Dosage assessment for radioiodine therapy in benign thyroid disorders

Dosisbepaling bij de behandeling van goedaardige schildklieraandoeningen met radioactief jodium (met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht,
op gezag van de rector magnificus, Prof.Dr. H.O. Voorma,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op dinsdag 16 januari 2001
des middags te 12.45 uur

door

Johannes Willem van Isselt
geboren op 14 februari 1949 te Steenbergen en Kruisland

Promotor: Prof.Dr. C.J.M. Lips

Co-promotors: Dr. J.M.H. de Klerk
Dr. A.P.G. van Gils

The research presented in this thesis was done at the Department of Nuclear Medicine of the University Medical Center Utrecht, The Netherlands

This publication was financially supported by:
Mallinckrodt Medical B.V., Petten, The Netherlands
Drukkerij Hoonte Bosch en Keuning, Utrecht, The Netherlands

Beoordelingscommissie: Prof.Dr. T.W.A. de Bruin
Prof.Dr. E.P. Krenning
Prof.Dr. W.P.Th.M. Mali
Prof.Dr. G.J.J. Teule
Prof.Dr.Ir. M.A. Viergever
Prof.Dr. W.M. Wiersinga

ILLUSTRATIE KAMAGURKA

This thesis was type-set in Stone.

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Chapter One

Radioiodine therapy: from medical tradition to clinical science

Johannes W. van Isselt

Summary

Shortly before Becquerel's discovery of radioactivity in 1896, the role of iodine as a precursor of thyroid hormones had been recognized. The thyroid's functioning and metabolism had been probed with several radioactive isotopes of iodine when in 1946 iodine-131 sodium iodide (^{131}I) was used as a treatment form for both benign and malignant thyroid disease. In retrospect, this can be seen as the birth of nuclear medicine as a medical specialty.

Over the past fifty years, it has become clear that radioiodine therapy is a safe and effective form of treatment. The mechanism of action of ^{131}I is relatively easy to understand from its physical properties and from radiobiologic principles. Yet, it is hard to predict the outcome of radioiodine therapy. The success rate varies significantly between different thyroid disorders, and between patients under apparently similar circumstances. This had led to much speculation about which factors influence the efficacy of radioiodine therapy, and consequently to experimental adaptations of dosage calculation algorithms. In view of the many co-existing dosage regimens, it is evident that none are perfect.

In Graves' disease, different outcomes can be partly explained by different starting points. It is argued that the natural course of Graves' disease (with hypothyroidism as the inevitable end-stage in most patients) doesn't warrant an individualized approach, because this carries a relatively high risk of persisting hyperthyroidism. In this view, the early induction of hypothyroidism is a logical therapeutic goal. In some European countries, guided by the ALARA principle, physicians are obliged by government regulations to perform individualized dosage calculations in order to keep the total radiation burden as low as possible. This approach, leading to several years of normal endogenous thyroid function in a majority of the patients, may well be worth the extra cost and effort involved.

In later years, benign thyroid diseases other than Graves' disease (thyroid adenoma, toxic goiter and most recently nontoxic multinodular goiter) have also gained recognition as good indications for radioiodine therapy. The therapy goals and the therapeutic dosage assessment in benign thyroid disorders are determined by different specifications for each of these disorders.

Improvement of the clinical results of radioiodine therapy seems to be feasible, especially in Graves' disease. This should be achieved chiefly through adjustments to the radioiodine dosage modeling and through standardization of nuclear medicine procedures pertaining to the therapeutic dosage calculation, such as thyroid volume measurements and radioiodine uptake measurements.

1.1 The history of radioiodine therapy

"All those who drink from this remedy recover in a short time, except those whom it does not help and who all die. Therefore, it is obvious that it fails only in incurable cases." This beautifully ironic quote from Galenus (130-200 AD) may serve to illustrate how little tendency there is to question the efficacy of treatment forms once they have established a place in common practice. Not many procedures in nuclear medicine have as long a history or as proud a conduct record as that of iodine-131 sodium iodide (^{131}I-NaI, or ^{131}I for short) in the diagnosis and treatment of thyroid disorders. However, in comparison with more recently introduced applications of radiopharmaceuticals both the technical and the clinical quality assurance of radioiodine therapy have been relatively underexposed. The clinical practice of radioiodine therapy is mostly based on long-standing traditions, the validity of which in some cases is still to be substantiated.

The history of radioiodine therapy stems from two roots: thyroid research and radiochemistry. As early as 1895 Baumann established that stable iodine is present in the normal thyroid gland,[1] and some twenty years later Marine found that iodine is cleared from the blood by the thyroid.[2] In 1914 Edward C. Kendall succeeded in isolating in crystalline form "the compound containing iodin, which occurs in the thyroid", later to be called thyroxine.[3] In 1896 Henri Antoine Becquerel had made a discovery in an entirely different field of science.

Figure 1.1 Marie Curie.

While studying the phospholuminescent properties of uranium, Becquerel came upon a form of energy emanating from matter, which resembled the 'X-rays' that Röntgen had discovered a year earlier.

