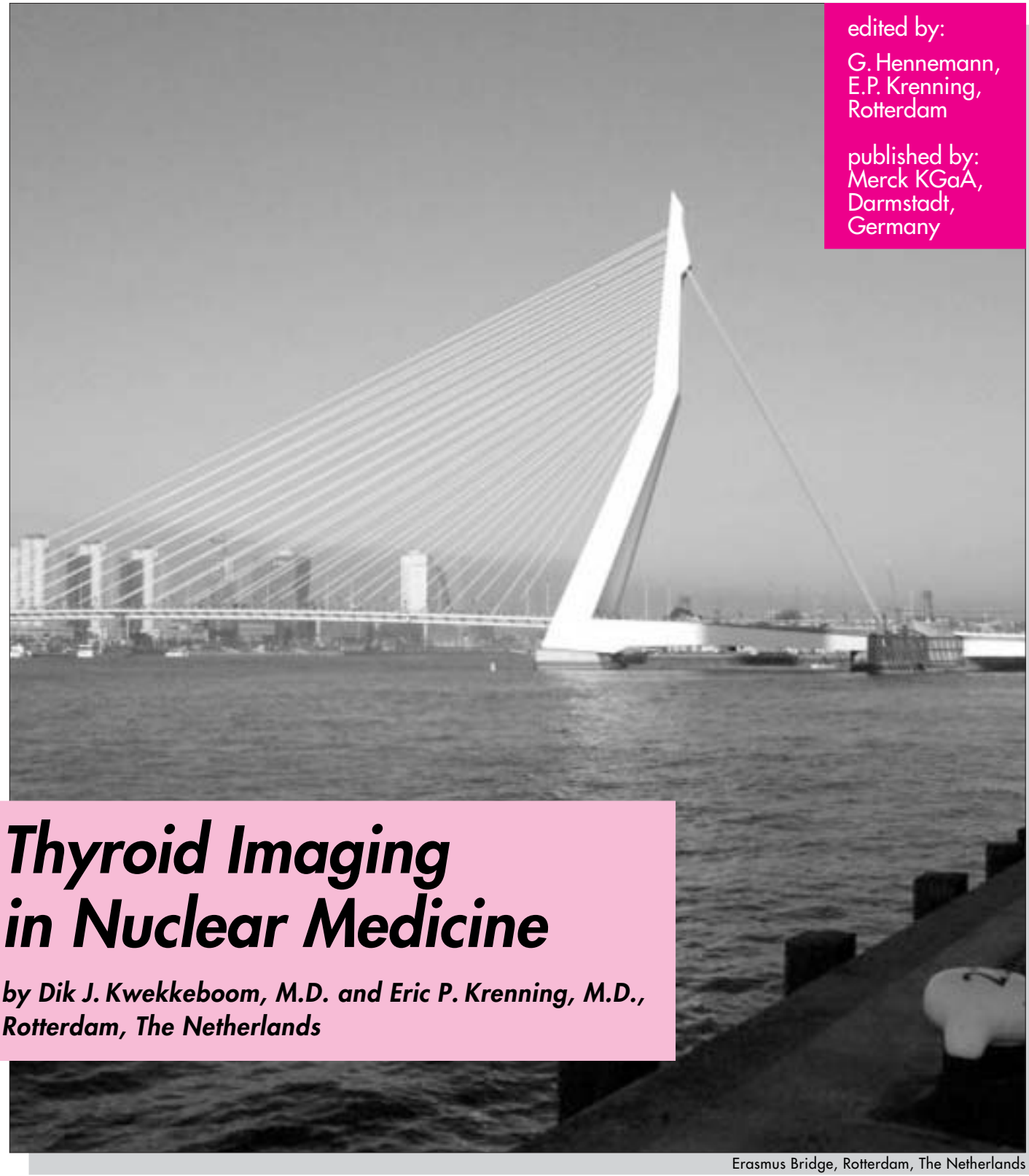
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Thyroid Imaging in Nuclear Medicine

