. A selection criterion for this treatment may be a small tumor load, indicated by a low pre-treatment Tg value.

Prospectives

Well-differentiated thyroid cancer is characterized by rare occurrence and a good prognosis. However, up to 20% of DTC patients develop locoregional recurrences, whereas even 8% of patients with such recurrences eventually die

from the disease [6] Well differentiated thyroid cancer mostly recurs in the cervical lymph nodes and thyroid bed [6-8].

In this thesis we focused on scintigraphy and therapy using ^{131}I. However, especially in patients with distant metastases a variable degree of dedifferentiation may occur. As a consequence, scintigraphy with RaI will yield falsely negative results and therapy with ^{131}I is not advantageous anymore. In this patient group presenting with detectable Tg, but a normal diagnostic or post-therapeutic RaI scintigram, staging is difficult and treatment options are few. Furthermore, recurrent disease, although less common, can be suspected despite normal Tg values.

High sensitivity rates of 95-100% are given in literature for ultrasound-guided fine-needle aspiration biopsy [9;10] However, it cannot be unequivocally concluded that ultrasonography should be performed as a solitary first line imaging modality. For the assessment of the neck, the most common site of metastases in papillary thyroid cancer, it is highly accurate. However, the most important findings are that even in patients with locoregional disease distant metastases in up to 18% will be missed and that the number of patients with distant metastases and no locoregional disease is up to 11% [6]. When MRI is performed it may be difficult to differentiate small malignant from small benign lesions.

It is suggested that functional imaging using positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) could resolve the problems described above. In thyroid neoplasms increased uptake of glucose seems to be restricted to more aggressive and high-grade tumors. Schönberger *et al.* [11] have shown that overexpression of glucose transporter 1 on the cell membrane of thyroid neoplasms, responsible for increased glucose uptake in malignancy, is closely related to tumors demonstrating a more aggressive biological behaviour and unfavourable prognosis. This is probably the explanation for the differences in sensitivity rates for FDG-PET mentioned in literature. High sensitivity rates

are given (82-95%) for FDG-PET, especially in patients with non-functioning metastases, i.e. more dedifferentiated malignancy [12-15] However, sensitivity rates decrease to 50% in patients with uptake on RaI scintigraphy [12]. FDG-PET could determine the location and extent of recurrence (solitary tumor or multiple lesions), facilitating the choice between surgery, radiotherapy or radionuclide therapy. Zuijdwijk *et al.* [15] concluded in their study that FDG-PET had an impact on patient management in approximately 50% of patients. An important issue in imaging with FDG-PET is the serum Tg value. The chance of positive findings increases with increasing Tg values, even in ^{131}I-negative DTC [6], because of the relationship between Tg values and tumor burden. This has been described by Bachelot *et al.* [16] and recently by Robbins *et al.* [17].

The use of another iodine isotope ([124]I) with positron emitting characteristics may allow better identification of recurrent disease compared to ^{123}I or ^{131}I gamma scintigraphy. Especially combined [124]I-PET/CT imaging has a better lesion detectability compared to conventional ^{131}I scintigraphy [18]. Therefore, this technique could probably identify patients with disseminated iodine avid metastases who otherwise would have been classified as iodine non-responsive thyroid cancer and thus allowing more patients to be treated with ^{131}I as a curative attempt. However, to date large prospective studies on the diagnostic value of [124]I-PET in the management of advanced DTC are lacking and therefore this would be an interesting research field for the future.

Imaging with a radiolabeled somatostatin analog is another option in the patient group with DTC presenting with detectable Tg, but a normal diagnostic or post-therapeutic RaI scintigram. In the present thesis we evaluated in chapter 7 the diagnostic and prognostic value of somatostatin receptor scintigraphy (SRS), using ^{111}In-DTPA-octreotide, in DTC patients with non-functioning metastases. The advantage of SRS is that it can be used in this group to select patients for therapy based on somatostatin receptor binding. In chapter 8 we described the

therapeutic effect of high activities of ^{111}In-DTPA-octreotide, which is based on the toxicity of short range Auger electrons (emitted by ^{111}In) on cellular DNA. However, somatostatin analogues labeled with β-emitting radionuclides theoretically should give a better therapeutic effect, because this type of radiation can extend over a longer distance and is therefore probably be able to destroy both somatostatin receptor positive and somatostatin receptor negative tumor cells. Teunissen *et al.* [19] concluded in a review article that peptide receptor radionuclide therapy with β-emitting radionuclides [90]Yttrium (^{90}Y) and [177]Lutetium (^{177}Lu) gives the best results in terms of objective tumor response.

