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Differentiated thyroid carcinoma : nuclear medicine studies

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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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