Becquerel's student Marie Curie, *née* Marya Sklodowska (figure 1.1), named the newly discovered physical phenomenon 'radioactivité'. Radioactivity would become a lifetime commitment for Madame Curie, the first woman to receive the Nobel Prize (for physics, which she shared with Henri Becquerel and her husband Pierre) and later the first person ever to be awarded a second Nobel Prize (for chemistry). Marie Curie died at the age of 66, most likely from excessive exposure to radium, polonium and X-rays.[4] In the same era Lord Ernest

Rutherford had founded the physico-mathematical concepts of 'decay constant' and 'half-life' and had drawn up the formula $I_t = I_0.e^{-\lambda t}$. Alpha, beta and gamma radiation were discerned as different types of radiation. Pierre Curie experimentally confirmed Becquerel's accidental finding of a biological effect (skin burns) of uranium. Within a couple of years after these discoveries, medical experiments with external applications of radioactive materials were freely conducted. Danlos and Bloch applied radium to tuberculous skin lesions, Alexander Graham Bell suggested the use of radium sources to tumors, and Robert Abbé successfully handled (external) radium sources in the treatment of hyperthyroidism.[5] Frederick Proescher published the first results of intravenous radium application for a number of diseases in 1913. Many new radioisotopes were discovered in the early years of the 20th century, and several more after Irène Joliot-Curie (Marie and Pierre Curie's elder daughter) and her husband Frédéric Joliot found that radionuclides could be produced artificially.[6] It took until 1924 before the Hungarian chemist Georg von Hevesy, one of the founding fathers of nuclear medicine, started diagnostic animal experiments with internal applications of unsealed lead-210 and bismuth-210 sources. In 1925, almost 30 years after the discovery of radioactivity, the first human diagnostic nuclear medicine procedure in history was performed – the measurement of the circulation time by Blumgart and Yens, who used bismuth-214 ('radium-C') in this experiment.[7]

In the 1930s, as a result of the work of Lawrence and Livingstone, the production of radionuclides in larger quantities created the facilities for large-scale laboratory and clinical experiments. A new window was opened to the study of human physiology and pathophysiology. Until the foreclosure of civil radiophysics research by the outburst of World War II substantial progress had been made also in the therapeutic use of radionuclides. In 1935, Chievitz and Von Hevesy demonstrated the physiological process of mineral bone component renewal using ^{32}P-phosphate. A year later J.H. Lawrence applied ^{32}P-phosphate in the treatment of leukemia, which event marks the first documented clinical therapeutic use of an artificial radionuclide. Pecher described the uptake of strontium-89 in bone metastases. In the following years J.J. Livingood and Glenn T. Seaborg were involved in the discovery of several radionuclides, among which iodine-131 in 1938. Later Seaborg (now with Segré) was also responsible for the discovery of technetium-99m, which was to become the workhorse of nuclear medicine.

During these prewar years *in vitro* and *in vivo* experiments with radioactive iodine isotopes had been instrumental in the elucidation of the thyroid's physiology (including the identification of the thyroid hormones) and its patho-

physiology. In 1937, Hertz, Roberts and Evans investigated the rabbit's thyroid function with ^{128}I.[8] With ^{130}I they also pursued therapeutic goals, in doses that we now know would have been mere diagnostic if it were not for a probable 10% ^{131}I contaminant.[9] As medical interest in thyroid research was gradually building up, ^{131}I – a cyclotron product with a very useful half-life of 8.03 days – was found by Livingood and Seaborg. The paucity of clinical and scientific developments during World War II is explained by the internment of many of the allied forces' radiophysicists at the Atomic Research Laboratory at Los Alamos, New Mexico, for the development of a weapon with hitherto unimaginable force. The devastating potential of radiation, as demonstrated by the bombs on Hiroshima and Nagasaki, drove large parts of society away from nuclear warfare, nuclear testing, and nuclear power. The adjectives 'atomic' and 'nuclear' acquired a negative connotation. To date some of the leading scientists in nuclear medicine prefer to name their specialty 'molecular medicine'. Nonetheless, the postwar period was characterized by a rapid expansion of nuclear science into the medical world. In 1942 radioiodine entered the clinical arena when two groups independently reported on the successful treatment of hyperthyroidism with ^{131}I-sodium iodide, which at that time was available only in very small quantities.[10,11] In that same year Reid and Keston discovered ^{125}I, and Seidlin, Marinelli and Oshry successfully applied ^{131}I in a thyroid cancer patient. The news of a potential cure for terminally ill patients fuelled the public imagination to such a degree that it hit the political agenda.[12] Effective on 1 August 1946, the Atomic Energy Act (AEA) made radioisotopes available for medical use in the USA. This date marks the beginning of 'atomic medicine', later renamed 'nuclear medicine'. In 1951, the FDA approved the use of ^{131}I for the treatment of benign thyroid diseases. From 1940 to 1970, countless experiments with radioiodine have brought us knowledge of iodine uptake mechanisms, the basis of the therapeutic effect of radioiodine, complete identification of thyroid hormonosynthesis, serum transport of thyroid hormones, and thyroid imaging. More recently immunological and molecular studies have changed the understanding of thyroid diseases.[13]

In the 1950s, more than fifty years after the discovery of radioactivity, studies with radiotracers were still done with Geiger counters and scintillation probes. Although with these instruments precise quantitative measurements could be performed of specific physiologic processes within the human body, they lacked imaging potential. In our day it may be hard to imagine that there once was a time when brain tumors could not be visualized, but in 1959 the construction

of the first 3-in rectilinear scanner meant a real breakthrough. Medical imaging, until then the exclusive domain of radiology, had acquired a pathophysiological dimension. ^{131}I-scanning of the thyroid provided new insight in the pathophysiology of various thyroid disorders. The development of a range of physiologic radiopharmaceuticals was boosted by Hal Anger's introduction of the gamma camera with its revolutionary whole-body imaging technique. By this time, the unique physical, chemical and radiobiologic properties of technetium-99m (^{99m}Tc) were also recognized. 'Off the shelf' kit preparations with ^{99m}Tc came within clinical reach by the commercial production of the ^{99m}Tc-generator in 1964, seven years after Tucker invented it. One of the simplest technetium-labeled compounds, ^{99m}Tc-pertechnetate, stereometrically resembling iodine, caused a boom in thyroid imaging publications.