There are only few other therapies in addition to the above-mentioned radionuclide therapies in extended radioiodine-resistant DTC. Cytotoxic chemotherapy yields low response rates of short duration and does not prolong survival. There may be a place for vascular endothelial growth factor (VEGF) receptor inhibitors as increased expression of VEGF, a potent angiogenesis stimulator, is characteristic of aggressive DTC [20]. In a recent study by Sherman *et al.* [21] and Gupta *et al.* [22] novel oral tyrosine kinase inhibitors (motesanib and sorafenib) are investigated and they concluded that this may be an effective treatment in some patients with progressive, metastatic, RaI-resistant DTC.

It can be concluded that further studies are required in patients with extended RaI-resistant DTC. Probably a combination of peptide receptor radionuclide therapy and specific molecular therapies, as mentioned above, are potential therapeutic strategies in this patient group which can be investigated in the future.

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Chapter 10

Samenvatting

De therapie die de voorkeur heeft voor patiënten die lijden aan gedifferentieerd schildkliercarcinoom (onderverdeeld in papillair en folliculair schildkliercarcinoom) is een (bijna-) totale operatieve verwijdering van de schildklier. Deze behandeling wordt gevolgd door toediening van radioactief jodium-131 (^{131}I) om alle overblijvende, zowel goedaardige als kwaadaardige, schildklierresten te vernietigen. Dit wordt ablatie genoemd.

Ofschoon vele aspecten van diagnose, initiële therapie en follow-up procedures beschreven zijn in recent gepubliceerde richtlijnen (gepubliceerd door de Amerikaanse en Europese schildklierverenigingen en door de Nederlandse CBO schildkliercarcinoom consensus groep (www.cbo.nl)) [1;2], blijven toch vele vragen onbeantwoord met betrekking tot de klinische aanpak van patiënten met een gedifferentieerd schildkliercarcinoom. Dit proefschrift richt zich op een aantal belangrijke klinische vragen gerelateerd aan de conventionele (^{131}I) en experimentele therapieën met radionucliden bij gedifferentieerd schildkliercarcinoom.

Jodium-131 wordt al vele jaren gebruikt voor de ablatie van een schildklierrest na chirurgie van de schildklier, maar een optimale eenmalige toegediende activiteit van ^{131}I werd nog niet eerder vastgesteld. De gegevens in de literatuur zijn wat dat betreft tegenstrijdig; sommige studies concluderen dat een activiteit van 1110 MBq ^{131}I net zo effectief is als een hogere activiteit, zoals 3700 MBq. Daarentegen wijzen andere auteurs erop dat een hogere activiteit het succes van de ablatie juist verhoogt. Twee protocollen worden in Nederland gebruikt: de z.g. opname-gerelateerde ablatiestrategie, waarbij een relatief lage hoeveelheid activiteit van ^{131}I wordt gebruikt en de z.g. vaste-dosering, ofwel het tumor-gerelateerde protocol, waarbij een hogere hoeveelheid activiteit wordt toegepast. De belangrijkste doelstelling van dit proefschrift is om zowel de resultaten van de ablatiebehandeling bij gedifferentieerd schildkliercarcinoom volgens het opname-gerelateerde protocol op korte termijn als die op langere termijn te bestuderen en het vergelijken van het succespercentage bij beide strategieën.