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Thyroid Imaging in Nuclear Medicine

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Dr Kwekkeboom, MD, did his thesis on pituitary adenomas in 1989 and from 1990 to 1994 worked as a research associate at the Department of Nuclear Medicine in Rotterdam, investigating the value of somatostatin receptor imaging in patients with neuroendocrine and other receptor expressing tumors. He registered as nuclear medicine physician in 1998 and from then on worked as a staff member at the Department of Nuclear Medicine at the University Hospital Rotterdam. His major research topic is peptide receptor imaging and he coordinates the studies on therapy with the radiolabelled somatin analogue 177Lu-octreotate in patients with neuroendocrine tumors. He has numerous publications in international journals and textbooks, mainly in the field of endocrinology and peptide receptor scintigraphy and therapy.



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Thyroid Imaging in Nuclear Medicine

INTRODUCTION

Scanning of the thyroid using iodine isotopes is one of the oldest investigations in Nuclear Medicine. Many other nuclear medicine imaging techniques that were developed after the description of a scanning device for visualizing the distribution of ^{131}I in the thyroid gland by Cassen et al. in 1951[1], like liver and spleen and bone marrow scintigraphy, are nowadays obsolete, whereas thyroid scanning still constitutes an important part of the routine output of a standard nuclear medicine department. The most important reason for this is without doubt that diagnostic scanning of the thyroid with ^{123}I or ^{131}I has a sequel in therapy. For instance if therapy with ^{131}I were non-existent, conventional radiological imaging techniques combined with serum hormone and tumour marker assays would long ago have reduced nuclear medicine's role in thyroid imaging. Newer, promising imaging techniques that have emerged in recent years also combine functional diagnostic imaging with the potential of subsequent treatment with the same radiopharmaceuticals. It is in this field of research, specifically in that of radiolabelled peptides, that progress in the treatment of thyroid cancer is expected to be made within the next years.

THYROID SCINTIGRAPHY IS DONE BOTH IN THE CASE OF BENIGN AND MALIGNANT THYROID DISEASE

Benign thyroid diseases

The most common indications for thyroid scintigraphy are, in decreasing frequency: hyperthyroidism, euthyroid multinodular goiter, and hypothyroidism. Imaging for all three indications can be performed with either ^{123}I, ^{131}I, or ^{99m}Tc-pertechnetate. The advantage of using isotopes of iodine are that the amount of thyroidal uptake of radioactivity of the images can be used to compute the amount of ^{131}I that is to be administered for therapy of hyperthyroidism or goiter. With ^{99m}Tc this cannot be done reliably because of the rapid wash-out of the radioactivity and because of the relatively low target-to-background ratios. If logistically possible, ^{123}I should be preferred over ^{131}I, because of the lower patient radiation burden, and also if diagnostic scanning is followed by treatment with ^{131}I, because of the absence of so-called "stunning", i.e. lower retention of ^{131}I at the time of treatment due to a radiation effect by the beta-emission of the diagnostic dose of ^{131}I.

Figure 1



^{123}I scintigrams of thyroid pathology. Top left: diffusely increased uptake in Graves' hyperthyroidism; top right: typical aspect of a multinodular goiter; bottom left: hot nodule in the left lobe with suppressed uptake in the normal thyroid; bottom right: cold nodule in the left lobe caused by a cyst.

In case of thyrotoxicosis, 4 distinct patterns of radioiodine uptake in the thyroid can be encountered:

1. A diffusely increased uptake which is seen in Graves' hyperthyroidism and TSH-mediated hyperthyroidism;
2. Increased uptake in a hot nodule;

3. Adjacent areas of increased and decreased radioiodine uptake in multinodular goiter; and
4. General decreased uptake in subacute- and lymphocytic thyroiditis (often patchy) and factitious thyrotoxicosis *(Figure 1, see page 3).*