Once more military technology was to stand at the cradle of modern nuclear medicine. When NASA's space program necessitated the construction of fast mainframe computers, nuclear medicine physicists took advantage of the emerging information technology. In less than a decade ever faster and smaller computers accelerated the development of sophisticated gamma cameras and dedicated software. Kuhl had already described three-dimensional image reconstruction algorithms in 1964,[14] but it took until the mid seventies before hardware developments made the clinical application of single photon emission computer tomography (SPECT) feasible. By that time, astrophysicists had fruitfully brought these theorems to practice.[15] Radiology's transmission CT-scanner was another derivative from Kuhl's innovating activities.[16] From 1976 onwards, SPECT cameras and dedicated PET cameras have brought 3D functional imaging to the clinic.

The growth of this new medical field had been so rapid that in 1971 nuclear medicine was recognized as a regular medical specialty in the USA, and in 1984 in The Netherlands. The impact of nuclear medicine is still growing. Nuclear medicine has been instrumental to the understanding and broadening of several areas in medicine. Some more recent examples are: receptor scintigraphy in (neuro)oncology, neurology and biologic psychiatry; immunoscintigraphy in oncology and infectious disease; and ^{18}F-FDG PET in all of these medical areas. In most disciplines, therapeutic applications are seen as the ultimate goal. The 'magic bullet' concept of specific targeting with radiopharmaceuticals is indeed attractive. Some scientists define the future of nuclear medicine by the triad 'quantitative emission tomography–dosimetry–radionuclide therapy'. Radioiodine therapy, once instrumental in the birth of nuclear medicine, is still very much part of its future.

1.2 Physical and radiobiologic properties of iodine-131

The key to the applicability of radioiodine as a therapeutic agent

Iodine as a dietary ingredient is essential for the synthesis of the thyroid hormones triiodothyronin (T_3) and thyroxine (T_4). The recommended daily intake varies between 150 and 200 µg.[17] The thyroid's avidity for iodine is the key to therapeutic applications of radioiodine in thyroid disorders. The thyroid gland is one of the few organs in the human body that can concentrate iodine, and the only one that metabolizes it. In subjects with normal thyroid function up to 20-30% of orally administered iodine is taken up by the thyroid.[17] In hyperthyroid patients this percentage is increased – in extreme cases close to 100% may be incorporated – and administration of radioiodine therefore leads to a highly specific delivery of the radiation dose to the thyroid gland and a relatively low radiation burden to other organs. Organ doses vary with the administered amount and with the route of administration. The radiation dose to internal organs does not preclude the use of radioiodine for thyroid therapy except in pregnant women.[18-21] At present there is broad consensus that all benign thyroid disorders associated with hyperfunctioning or with goiter can be adequately treated with radioiodine.[17]

Physical characteristics of ^{131}I

The element iodine (from the Greek *iodes* = violet-colored, which iodine is when vaporized) was discovered by Courtois in 1811. Iodine-127 is the only stable iodine isotope; for isotopes with a mass number over 127, the daughter product is xenon. Iodine-131, which is formed by neutron bombardment of tellurium-131, decays to stable ^{131}Xe by beta emission (figure 1.2). Physical characteristics

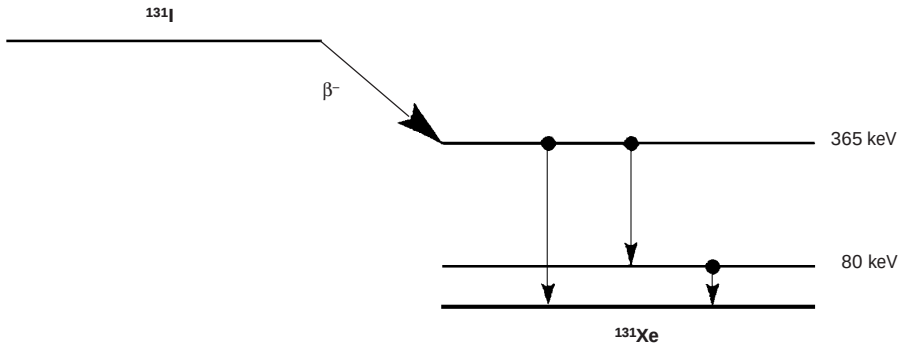

Figure 1.2 Simplified decay schema of ^{131}I.

of ^{131}I: $T_{1/2\ phys}$ = 8.04 d; β^- = 0.807 MeV; 19 γ's, ranging from 80 to 637 keV, most abundant γ: 364 keV (83%).[18,22,23] The average range of the 0.807 MeV beta particles in soft tissue approximates 1 mm, the maximum range is about 3 mm.[24]