Bovendien onderzochten wij in hoeverre er een relatie is tussen het mislukken van de ablatie en de pre-ablatie 24-uurs opname-meting (het z.g. stunning effect). Door het vaststellen van de prevalentie van tweede primaire tumoren bij patiënten die behandeld werden voor schildkliercarcinoom wilden wij bewijzen dat behandeling met ^{131}I veilig is met het oog op de lange termijn effecten. Tenslotte hebben wij gekeken naar scintigrafie en behandeling met ^{111}In-DTPA-octreotide bij een progressief schildkliercarcinoom dat niet meer reageert op radioactief jodium.

In **hoofdstuk 2** wordt de effectiviteit van de opname-gerelateerde ablatiestrategie bestudeerd. Bij deze strategie wordt een relatief lage hoeveelheid activiteit ^{131}I gebruikt. De dosering is afhankelijk van een [131]I 24-uurs meting van de opname in de hals. Voor het opname-gerelateerde ablatieprotocol wordt 1100 MBq (opname >10%), 1850 MBq (opname 5-10%) en 2800 MBq (opname <5%) gebruikt. Voor deze studie werden 235 patiënten geselecteerd die primaire chirurgie hadden ondergaan voor gedifferentieerd schildkliercarcinoom, gevolgd door ablatie met [131]I. Ongeveer zes maanden na ablatie werd de effectiviteit geëvalueerd m.b.v. een radioactief jodium scintigram en thyroglobuline (Tg) metingen. Succesvolle ablatie werd hierbij gedefinieerd op basis van twee criteria: de afwezigheid van opname van radioactief jodium in de halsstreek (criterium 1) en gebaseerd op Tg serum waarden gemeten gedurende TSH stimulatie (Tg-off), bepaald 3-12 maanden na ablatie (criterium 2). Gebaseerd op criterium 1 werd bij 43% van de patiënten niet-succesvolle ablatie geconstateerd en gebaseerd op criterium 2 was de ablatie mislukt bij 52% van de patiënten. Deze gegevens tonen een relatief hoog percentage van niet-succesvolle ablaties aan bij deze ablatiestrategie. Op basis van deze resultaten stelden wij vast dat een lager percentage van niet-succesvolle ablaties kan worden bereikt door het toepassen van een hogere hoeveelheid activiteit van ^{131}I bij de ablatie van schildklierresten bij patiënten met een gedifferentieerd

schildkliercarcinoom. In het geval van lymfkliermetastasen kan een verdere aanpassing van de activiteit ook nog raadzaam zijn.

In **hoofdstuk 3** vergelijken wij het succespercentage van het eerder genoemde opname-gerelateerde ablatieprotocol met het succespercentage van het vaste-dosis ablatieprotocol, waarbij de hoeveelheid activiteit afhankelijk is van het tumorstadium. Bij het vaste-dosisprotocol wordt een relatief hoge hoeveelheid activiteit van ^{131}I gebruikt, vergeleken met het opname-gerelateerde ablatieprotocol. Alle gedifferentieerd schildkliercarcinoom patiënten met M0 ziekte die een (bijna-)totale operatieve verwijdering van de schildklier ondergingen, gevolgd door ^{131}I ablatie werden in het onderzoek betrokken. De toegepaste activiteit bij het opname-gerelateerde ablatieprotocol zijn hierboven beschreven. Bij de vaste-dosis ablatiestrategie werd behandeling met 3700 MBq (T1-3, N0 stadium) en 5500 MBq (N1 en/of T4 stadium) toegepast. Twee criteria werden gebruikt om het ablatieresultaat vast te stellen: (1) ^{131}I-opname in de hals en (2) ^{131}I opname op een scintigram van het gehele lichaam gecombineerd met Tg-off waarden. Overeenkomstig criterium 1 was het opname-gerelateerde protocol succesvol bij 89 van de 153 patiënten (58%), vergeleken met 174 van de 206 patiënten (84%) die behandeld werden overeenkomstig het vaste-dosis ablatieprotocol (p<0,001). Overeenkomstig criterium 2 was het opname-gerelateerde ablatieprotocol succesvol bij 60 van de 139 patiënten (43%), versus 111 van de 199 patiënten (56%) voor het vaste-dosis ablatieprotocol (p=0,022). Op basis van deze gegevens concludeerden wij dat het vaste-dosis ^{131}I ablatieprotocol doeltreffender is bij de ablatie van schildklierresten voor het gedifferentieerd schildkliercarcinoom dan het opname-gerelateerde ablatieprotocol.