In case of acquired hypothyroidism, the uptake of radioiodine or ^{99m}Tc-pertechnetate is decreased. A distinct entity is congenital hypothyroidism: in this case complete absence of uptake (agenesis), a decreased uptake in a normal or enlarged thyroid or uptake in ectopic thyroid tissue may be found. The location of this ectopic tissue may be anywhere along the path that the embryonic thyroid tissue traverses, that is between the base of the tongue and the retrosternal mediastinum. In order to demonstrate deficient iodide organification as a cause of congenital hypothyroidism, a perchlorate discharge test can be performed: 2 hours after the administration of radioiodine, potassium perchlorate is administered. If a defect is present, insufficient or no organification (i.e. irreversible binding to thyroglobulin) of radioiodine occurs. The perchlorate blocks further uptake of radioiodine in the thyroid and the radioiodine that was taken-up before, leaves the thyroid because it is not bound to thyroglobulin. This results in a decrease of radio-activity in the thyroid and a simultaneously increase in blood radio-activity.

Thyroid malignancy

It makes sense to distinguish between imaging methods used for investigation of possible thyroid malignancy and those that can be applied to localize metastatic disease.

Radioiodine imaging of the thyroid is certainly of great value in patients with nodular thyroid disease as increased uptake of the isotope in the nodule as compared to the surrounding tissue renders malignancy less likely. However it may be questioned whether there is a role for any nuclear medicine imaging technique for diagnosis of malignancy: fine needle biopsy cytology or pathology of removed tissue will always be necessary to reach the diagnosis. Apart from this, all currently available radiopharmaceuticals have a relatively low specificity for detecting malignancy: only 20% of "cold" nodules on radioiodine or pertechnetate scans are malignant[2]; medullary cancer may be missed with somatostatin receptor imaging (SRI)[3]; both benign and malignant thyroid nodules may accumulate 18Fluoro-Deoxy-Glucose (18FDG)[4]; other imaging agents like ^{201}Thallium (^{201}Tl), ^{99m}Tc-(V)-dimercapto succinic acid (DMSA), and ^{99m}Tc-methoxyisobutylisonitrile (MIBI) all lack specificity[5,6]. It can therefore be concluded that nuclear medicine has no "magic bullet" to identify malignancy in thyroid nodules.

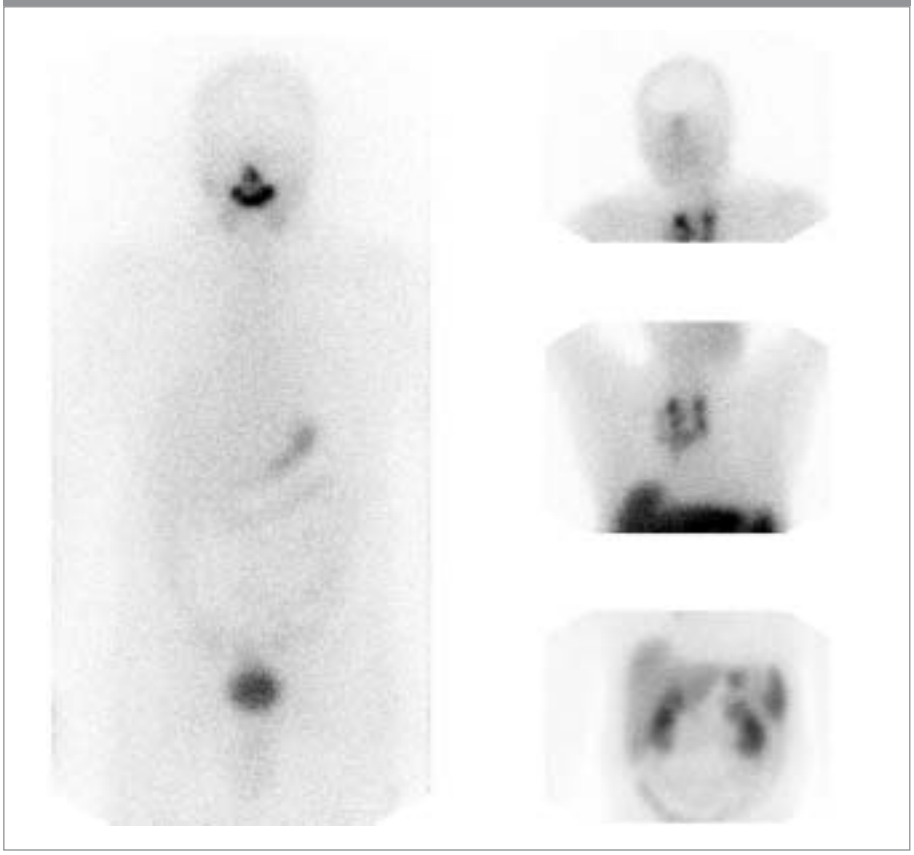
Quite different is the situation in the follow-up of patients who have been operated for thyroid cancer. In patients with differentiated thyroid carcinoma (DTC; papillary and follicular carcinoma), surgery is followed by ablative therapy with ^{131}I, and further follow-up imaging, guided by serum thyroglobulin (Tg) concentrations, whether during TSH suppression or just serum TSH elevation, consists of radioiodine scanning as long as the tumour is radioiodine-avid. The reason for this policy is twofold:
1. If a limited number of lesions is identified, they can be removed by (probe-guided) surgery;
2. If further surgery is precluded, diagnostic scanning can be followed by high dose ^{131}I therapy.