Radiation effects of ^{131}I on the thyroid cell

The biologic effects expressed in cellular organisms following exposure to ionizing radiation result from chemical changes induced by the radiation in biomolecules. Such changes may be brought about directly or indirectly.[19,25] *Direct* action is produced predominantly by high linear energy transfer (LET) radiation, such as from beta particles (cf. ^{131}I). It occurs when radiation energy is deposited within a target macromolecule that is critical for cell survival (often DNA), causing ionization or excitation of the macromolecule and thereby altering its biologic function. *Indirect* action results when the radiation interacts with other atoms or molecules producing free radicals that in turn react with the critical macromolecules. A free radical is a species that has an unpaired electron in its outer shell and is for that reason highly reactive. The simplest free radical, a proton with a single electron ($H^{\bullet}$), is highly reactive in aqueous medium. Because water is the major component of cells and tissues, including the thyroid gland, the production of free radicals ($H^{\bullet}$, $OH^{\bullet}$) is the most common result of irradiation of biological systems. Radiation effects are not identical for different biological structures. Cell constituents consisting of carbohydrates, lipids or proteins (e.g., enzymes or membranes) are inactivated only by very high radiation doses, because they are present in many copies. In contrast, DNA is present in limited copies. Furthermore, its integrity is vital for cell survival.[25] For these reasons DNA is considered a critical target for cell inactivation by ionizing radiation. One sievert (1 Sv) of ionizing radiation can produce 6.1×10^{13} ionizations per gram tissue; since each cell contains 4×10^{-12} g of DNA, 1 Sv can produce 244 ionizations in the DNA of each cell, or 5.3 ionizations per chromosome.[19] Free radicals react with both the base and sugar components of DNA; $OH^{\bullet}$ reacts with bases by addition to a double bond, and with sugars by hydrogen atom abstraction. These reactions can result in several types of damage to the DNA molecule: (i) breakage of hydrogen bonds with loss of structure, (ii) loss or change in nitrogenous base which may be lethal or may result in a mutation, (iii) DNA single strand breaks which are enzymatically repairable, (iv) DNA double strand breaks which may be lethal, and (v) cross-linking between two different DNA molecules or of DNA to a protein. These effects occur after all forms of ionizing radiation, including the beta emissions from ^{131}I. The net result is loss of function or cell death.

Dose response relationships

One of the most difficult issues in the radioiodine treatment of thyroid disorders, and particularly in Graves' disease, is the relationship between the administered amount of ^{131}I and its therapeutic effect. Dose response relationships are quantitative descriptions of the effects of radiation on cells. The most widely used in radiation biology is the cell survival curve. It reflects radiation induced loss of reproductive capacity, i.e., damage is only expressed when a cell attempts to divide.[26] Although at the cellular level this model works, the cell survival curve has very limited applicability to whole organs *in vivo*. In the earliest clinical applications, the dosage was worked out by a trial-and-error method and by successive approximations. A higher incidence of hypothyroidism generally resulted from larger ^{131}I dosage schemas, while persisting hyperthyroidism was more frequently observed after smaller ^{131}I dosages.[22] By about 1950 the standard dosage had become 160 μCi/g (5.9 MBq/g) estimated thyroid weight.[26] Estimations of the optimal radiation absorbed dose to the thyroid gland in patients with Graves' disease at present vary from 200 Gy to 300 Gy.[27] Under clinical circumstances the theoretical optimum as well as the actually delivered doses are not easily verified. Without calibrated dosimeters, absorbed dose calculations and measurements harbor a number of uncertainties.[28]

1.3 Factors influencing the outcome of radioiodine therapy

The dosage model

As was stated before, different dosage models are used depending on the therapeutic aim. Higher radioiodine dosages are usually administered with fixed dosage regimens, lower dosages with individualized schemas. Errors in ^{131}I dosage may result from inappropriate radiobiologic modeling or incorrect measurements. The presently applied dosage models may be oversimplifying the biologic properties of the thyroid gland in individual patients. The radioiodine turnover by the thyroid gland varies greatly with disease activity, and consequently affects the effective half-life of radioiodine.[29] Inaccurate ^{131}I uptake measurements or thyroid volume measurements have a direct bearing on calculations of the radioiodine therapy dosage. Although substantial changes in techniques have been introduced after the first therapeutic dosage formula was proposed, validation and verification are still lacking in some respects.

Radiosensitivity

Given the difficulties in predicting the amount of ^{131}I required to establish euthyroidism in individual patients with Graves' disease, the therapeutic range of radioiodine is probably small. The therapy outcome is influenced not only by the amount of ^{131}I administered per gram thyroid tissue, but also by biological properties of the thyroid gland itself. Based on empirical clinical data it has been established that the radiosensitivity of the thyroid gland as a whole decreases with increasing size. There are no generally accepted radiodosimetric models to explain this finding.[25,28] The differential radiosensitivity within the thyroid gland is probably caused by histopathologic changes such as the development of nodular abnormalities and autonomously functioning thyroid tissue,[30-32] and the resulting inhomogeneous distribution of radioiodine within the thyroid gland.[17] Yet, when the maximum range of ^{131}I beta particles (3 mm) is taken into consideration,[30] the distribution of radioiodine is relatively homogeneous in Graves' disease in comparison with nodular goiters.

Thyroid blocking medication

Antithyroid drugs (ATD) are often used in the initial treatment of patients with Graves' disease. Medication for up 1-1.5 years is relatively inexpensive, and leads to restoration of normal function in about 10-50% of all patients. The therapeutic effect of ATD is less in patients with larger goiters.[34] ATD have a decelerating effect on iodine uptake by the thyroid, whereas the release of thyroid hormones is not being blocked. ATD also constitute a safe patient preparation for radioiodine treatment, preventing the rare occasions of thyroid storm in patients with very active disease.[26,35] If thyroid blocking medication is not interrupted at least three days before radioiodine administration, a diminished therapy effect must be anticipated.[36] This is partly explained by the decrease of the radioiodine's effective half-life through depletion of the thyroidal iodine pool, but the reduced therapy effect is still present when T_{eff} is compensated for. This is suggestive of a 'radioprotective' action of ATD.[30]

Iodine excess

Iodine in its nonradioactive isotopic form (^{127}I) competes with radioiodine at the level of the thyroid cell. Seafood (especially clams, seaweed, and some fish) can be very rich in iodine. Although dietary iodine intake seldom leads to iodine excess, food additives sometimes do. In such cases maintaining an iodine-free diet for three days may help to overcome problems of reduced radioiodine uptake. A detailed list of drugs and contrast media interfering with radioiodine

uptake was presented by Shackett.[37] Radioiodine treatment should be postponed, sometimes for three months or more, in case such substances have been administered.

