Differentiated thyroid carcinoma : nuclear medicine studies

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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.

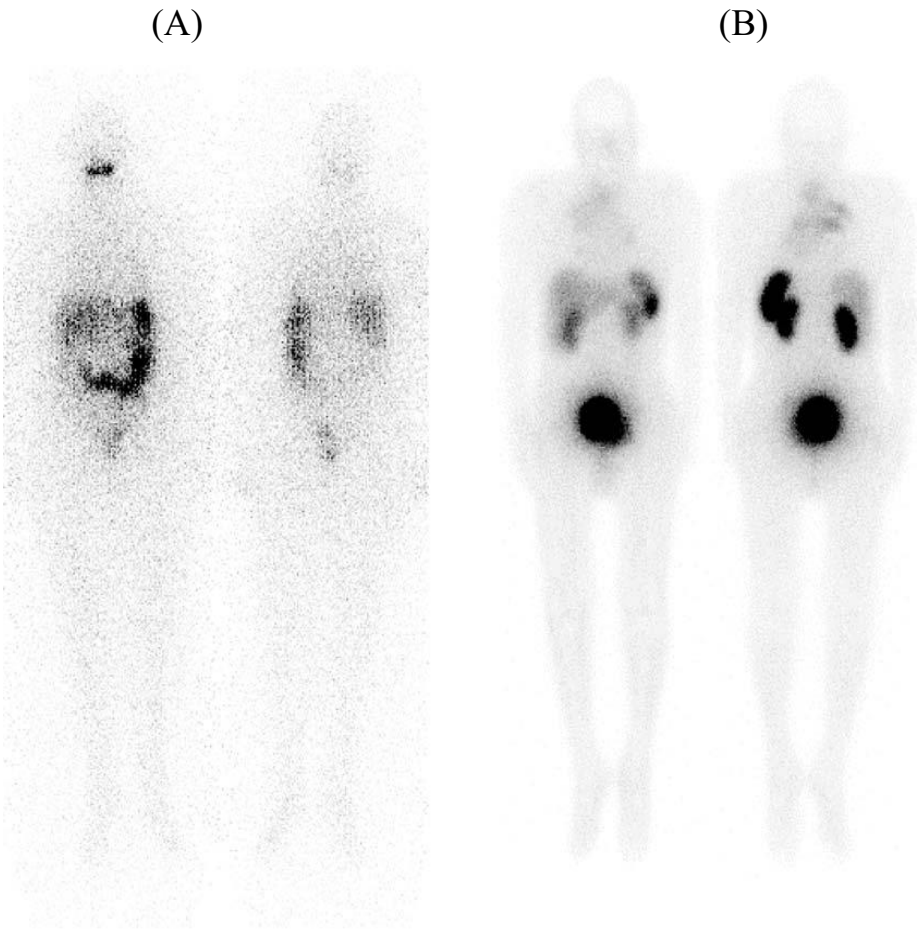

Figure 1. Post-treatment ^{131}I whole body scintigraphy (8000MBq) (A) in a 57-year-old man with a history of a T3N0M1 follicular thyroid carcinoma and an increasing thyroglobulin (Tg) level showed a normal, physiological distribution. The accumulation in the pelvic region is physiological excretion 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.

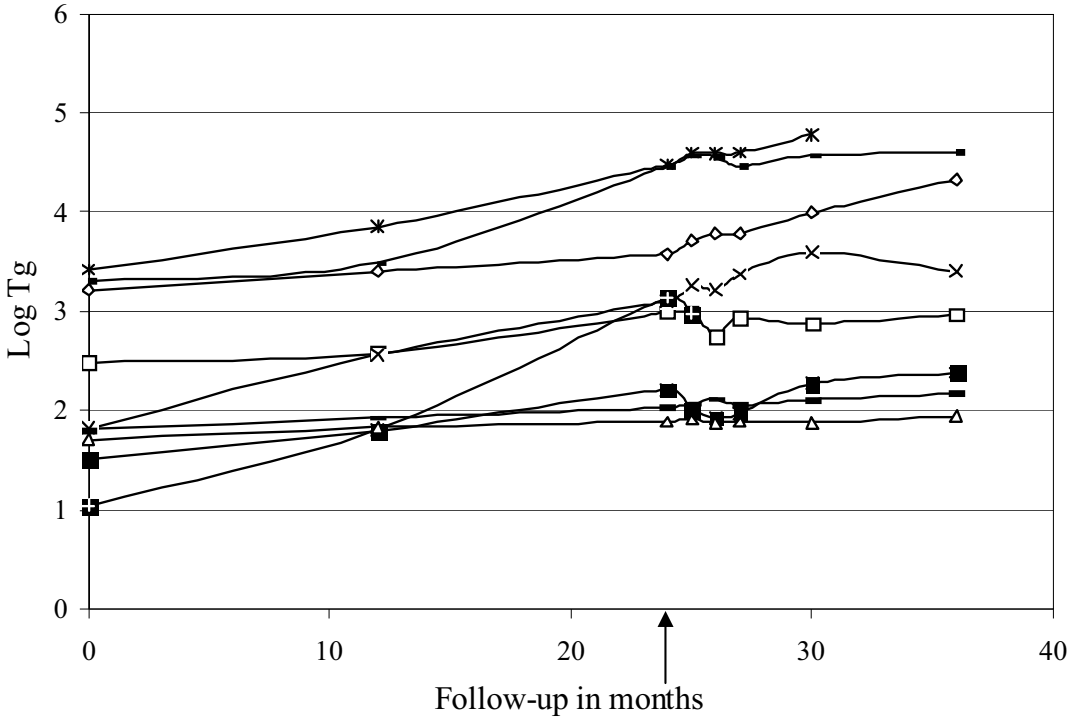

Figure 2. Tg levels from 2 years before up to 1 year after treatment with high activity ^{111}In-octreotide. The arrow indicates the start of the treatment course with high doses of ^{111}In-octreotide. Because of the skewed distribution of the Tg levels, log Tg levels were used. Symbols represent the 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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