In **hoofstuk 4** hebben wij ons geconcentreerd op het z.g. stunning-effect. Dosimetrische studies laten zien dat 10-20 Mbq ^{131}I toch een significante dosis

levert aan de schildkliercellen en daardoor het z.g. stunning effect veroorzaakt. Een resultaat van dit stunning effect kan wellicht een lager slagingspercentage van de ^{131}I behandeling zijn. De doelstelling van het onderzoek zoals beschreven in hoofdstuk 4 is om vast te stellen in hoeverre opname meting met 40 MBq ^{131}I voorafgaand aan de ablatie een lager slagingspercentage van de ablatie veroorzaakt. Wij hebben het succespercentage van de ablatie in twee ziekenhuizen vergeleken, waarbij de ablatieprotocollen verschilden met betrekking tot slechts één aspect: in het ene ziekenhuis werd geen opname meting met 40 MBq ^{131}I voorafgaand aan ablatie toegepast (groep 1), terwijl in het andere ziekenhuis dit wel werd gedaan (groep 2). De gegevens van beide groepen werden vervolgens onderzocht. Alle T0-4, N0-1, M0 patienten die een ablatie hadden ondergaan tussen juli 2002 en december 2005 en waarbij een ^{131}I follow-up scintigram beschikbaar was, werden in het onderzoek betrokken. Ablatie werd als succesvol beschouwd in die gevallen waarbij er geen pathalogische ^{131}I opname op het scintigram van het gehele lichaam te zien was en er ook sprake was van een onmeetbaar Tg onder TSH stimulatie. Een totaal van 99 patiënten werd in het onderzoek betrokken (48 in groep 1 en 51 in groep 2). In totaal was bij 31 van de 48 patiënten (65%) ablatie succesvol in groep 1 en bij 17 van de 51 patiënten (33%) in groep 2 (p=0,002). Wij concludeerden hieruit dat opname meting met 40 MBq ^{131}I voorafgaand aan ablatie, het succes van ablatie vermindert en dat daarom stelselmatige toepassing van ^{131}I voor een diagnostisch scintigrafie of opname meting voorafgaand aan ^{131}I ablatie moet worden vermeden.

In **hoofdstuk 5** hebben wij getracht patiënten in het begin stadium (d.w.z. op het moment van de ablatie) te identificeren die een hoog risico hebben op het ontwikkelen van een recidief schildkliercarcinoom. Daarvoor evalueerden wij het terugkeren van de tumor bij patiënten die waren behandeld voor een gedifferentieerd schildkliercarcinoom. Algemeen bekende prognostische

factoren werden statistisch geanalyseerd. Wij bepaalden prognostische parameters gebaseerd op Tg waarden, 24-uurs ^{131}I opnamewaarden en TSH waarden: (a) Tg/TSH, (b) Tg/24-uurs ^{131}I opnamewaarde en (c) Tg/(TSHx24-uurs ^{131}I opname). Wij includeerden 190 patiënten (50 mannen, 140 vrouwen, gemiddelde leeftijd 47 jaar) met een gedifferentieerd schildkliercarcinoom in onze analyses, 146 zonder metastasen en 44 met M1 ziekte bij initiële presentatie. De gemiddelde follow-up duur was 10,4 jaar (SD ±3,7 jaar). Bij 18 patiënten van de 146 gedifferentieerd schildkliercarcinoom patiënten met M0 ziekte (12,4%) werd een recidief van de tumor gevonden gedurende de follow-up. Alhoewel er tussen tumorstadium, leeftijd en standaard biochemische waarden aanzienlijke verschillen zijn tussen patiënten met en zonder een recidief of tussen patiënten met M0 en M1 ziekte, is de nieuwe gedefinieerde parameter Tg/(TSHx24-uurs ^{131}I opname) de beste onafhankelijke significante prognostische parameter bij de schatting in hoeverre patiënten wel of niet een recidief zullen ontwikkelen gedurende de follow-up. Wij kwamen tot de conclusie dat hoge Tg/(TSHx24-uurs ^{131}I opname) ratio's een aanpassing van de ^{131}I activiteit voor ablatie rechtvaardigen. Wat betreft de bepaling van de optimale cut-off waarde voor deze aanpassing zijn aanvullende studies met meer patiënten nodig.