In patients with detectable serum Tg concentrations but negative post-therapy ^{131}I scans, there are several nuclear medicine techniques that may demonstrate tumour sites.

^{201}Tl whole-body scintigraphy can be used to identify metastatic sites of DTC. After concentration of ^{201}Tl via the ATPase-mediated sodium-potassium pump, the tumour uptake is dependent on, amongst others, vascularity and cellularity of the tumours, and also prolonged retention in the tumours plays a role[7,8]. The sensitivity in detecting metastatic sites is 60–90% and does not require (endogenous or exogenous) TSH stimulation[9–12]. ^{201}Tl scanning is not specific for thyroid carcinoma, however, as other tumours also concentrate the radiopharmaceutical.

^{99m}Tc-MIBI is another radiopharmaceutical that can be used to image DTC. The exact mechanism of ^{99m}Tc-MIBI tumour uptake is not known, but the uptake is related to the intracellular mitochondrial

Figure 2



^{131}I scan and SRI in a patient with papillary thyroid carcinoma. Left: post-therapy scan, 7 days after the administration of 150 mCi (5550 MBq) ^{131}I. No tumor uptake is seen. Right: SRI of the head / neck (top), chest (middle), and abdomen (lower panel); anterior views. Note the absence of normal thyroid uptake (status after thyroidectomy), and the pathological uptake in the chest in a pretracheal thyroid carcinoma mass. The uptake in the liver, spleen, and kidneys in the lower image is physiological.

density. It has been used in thyroid carcinoma, with high sensitivity[13,14].