Iodide in high dosage acutely decreases the release of thyroid hormone from the thyroid gland – apparently by inhibition of proteolysis – with a more marked effect in thyrotoxicosis than in the normal gland. This is called the Wolff-Chaikoff effect. Most sources of iodine excess are iatrogenic; radiologic contrast agents and a number of drugs contain large quantities of iodine, which may be freed and absorbed in the human body.

Lithium

Lithium blocks the release of iodine from the thyroid gland without hampering its uptake, as a result of an apparent decrease in proteolysis of thyroglobulin.[38] The intrathyroidal persistence of (radio)iodine is thus enhanced, and the effective half-life of ^{131}I is increased.[39,40] It has recently been demonstrated that the curation of hyperthyroidism is prompter and more effective when radioiodine is administered in combination with lithium.[41] Also the shrinkage of goiters is more effective, especially of larger goiters.

Other drugs, dietary ingredients

Many drugs have an effect on thyroid function. Amiodarone and glucocorticoids are well-known examples, but at least a hundred other drugs are known to cause either an increase or a decrease of thyroid hormone or TSH serum concentrations.[42] As with ATD, their use can hardly be titrated so there is no practical use of these medications in controlling thyrotoxicosis. Moreover, some should be considered as potential causes of thyrotoxicosis.

Dietary factors other than iodine may influence the functioning of the thyroid. Cyanoglucosides, found mostly in staples – such as cassava, corn, sweet potatoes, bamboo shoots, lima beans, and as such consumed mostly in the third world – are transformed *in vivo* to thiocyanate and isothiocyanate. These are powerful goitrogenic agents that act by inhibiting thyroid iodide transport, and at higher doses by competition with iodide in the organification process.[43] They may cause prolonged periods of thyroid blockage and thus interfere negatively with radioiodine treatment.

Medicolegal background

In most Anglo-Saxon countries, treatment with relatively large amounts of radioiodine (up to 30 mCi, or 1.1 GBq) is allowed on an outpatient basis. In many

European countries (e.g., in The Netherlands) national regulations prohibit the therapeutic administration of radioiodine on an inpatient *or* outpatient basis unless hospitals have the infrastructure and facilities designed and approved for this use. In Germany and in some Eastern European countries outpatient treatment is prohibited altogether.[44] Differences in administered dosages are evident consequences of such differences in medicolegal background, and different clinical outcomes will result from otherwise similar therapeutic applications in patients treated for the same disease.[45]

1.4 Indications for radioiodine therapy

Over the years, several benign thyroid disorders have been recognized as good indications for radioiodine therapy, although the therapeutic aims may vary. The various indications and suggested radioiodine dosage models are summarized.

1.4.1 Toxic nodular thyroid disorders

Although toxic multinodular goiter and toxic adenoma are often viewed as distinct and separate entities,[46,47] they truly represent a spectrum of autonomously functioning thyroid disorders.[35]

Toxic multinodular goiter

In 1913 Henri Plummer described a type of hyperthyroidism in which nodular lesions are present in the thyroid.[48] This disease, now known as toxic multinodular goiter, mainly afflicts persons over 50 years of age. The typical phenomenology of the toxic goiter is a conglomerate of hyperfunctioning and hypofunctioning nodules embedded in normal thyroid tissue, with inhomogeneous radioiodine uptake in the thyroid. A large goiter and autonomous function often precede the onset of hyperthyroidism by many years.[46,49] The natural heterogeneity of thyroid cells and impulses for thyreocytes to grow form the basis of the nodular growth.[31] Presumably, in the absence of naturally occurring goitrogens or goitrogenic drugs, hereditary as well as hormonal factors and external stimuli are involved in the etiology of all nodular thyroid diseases.[31,50,51] The function of the follicular components of the nodular lesions is autonomous, i.e. independent of extrathyroidal stimulators such as TSH.

Toxic adenoma

Goetsch in 1918 described the pathophysiology of autonomously functioning thyroid nodules as originating from fetal rests, groups of cells found between thyroid follicles, and rich in mitochondria. According to Studer's later theory focal hyperplasia and adenoma formation inevitably occur with time, since the thyroid (similar to other organs) naturally contains a small fraction of cells with high inborn replication power and since this property is a stable and inheritable trait.[31] Recent research in molecular biology has revealed that many toxic thyroid adenomas are caused by activating somatic 'gain of function' mutations in the TSH receptor itself or in the Gsα protein linked to it.[52] The mutation results in the accumulation of cAMP, which causes autonomous function as well as proliferation of adenomatous tissue. Many nodules degenerate during this process. They are usually solitary nodules that may occur at any age from the teens to the elderly. Only about one quarter of these are associated with hyperthyroidism, which usually sets in about 15 years after the first presentation of the nodule. Autonomous thyroid nodules without hyperfunction are much more common than toxic lesions. In patients with toxic adenoma, the degree of hyperfunctioning of adenomatous thyroid tissue can be easily demonstrated by thyroid scintigraphy using either ^{99m}Tc-pertechnetate or ^{123}I-NaI. In thyrotoxic patients adenomas will take up a large portion of the radiopharmaceutical and the normal thyroid tissue is suppressed, i.e. it hardly shows any uptake. This scintigraphic phenomenon is further enhanced by 'suppression imaging', i.e. scintigraphy after administration of triiodothyronine (T_3) which reduces the uptake by normal thyroid tissue through suppression of TSH.

