Differentiated thyroid carcinoma : nuclear medicine studies

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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 recorded 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).

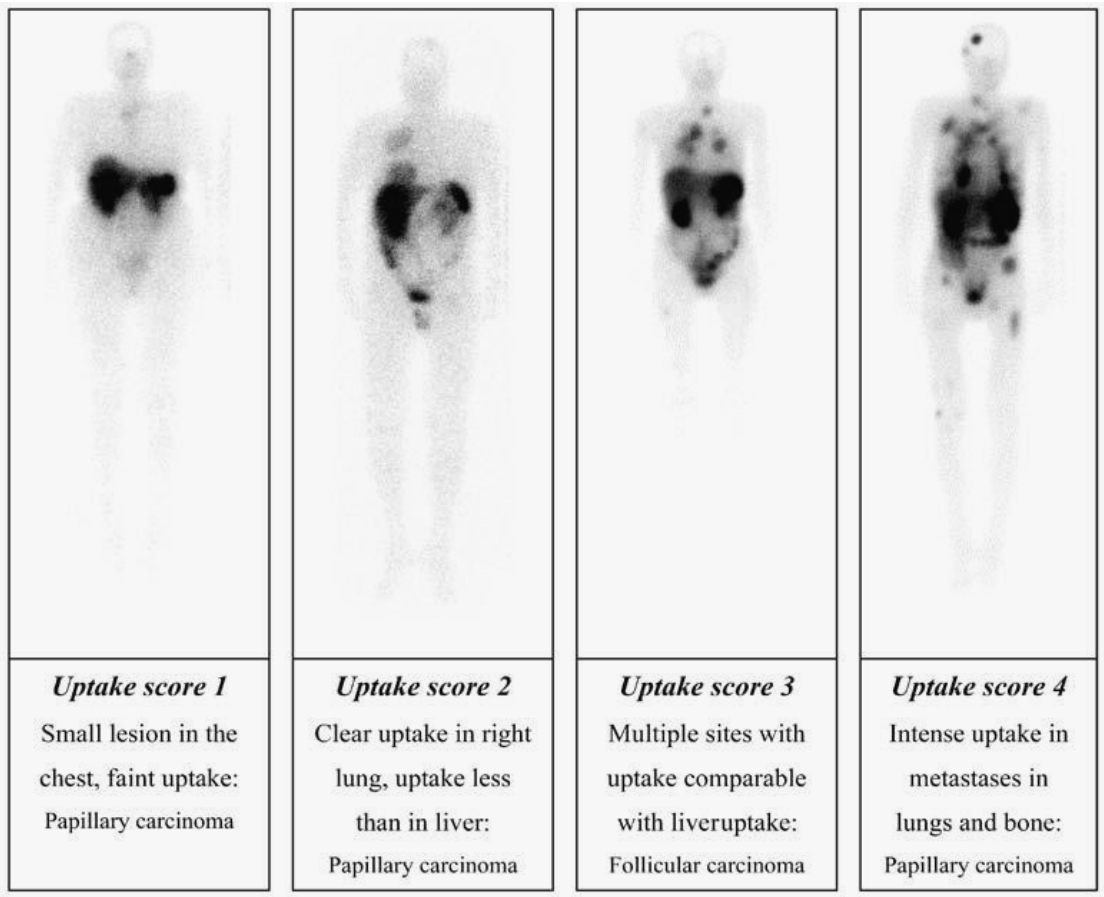

Figure 1. Uptake scores on ^{111}In-octreotide scintigraphy.

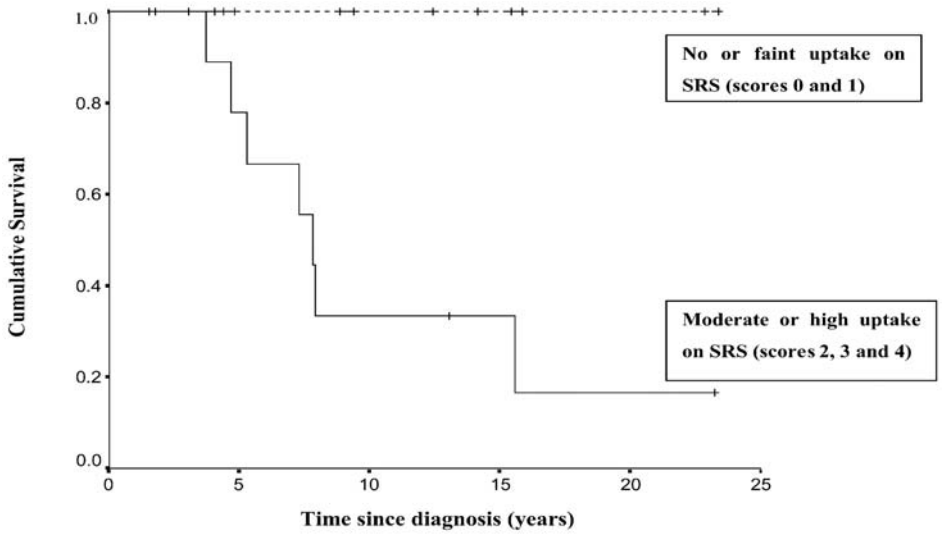

Figure 2. Kaplan-Meier curves for patients with different uptake scores on ^{111}In-octreotide scintigraphy.

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. Moreover, 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 undetectable 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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