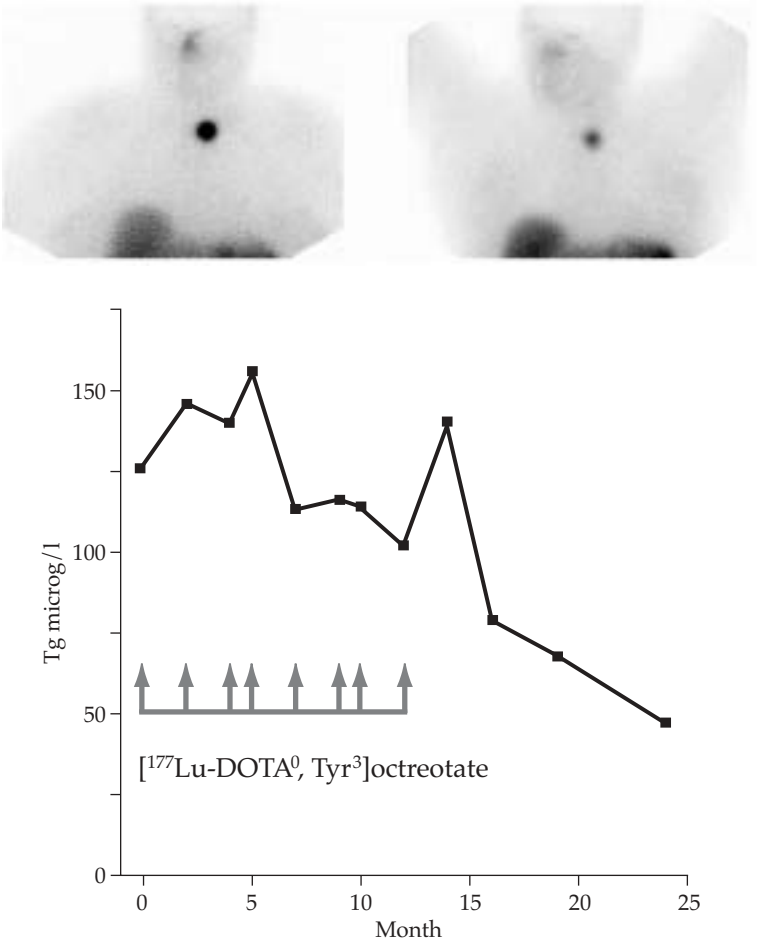
^{99m}Tc-(V)-DMSA resembles the phosphate ion and readily accumulates in calcifying tumours like medullary thyroid carcinoma (MTC). The sensitivity in patients with MTC is high[15]. False negative findings, however, are more frequent in patients with minimally increased serum tumour markers.

Over the last years an increasing amount of papers have been published that stress the importance of ^{18}FDG Positron Emission Tomography (PET) scanning in patients with recurrent thyroid carcinoma. Because most tumours have an increased metabolism and also an increased number of glucose transporter proteins, they can be imaged with ^{18}FDG, a glucose mimic that remains trapped in the tumour cells. Due to the fact that many tumours, but also infections, show increased glucose metabolism, the specificity of ^{18}FDG PET imaging for recurrent or metastasized thyroid carcinoma may be low, but sensitivity is high. Several groups have reported sensitivities of 80–95% for both MTC and DTC[16–19].

A new development that is expected to gain importance in the clinical decision making in patients with thyroid cancer is combined CT-PET camera imaging, which has a high image resolution and combines functional with anatomical information. As with other imaging techniques, the value of ^{18}FDG PET is greatest in patients with DTC who have elevated serum Tg concentrations but in whom no tumour uptake is found with ^{131}I. The results of this type of investigation in terms of tumour to background contrast and tumour detection is better after TSH stimulation, whether by thyroid hormone withdrawal or stimulation with recombinant TSH[20,21].

Somatostatin Receptor Imaging (SRI) can be used to demonstrate MTC and DTC. Somatostatin receptors are present on a variety of neuroendocrine tumors, and these can be visualized with the radiolabelled somatostatin analogue [^{111}In-DTPA^{0}]octreotide. In patients with medullary thyroid carcinoma (MTC) the sensitivity of SRI to detect tumour localizations is 50–70%[3,22]. In a series of 17 patients with MTC whom we studied[3], the ratio of serum calcitonin over carcinoembryonic antigen (CEA) levels was significantly higher in patients in whom SRI was successfully applied. This may imply that somatostatin receptors can be detected in vivo on the more differentiated forms of MTC. Also, SRI is more frequently positive in patients with high serum tumour mark-

Figure 3



Comparison between the uptake after [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and [^{111}In-DTPA^{0}]octreotide in a patient with an inoperable pretracheal Hurthle cell carcinoma remnant. Note the higher tumor uptake after [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (top left) compared to [^{111}In-DTPA^{0}]octreotide (top right), due to a higher affinity for the somatostatin receptor-subtype 2 of [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate. The patient was treated 8 times with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (arrows in lower panel) up to a cumulative dose of 750 mCi (27.8 GBq), eventually resulting in CT assessed tumor shrinkage and a decrease in serum Tg concentrations (lower panel).

ers and large tumours[22], and seems therefore less suitable to demonstrate microscopic disease[22,23].