Treatment options in toxic nodular thyroid disease

Surgery, ATD and/or levothyroxine medication and radioiodine therapy have long been regarded as equally useful treatment options for toxic multinodular goiter and toxic adenoma, but although ATD can normalize serum FT_4, FT_3 and TSH concentrations, thyrotoxicosis recurrence after cessation of therapy is greater than 95%.[35,53] In view of this evidence it is surprising that currently many patients with these disorders are still being treated with antithyroid drugs.[55] Rational use can be made of ATD to render the patient euthyroid before more definitive therapy. This reduces both the risk of hypothyroidism after radioiodine therapy, and the risk of acerbations of hyperthyroidism after radioiodine therapy or surgery.[54-56] The preferred treatment modality in individual patients varies with the size of the nodule or goiter, the age of the patient, the percentage of radioiodine uptake, the presence of compressive symptoms, concomitant ill-

ness, and pregnancy or breast-feeding status.[35] Large nodules and large goiters are preferentially treated with surgery because the reduction in size is fast and seizable. This is especially relevant if there are compressive symptoms.[35] A solitary toxic adenoma in a young patient is often treated by unilateral lobectomy rather than radioiodine. This preference stems from concerns of an increased risk of development of benign thyroid nodules or even thyroid cancer.[57] However, in a very large study it was shown that the incidence of thyroid cancer is actually lower after radioiodine treatment than after surgery.[58] In patients with toxic adenoma, subtotal thyroidectomy is associated with a low recurrence rate (10-20%) but with a very high rate of hypothyroidism (close to 90% at 1 year).[59]

Radioiodine therapy has been used successfully for three decades in patients with toxic adenoma. The situation in this disorder is almost ideal for radioiodine treatment: relatively large amounts of radioiodine can be used for a complete ablation of the target tissue (the adenoma), whereas the normal thyroid tissue will be relatively spared because its iodine uptake is suppressed as a consequence of the suppressed TSH. In a recent report, however, it was indicated that the radiation absorbed dose to the normal thyroid tissue is higher than has generally been assumed.[60] The success of radioiodine therapy may be demonstrated scintigraphically; if the ablation was successful the TSH level will have normalized, and the uptake of iodine or technetium will be almost homogeneous.[61] The radioiodine dosage may be selected using different methods, such as the delivered dose method (e.g., 200 Gy), megabecquerel-per-gram (e.g., 3.7-7.4 MBq/g), or fixed dosage (e.g., 740 MBq).[35] Dosages smaller than 370 MBq result in treatment failures in 25% or more.[62]

In toxic multinodular goiter, the uptake of ^{131}I throughout the gland is often very inhomogeneous. The radioiodine dosage per gram thyroid tissue should be lower than in cases of toxic adenoma if ablation of normal thyroid tissue is to be avoided. In some patients goiter reduction is a secondary therapy goal, under which circumstances posttherapeutic hypothyroidism may be inevitable. The most commonly used dosage schemas for radioiodine treatment of toxic multinodular goiter are the megabecquerel-per-gram method (e.g., 3.7-7.4 MBq/g) and the fixed dosage method (e.g., 185-5500 MBq).[35] Toxic adenoma and toxic multinodular goiter together now contribute about 25% to all radioiodine treatments in The Netherlands.

1.4.2 Nontoxic goiter

The term nontoxic goiter refers to thyroid gland enlargement that is not associated with hyperthyroidism. The disease may either be sporadic or, in iodine

deficient areas, endemic. It is the most common thyroid problem encountered in clinical practice with a prevalence of less than 1% of the male population up to 5% in females – which is suggestive of a hereditary factor. There is an increase in frequency after the age of 45 to about 9% in women aged 75 or older.[63] When untreated, nontoxic goiter increases about 20% in volume every 9 months.[51] Obstructive symptoms and cosmetic problems are the predominant clinical features, and frequently a reduction of the thyroid mass is necessary. In one double-blind controlled study it was shown that this therapy is not effective in shrinking goiters.[64] Life-long levothyroxine (LT_4) therapy has an effect in shrinking goiters and in arresting further growth,[51] but it is associated with serious side effects such as decreased bone mineral density and cardiac complications. Surgery is very effective, but it carries the same risks as in toxic multinodular goiter.[65-67] After subtotal thyroidectomy a recurrence of the goiter has been found in almost 20% of the patients.[66] For these patients, as well as for those with high surgical risk, a nonoperative reduction of the thyroid volume is desirable.