De doelstelling van de studie beschreven in **hoofdstuk 6** is om de prevalentie van een tweede primaire tumor bij patiënten die behandeld waren voor schildkliercarcinoom te beoordelen. Bovendien beoordeelden wij de standaard risico's voor alle tweede primaire tumoren en in het bijzonder die voor borstcarcinoom, omdat gegevens in de literatuur een groot risico aantonen voor deze tumor bij patiënten met een gedifferentieerd schildkliercarcinoom. In de studie werden patiënten opgenomen die een ablatiebehandeling met ^{131}I ondergingen in het Leids Universitair Medisch Centrum in de periode tussen januari 1985 en december 1999 (n=282). De gemiddelde follow-up periode was

10,6±4,1 jaar. Vijfendertig van de 282 patiënten (12,4%) hadden een tweede primaire tumor, zowel voorafgaand of volgend op de diagnose schildkliercarcinoom. Vijf andere patiënten hadden drie primaire tumoren inclusief een gedifferentieerd schildkliercarcinoom. Er werden 40 additionele tumoren in deze groep gevonden, dus een prevalentie van 14,2%. Twintig tumoren (7,1%) gingen vooraf aan het schildkliercarcinoom met een gemiddeld interval van 5,7 jaar (spreiding: 0,5-22,0 jaar), terwijl twintig tumoren (7,1%) werden geconstateerd na schildkliercarcinoom met een gemiddeld interval van 6,7 jaar (spreiding: 1,0-15,0 jaar). Bij dertien vrouwelijke patiënten werd borstcarcinoom geconstateerd als tweede primaire tumor. De standaard incidentie voor alle carcinomen na de diagnose gedifferentieerd schildkliercarcinoom in deze studiepopulatie was niet toegenomen (1,13; betrouwbaarheidsinterval: 0,68-1,69). Wij vonden echter een verhoogd gestandaardiseerd incidentie percentage (SIR) van 2,26 (betrouwbaarheidsinterval: 1,60-3,03) voor alle carcinomen, zowel volgend op als voorafgaand aan gedifferentieerd schildkliercarcinoom, wat grotendeels wordt veroorzaakt door een SIR van 3,95 (betrouwbaarheidsinterval: 2,06-6,45) voor borstcarcinoom. Wij kwamen tot de conclusie dat patiënten met een gedifferentieerd schildkliercarcinoom in het algemeen een verhoogde SIR hebben voor tweede primaire tumoren (in het bijzonder voor borstcarcinoom), maar niet voor tweede primaire tumoren volgend op een ^{131}I therapie. Deze bevindingen wijzen op een etiologisch en/of genetisch mechanisme in plaats van een oorzakelijk verband.

Wij realiseren ons dat deze bevindingen in strijd zijn met andere publicaties [3;4]. Dit heeft geleid tot een zorgvuldigere plaatsing van radioactief jodium in recente artikelen [2;5], waarin schadelijke effecten van radioactief jodium worden gesuggereerd.

In de laatste twee hoofdstukken besteedden wij aandacht aan een minderheid van de schildkliercarcinoom patiënten bij wie dedifferentiatie van de tumor is opgetreden, waardoor slechtere resultaten van de behandeling met radioactief jodium optreden. Deze dedifferentiatie wordt geconstateerd bij 50% van de patiënten met afstandsmetastasen. Hierbij verliezen tumorcellen hun vermogen om ^{131}I op te nemen, dat doorgaans wordt geassocieerd met een toenemende groeisnelheid en een grotere tumormassa. Dientengevolge zal een totale lichaamsscintigrafie met ^{131}I onjuiste negatieve resultaten opleveren, terwijl in de meeste gevallen stijgende Tg waarden werden gemeten tijdens de follow-up.