Although papillary, follicular and anaplastic thyroid cancers, and also Hürthle-cell carcinomas, do not belong to the group of classical neuro-endocrine tumours, the majority of patients with these cancers show uptake of radiolabeled octreotide during SRI[24,25] *(Figure 2, see page 5).*

Also here, it is not necessary to use TSH stimulation to perform SRI[26]. Interestingly, also differentiated thyroid cancers that do not take up radioactive iodine, may show radiolabeled octreotide accumulation[24]. In some patients, this could open new therapeutic options: operation, if the number of observed lesions is limited, or, alternatively, Peptide Receptor Radionuclide Therapy (PRRT; see below) if the uptake is sufficient.

In patients with somatostatin receptor-positive pathology, SRI is useful if it can localize otherwise undetectable disease, or if it can be used for treatment selection (usually the choice between symptomatic treatment with somatostatin analogues or other medical treatment). In patients with known metastatic disease, however, in whom little or no treatment alternatives are available, SRI has a limited role. This situation changes if imaging has a sequel in PRRT. Because of the promising results in patients with neuroendocrine tumours of treatment with Auger electrons or beta-particle emitting somatostatin analogues[27–30], we expect that SRI will be increasingly used to select patients for such therapy *(Figure 3).*

Beta-particle emitting octreotide analogues used for PRRT are [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and [^{177}Lu-DOTA0,Tyr^{3}]octreotate, which have a 3 to 4-fold higher uptake than [^{111}In-DTPA^{0}]octreotide in most neuroendocrine tumors[31]. PRRT with these analogues leads to an anti-tumor effect in about two-thirds of the patients with neuro-endocrine tumors. It should be taken into account however, that in most patients with MTC the uptake of radioactivity in the tumour sites is low if compared with other neuro-endocrine tumours like carcinoids and endocrine pancreatic tumours. Also, in our experience, in most

patients with DTC the tumour uptake after [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate is not higher than after [^{111}In-DTPA^{0}]octreotide. This is most likely due to the fact that not the somatostatin receptor-subtype 2 is over-expressed in these tumours, but other subtypes, in agreement with an in vitro study using RT-PCR on human thyroid carcinoma cell lines and demonstrating a predominance of mRNA for somatostatin receptor subtype 3 and 5, but only very low amounts of mRNA for subtype 2[32]. [^{90}Y-DOTA^{0},Tyr^{3}]octreotide has a higher affinity for the somatostatin receptor subtype 5 than [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate, but its importance for PRRT of DTC has to be shown. It is to be expected that in the near future somatostatin analogues will be introduced for SRI and PRRT that show higher affinity for the somatostatin receptor subtype 3 and 5, in addition to a high affinity for the subtype 2. This will open a new area for the staging and treatment of DTC.

Cholecystokinin-B (CCK-B) receptors, which bind both CCK and gastrin, have been demonstrated in human medullary thyroid carcinoma[33]. The presence of this receptor is probably the molecular basis for the well-established pentagastrin stimulation of serum calcitonin (CT) to diagnose otherwise undetectable MTC. In a study using in vivo scintigraphy with an ^{111}In-labelled CCK analogue in 7 patients with biochemical or radiological evidence of MTC, presumed tumour sites were demonstrated in 2 patients[34]. The uptake was however low *(Figure 4)*.

Figure 4



Anterior view of the chest, 24 h after the injection of [^{111}In-DTPA]-CCK analogue in a patient with MTC who had elevated serum CT and CEA concentrations and negative imaging studies. There is normal uptake in the liver and stomach (lower edge of the image) and accumulation at a presumed, but unconfirmed tumor localization (arrow).