For a long time radioiodine has not been regarded as a therapeutic option, but since the 1990s it has been used to reduce the goiter volume in this patient group.[68-72] In most of these studies the volume reduction was measured by ultrasound. Ultrasound equipment is relatively inexpensive, widely available, seemingly easy to operate, and without harmful side effects. Ultrasonographic thyroid measurements have been reported chiefly in healthy volunteers and in patients with Graves' disease. For large nodular goiters with intrathoracic extension of the thyroid gland, this technique is much less reliable. Observer dependency is substantial in the case of large goiters, because of the impossibility to visualize the whole gland in one view. CT volume measurements of thyroid specimens are within 5-10% of direct volume measurements. There have been several reports confirming the accuracy of volumetry with CT in patients with nodular goiters.[70,73-75]

1.4.3 Graves' disease

Graves' disease is an autoimmune disease that is characterized by a course of remission and relapse. The hyperfunctioning of the thyroid is initiated by stimulatory autoantibodies directed to the thyrotropin (TSH) receptor protein on thyrocytes.[76,77] Graves' disease is more common in young adults (15-35 years), with an estimated incidence of between 2-5 cases per 1000 individuals, and is about four times more frequent in women than in men.[63] Three not entirely satisfactory therapeutic options exist: thionamide drug therapy, subtotal thyroidectomy, and radioiodine.[53,78-80]

In areas where the diet contains sufficient iodine, like most of the USA, 11-54% of cases are still euthyroid one year after ATD treatment.[77] Analyses of prospective studies and follow-up studies in Europe have shown higher percentages (50 ± 7%) one year after therapy.[30,77,81]

Subtotal thyroidectomy is an immediate and effective form of treatment; however, it is associated with complications such as hypothyroidism, hypoparathyroidism, laryngeal nerve palsy, bleeding and infections. The relapse rate after surgery is about 20%.[30,65,67]

Radioiodine has been recommended as the best treatment option for patients with Graves' disease because of its ease, low cost and low rate of serious complications.[53,79,80,82] It is based on the unique ability of the thyroid follicular cells to trap and organify iodine.[17] After intracellular uptake, radioiodine causes sterilization and destruction of a number of these cells: the effect is to a large extent dependent from the absorbed radiation dose. The relative risk of late hypothyroidism after ^{131}I therapy is approximately 20% after two years, and additionally 2-4% each year after treatment; the accumulated incidence of late hypothyroidism after standard radioiodine treatment is 40-70%.[53,80,83,84] In comparison, late hypothyroidism is found in 20-50% of surgical cases.[53,67] No mathematical relationship has been found between the administered ^{131}I dosage, or the ^{131}I dosage per gram thyroid tissue, and the appearance of hypothyroidism.[53,80] The risk of hypothyroidism is connected with the autoimmune nature of the disease and with the radiosensitivity of the thyroid tissue.[79,80,84] With an administered dosage of 1.85 MBq (50 µCi) per gram thyroid tissue the relapse rate is more than 50% after one year, and a dosage of 5.55 MBq (150 µCi) per gram is associated with a hypothyroidism rate of 30% or more after one year.[22,53,80,85] Therefore 3.7 MBq (100 µCi) per gram may be preferable.

Dosage strategies

Controversies over the preferred dosage regimen have existed ever since the first therapeutic dose, notwithstanding the wealth of publications over nearly six decades.[86] The indications, the therapy objective and the ^{131}I dosage vary considerably between institutions and countries.[87] The therapeutic aim varies from restoring euthyroidism with the lowest possible dose to quick induction of hypothyroidism. Two dosage strategies have been advanced for Graves' hyperthyroidism: the fixed dosage method (with or without modification factors for thyroid size, uptake, or severity of the disease), and the microcurie-per-gram method.[22] The latter seemingly more sophisticated method, while requiring a surplus of time and effort, thus far has not brought the reward of superior clinical effectiveness.

The course of Graves' hyperthyroidism is one of remissions and exacerbations over a protracted period of time unless the gland is destroyed by surgery or radioiodine. Hypothyroidism after many years is a frequently observed end stage (up to 70% of all patients). Because of this, many physicians favor high doses of ^{131}I to render the patient hypothyroid in the shortest possible time and follow this by permanent levothyroxine (T_4) replacement therapy.[80,88] In this strategy the high incidence of early hypothyroidism is counterbalanced with a low recurrence rate. In the American clinical tradition, any treatment that results in a cure of hyperthyroidism is regarded as successful. This is not reflected in Dunn's expressed opinion, less than twenty years after the very first patient was treated, that "hypothyroidism is the most important undesired effect of radioiodine therapy".[89] The latter view is shared by many clinicians, especially in Europe, who consider it suboptimal to replace one disease by another (iatrogenic) disease which is irreversible.[90] They are inclined to see euthyroidism as the only true curative outcome, even if this involves repeated therapeutic interventions in a large minority of their patients. In this approach, it is common practice to start with ATD treatment, later combined with levothyroxine. At discontinuation of the medication after 1-1.5 years, 20-50% of the patients will already have stabilized disease with normal thyroid function.[30,77,81] In patients with recurrent hyperthyroidism reinstating the medication appears to be of little use. Although the 1-year follow-up results in this strategy are poor when compared with the 'American' situation, the overall cure rates in the end are similar. The benefit from a more conservative approach is the larger number of patients who regain a normal thyroid function for a number of years. Not only is a prolonged state of well-being without dependency on drugs looked upon as highly desirable by the patients, the functioning of the individual may be better served with normal endogenous thyroid function than with external induction of constant thyroid hormone levels. In patients with hypothyroidism it has been demonstrated that partial substitution of triiodothyronine (T_3) for thyroxine improves mood and physiological and neuropsychological functions.[91] Although this observation is very suggestive of a specific effect of T_3, its preliminary nature is being stressed in an editorial comment.[92] In a survey concerning the patient valuation of radioiodine treatment of Graves' disease, 33% of patients who were biochemically well adjusted to thyroxine still had problems with mood, weight, and fatigue.[90]

The becquerel-per-gram model presents a rational but incomplete radiobiological principle for radioiodine treatment of Graves' disease. It incorporates some of the most important individual biological parameters. There is ample evidence that with this approach normal thyroid function may be preserved in

a large majority of patients with toxic goiter, nontoxic goiter and toxic adenoma. There seems to be no plausible reason why the same principle would not apply in Graves' disease. The modest success rate of radioiodine therapy in Graves' disease is more likely to be associated with the changes in disease activity, with medical interventions, and possibly with technical imperfections in the pre-therapeutic work up of patients. For these reasons, the bequerel-per-gram model may need adjustment.