In **hoofdstuk 7** evalueerden wij de diagnostische en prognostische waarde van ^{111}In-DTPA-octreotide scintigrafie voor een papillair en folliculair schildkliercarcinoom met stijgende Tg waarden en die niet reageerde op de behandeling met ^{131}I. Drieentwintig patiënten (13 vrouwen en 10 mannen, gemiddelde leeftijd 55 jaar, spreiding 13-81 jaar) met een progressief schildkliercarcinoom werden geselecteerd. Alle patiënten hadden metastasen die niet meer reageerden op behandeling met ^{131}I, hetgeen bepaald werd op basis van geen of slechts een beperkte opname van ^{131}I in die metastasen. De diagnose tumorprogressie werd gebaseerd op stijgende Tg waarden gedurende de follow-up en werd bevestigd door radiologisch onderzoek. De opname die gezien werd op het ^{111}In-DTPA-octreotide scintigram werd gescored van 0 tot 4. Zeven patiënten overleden gedurende de follow-up. De totale sensiviteit voor de detectie van metastasen was 74%. De sensiviteit was hoger bij patiënten bij wie het ^{131}I scintigram geen pathologische opname toonde (82%; 14/17), vergeleken met patiënten met een lage ^{131}I opname (50%; 3/6). De 10-jaars overleving was duidelijk verschillend tussen patiënten met een opnamescore van 0 of 1 (100%) en die met een opnamescore van 2, 3 of 4 (33%) (p=0,001). Geslacht, log Tg en opname op het ^{111}In-DTPA-octreotide scintigram correleerden duidelijk met overleving, maar in een stepwise analyse, werd ^{111}In-

DTPA-octreotide opname geselecteerd als de meest prognostische onafhankelijke variabele (hazard rate 6,25, p=0,006). Op basis hiervan kwamen wij tot de conclusie dat ^{111}In-DTPA-octreotide scintigrafie een waardevol klinisch hulpmiddel is voor het ontdekken van niet-reagerende metastasen van het schildkliercarcinoom.

De doelstelling van de studie zoals beschreven in **hoofdstuk 8** is om het effect te bepalen van ^{111}In-DTPA-octreotide therapie bij patiënten met een schildkliercarcinoom dat progressief is en niet meer reageert op radioactief jodium in relatie tot ^{111}In-DTPA-octreotide opname in metastasen, vastgesteld op diagnostische octreotidescans. ^{111}In-octreotide wordt via somatostatine receptor subtypen geïnternaliseerd door de schildklier en neuroendocriene tumoren, hetgeen vervolgens DNA-schade kan veroorzaken door de emissie van conversie en Auger electronen. Elf patiënten, geselecteerd m.b.v. diagnostische octreotide scans, werden behandeld met 7400 MBq ^{111}In-DTPA-octreotide met een interval van 2-3 weken tussen de toedieningen. Bij één patiënt werd de hoeveelheid activiteit aangepast in verband met sikkelcelziekte. Om de effecten gedurende de behandeling met ^{111}In-DTPA-octreotide te bepalen werden Tg waarden van twee jaar vóór de behandeling, gedurende de behandeling en tot één jaar na de behandeling verzameld. Drie maanden na de laatste behandeling werd computertomografie (CT) uitgevoerd. Twee patiënten overleden gedurende en kort na de behandelingskuur. De oorzaak van hun overlijden was niet gerelateerd aan de behandeling. Bij 44% van de patiënten was er sprake van een stabiele situatie in een periode tot 6 maanden na de eerste behandeling op basis van beide criteria (resultaten van radiologische studies en Tg waarden). Deze vier patiënten hadden een relatief lage Tg waarde (gemiddelde waarde 275 µg/l) vóór behandeling, wat wijst op een beperkte gemetastaseerde ziekte. Bij twee patiënten werd een biochemisch stabiele ziekte waargenomen, terwijl CT tumorprogressie toonde. Wij concludeerden dat behandeling met een hoge

activiteit van ^{111}In-DTPA-octreotide bij gemetastaseerd schildkliercarcinoom resulteert in een stabiele ziekte bij een subgroep van patiënten. Onze resultaten geven aan, dat een lage Tg waarde vóór behandeling, wijzend op een geringe tumorload, mogelijk een selectiecriterium kan zijn voor behandeling met ^{111}In-DTPA-octreotide.