Behr and Béhé, using a different analogue, were able to demonstrate tumour sites in all of 23 patients with known tumour localizations of MTC, as well as in 20 of 22 patients with occult disease[35]. Subsequently, they also treated MTC patients with ^{90}Y-labelled gastrin analogue, with promising results in terms of tumour growth control. Therapy related side-effects like myelodysplastic syndrome and nephrotoxicity, however, are still major concerns to be solved.

CONCLUSIONS

Scintigraphy and therapy with radioiodine remains nuclear medicine's cornerstone in the diagnosis and therapy of thyroid disease. In patients with recurrent or metastasized thyroid cancer that does not concentrate radioiodine, several other localizing techniques are available. Of these, ^{18}FDG PET scanning has a high sensitivity and also a good image resolution. Combined CT-PET camera imaging is expected to gain importance in the clinical decision making in part of patients with thyroid cancer. Peptide receptor scintigraphy and radionuclide therapy with somatostatin analogues and in the near future also with other peptides e.g. CCK-B analogues may be of crucial importance in patients with DTC and MTC. If the uptake in the tumour sites is sufficiently high, diagnostic scanning may be followed by PRRT, whether with a sole radiopharmaceutical or a cocktail of radiolabelled peptides.

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Statutes for the Merck European Thyroid von Basedow Research Prize donated by Merck KGaA, Darmstadt, Germany

1. The prize is to exclusively and directly honour special scientific work in the field of the thyroid gland and serves also to recognize and encourage young scientists. € 10,000 per year are available. In exceptional cases, the jury may decide to divide the prize.

2. Young scientists who are domiciled in Europe and have not completed their 40th year of life may apply for the prize. Employees of industrial firms are exclused. The candidates are to hand in manuscripts of (original plus nine copies) their as yet unpublished works to the President of the German Society of Endocrinology by October 31 of the year prior to the prize-giving.

3. In addition to basic research, work involved in both diagnostic as well as therapeutic problems in this specific field also may be considered for the prize. The submitted reports must not exceed 25 type-written pages à 30 lines. The number of figures and tables is to amount to no more than 1/3 of the complete report. The manuscript, in either English or German, must be drawn up according to the regulations of a scientific journal. All rights are exclusively in the control of the author. After confirmation of receipt, the author may offer his work to a journal for publication.

4. The prize project should not include more than two authors. If more authors have cooperated in a project, the team should decide on the two main authors to be named for the prize project; if necessary, the remaining authors must give their consent in writing. The curriculum vitae stating the scientific career of the author(s) must be enclosed with the prize project. The author(s) must affirm in writing that at the time of submission the manuscript had not been published or handed in for publication in a journal (exception: published abstracts).

5. A jury decides on who is to receive the prize. The jury may decide not to donate the prize if the manuscripts received are not worthy. The decision of the jury is mandatory for all participants and is not subject to judicial inquiry. If not awarded, the prize may in exceptional cases be made available in the following year for additional manuscripts which are worthy.

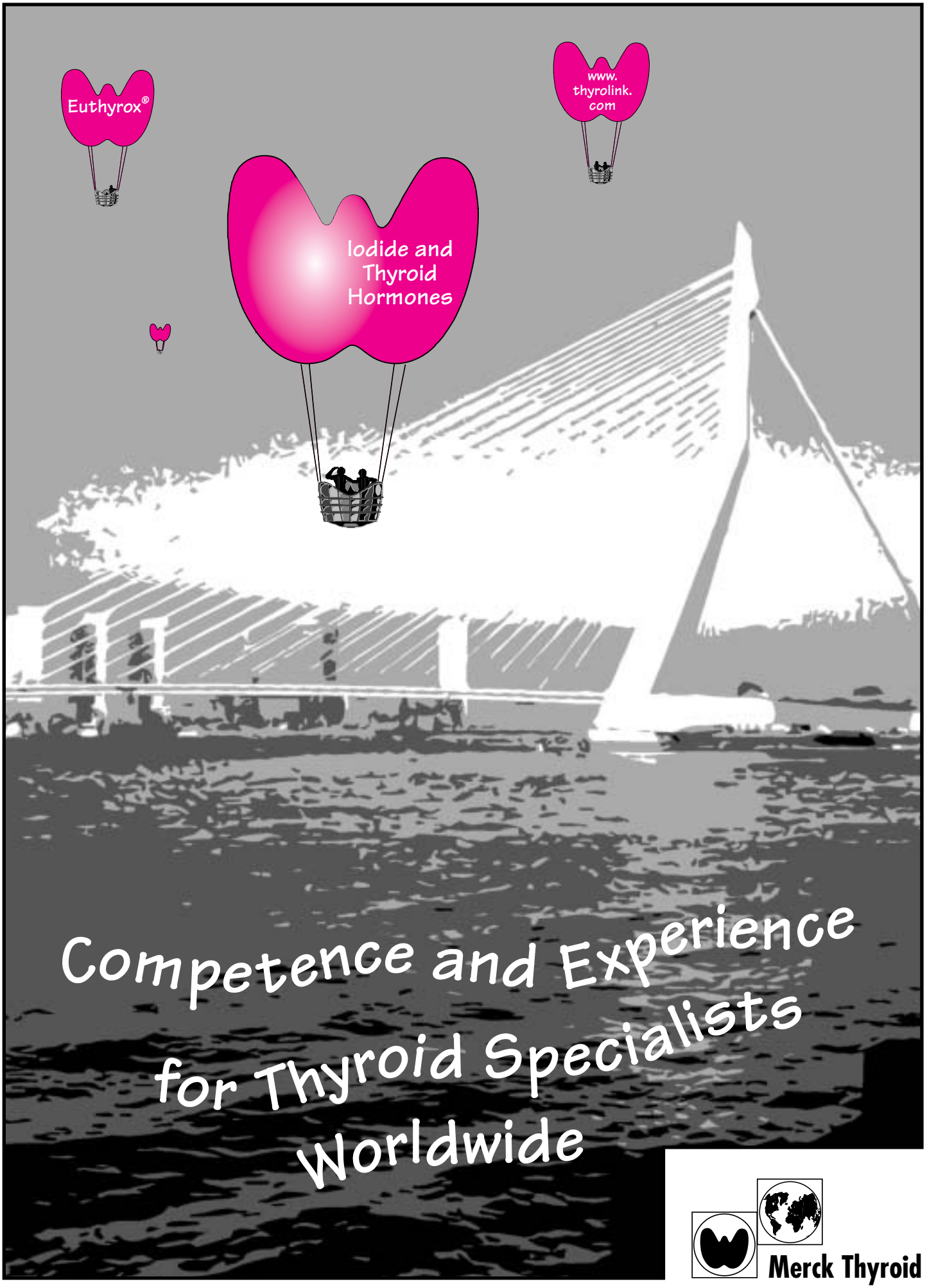
6. The jury comprises: The President and two members of the Board of the German Society of Endocrinology, the speaker and two members of the Thyroid Section nominated by the Board of the German Society of Endocrinology and one representative from the Pharmaceutical Section of Merck KGaA, Darmstadt. Other experts (without the right to vote) may be included in the assessment. The chairman of the jury is the President of the German Society of Endocrinology.

7. The jury decides with a 2/3 majority. In exceptional cases, decisions given in writing form absent jury members may be considered. A member of the jury may not take part in assessing a manuscript if it originates from his working circle. In this case, the President calls another member of the Society from the same field to the jury.

8. The prize is usually awarded once a year at the annual meeting of the German Society of Endocrinology.

9. The President of the Society will invite applications for the prize for the subsequent year at the annual meeting. The secretary and press agent of the Society will arrange announcements in several languages for the competition to be advertised in medical journals.

The President of the
German Society of Endocrinology


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