Afsluitende conclusies

- Bij de ablatiebehandeling van gedifferentieerd schildkliercarcinoom met ^{131}I resulteert de opname-gerelateerde ablatiestrategie in een relatief hoog percentage niet-succesvolle ablaties, in tegenstelling tot een vaste-dosisprotocol met een hogere activiteit.

- Diagnostische scintigrafie met 40 MBq ^{131}I voorafgaand aan een ablatiebehandeling ter vaststelling van de opname van ^{131}I vermindert het succes van ablatie en moet daarom worden vermeden.

- Hoge Tg/(TSHx24-uurs ^{131}I opname) ratio's rechtvaardigen een aanpassing van de ^{131}I activiteit voor de ablatie, omdat dit de beste onafhankelijke prognostische parameter is voor het ontwikkelen van een recidief gedurende follow-up.

- Schildkliercarcinoom patiënten hebben een verhoogde gestandaardiseerde incidentie voor tweede primaire tumoren (in het bijzonder voor borstcarcinoom) die echter niet samen lijkt te hangen met ^{131}I therapie, alhoewel dit een onderwerp blijft voor discussie.

- ^{111}In-DTPA-octreotide scintigrafie is een waardevolle methode voor het opsporen van niet op ^{131}I reagerende metastasen van gedifferentieerd schildkliercarcinoom, waarbij de opname van dit radiofarmacon correleert met de prognose.

- Behandeling met een hoge hoeveelheid activiteit van ^{111}In-DTPA-octreotide bij patiënten met gedifferentieerd schildkliercarcinoom met niet

op ^{131}I reagerende metastasen resulteert in stabiele ziekte bij een subgroep van patiënten. Een selectiecriterium voor deze behandeling kan mogelijk een geringe tumorload zijn, hetgeen wordt aangetoond door een lage Tg waarde voor behandeling.

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Nawoord

Dit proefschrift is tot stand gekomen op basis van een onderzoek waartoe ik in de gelegenheid werd gesteld door de afdeling Nucleaire Geneeskunde van het Leids Universitair Medisch Centrum tijdens mijn arts-assistentschap op deze afdeling.

Met veel enthousiasme ben ik aan dit onderzoek begonnen en het heeft mij geleerd dat promoveren een lange, maar ook leerzame weg is.

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Het geeft veel voldoening als een promotieonderzoek uiteindelijk resulteert in een proefschrift.

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Curriculum Vitae

Robbert Verkooijen werd geboren op 4 december 1972 te 's-Gravenhage. In 1991 behaalde hij het VWO-diploma aan het St. Janscollege te 's-Gravenhage. In september 1997 werd het artsexamen afgelegd aan de Rijksuniversiteit Leiden.

In de periode 1997 t/m 1999 was hij achtereenvolgens als arts-assistent werkzaam op de afdelingen Intensive Care van het Catharina-Ziekenhuis te Eindhoven en Anesthesiologie van het St. Antonius Ziekenhuis te Nieuwegein.

In het jaar 2000 startte Robbert als arts-assistent niet-in-opleiding op de afdeling Nucleaire Geneeskunde van het Leids Universitair Medisch Centrum. In die periode werd aangevangen met het in dit proefschrift beschreven onderzoek. In mei 2002 startte hij op deze afdeling met de opleiding Nucleaire Geneeskunde. In mei 2006 volgde de registratie als Nucleair Geneeskundige. Hierna was hij gedurende een jaar als fellow Nucleaire Geneeskunde werkzaam in het Universitair Medisch Centrum Utrecht. Vanaf 2007 werkt Robbert als Nucleair Geneeskundige in het Máxima Medisch Centrum te Eindhoven/Veldhoven.