Of the presently known prognostic factors concerning therapy outcome, the two most important are thyroid volume and radioiodine uptake. Both factors are expressed in the standard formula for therapeutic dosage calculation:

$$D = V \times (100\%/U) \times C,$$

where D is the administered ^{131}I dosage (in MBq), V is the thyroid volume, U equals the 24-h radioiodine uptake percentage, and C is a constant (usually 3.7 MBq/g in patients with Graves' disease).[22]

Protocols for radioiodine uptake measurements tend to be directed towards physical quality assurance and quality control rather than towards clinical and biological aspects.[94-96] In patients with Graves' disease, the accuracy and precision of planar ^{99m}Tc-pertechnetate thyroid scintigraphy in the assessment of the functioning thyroid volume are not well known. In view of the important role that is attributed to the thyroid volume in most radioiodine therapy dosage protocols, thyroid volume measurements should be done with an acceptable degree of accuracy.

1.5 Aims of this thesis

This thesis is aimed at the optimization of the radioiodine therapy dosage assessment in patients with benign thyroid disorders. The research converges on the following areas: establishment of rational therapeutic aims, identification of factors that influence the clinical outcome, and optimization and standardization of procedures for radioiodine uptake and thyroid volume measurements. A number of specific questions were formulated:

1 What is the clinical outcome after standardized radioiodine therapy for toxic adenoma and toxic multinodular goiter?
2 Can adequate goiter reduction be obtained with radioiodine therapy in patients with nontoxic goiter?
3 Is the required radioiodine dosage for the treatment of Graves' disease linearly related to the thyroid's volume and the radioiodine uptake, as is implicated by the standard dosage formula ($D = V \times [100\%/U] \times C$)?

4 How stable are the 5-h and 24-h radioiodine uptake values over time in patients with Graves' disease?
5 Does the timing of the radioiodine uptake measurement influence the clinical outcome of radioiodine treatment in patients with Graves' disease?
6 What is the accuracy of different imaging modalities in the assessment of the thyroid volume in patients with Graves' disease?

In the final chapter, a general discussion is presented of radioiodine treatment for benign thyroid disorders, with an emphasis on the difficulties that are encountered in the dosage assessment in patients with Graves' disease. General directions are indicated for adjustments to the standard radioiodine therapy dosage algorithms. Issues for future research are also proposed.

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Chapter Two

Standardized radioiodine therapy for toxic nodular thyroid disease

Johannes W. van Isselt, Cornelis J.M. Lips, Peter P. van Rijk,
John M.H. de Klerk

Summary

Toxic adenoma (TA) and toxic multinodular goiter (TMNG) are often viewed as distinct and separate entities, but they represent a spectrum of thyroid tissue disorders characterized by nodular growth and autonomous hyperfunction. Recent advances in molecular biology have helped to clarify the origin of toxic thyroid nodules. Gain of function mutations in the TSH receptor gene which activate the TSH receptor in the absence of its ligand result in the accumulation of cAMP. Cyclic AMP stimulates both the growth and differentiated thyroid function of the thyroid gland. Medical treatment cannot lead to a definitive cure of TA or TMNG. Since the decline in numbers of thyroid surgery, radioiodine has become the treatment modality of first choice also for TA and TMNG.

The clinical outcome of radioiodine in these disorders was studied in a retrospective follow-up study. Linear regression and ANOVA analysis were used to analyze the clinical results in 107 patients who had been treated with radioiodine for TA or TMNG, and for whom follow-up data were available at least one year after treatment.

In patients with TA, a single treatment resulted in 75% euthyroidism, 11% hypothyroidism, and 14% persisting hyperthyroidism. Euthyroidism was regained in all patients with a relapse who received repeat radioiodine treatment. Otherwise no change occurred during extended follow-up (1.5-8 yrs). In patients with TMNG, 70% of the patients became euthyroid, 22% hypothyroid, and 8% suffered a relapse of hyperthyroidism. Repeat radioiodine treatment was successful in all cases.

Good clinical results can be obtained with standardized radioiodine treatment in patients with toxic adenoma and in patients with toxic multinodular goiter. Dosage schemas vary widely between different research groups. Others had very good results with a fixed dosage (740 MBq) in patients with TA. It is argued that scintigraphic weight estimates of thyroid adenomas may be too inaccurate to allow their use for dosage calculation purposes. Ultrasonography may be a better alternative.

2.1 Introduction

Adenomas are usually solitary nodules that may occur at any age from the teens to the elderly. Only about one quarter of these are associated with hyperthyroidism, which usually sets in about 15 years after the first presentation of the nodule.[1,2] Most nodules degenerate during this process; nontoxic autonomously functioning thyroid nodules are in fact much more common than toxic lesions.[3] In toxic multinodular goiter multiple hyperfunctioning and hypofunctioning nodules are present in the thyroid. The iodine uptake capacity of these follicular nodules is as heterogenic as that of individual thyroid cells.[4] In toxic adenoma and in toxic multinodular goiter T_3 toxicosis, thyrotoxicosis with elevated serum T_3 concentrations and less markedly elevated serum T_4 concentrations, is relatively frequent.[3,5] The state of the art in the diagnosis and treatment of toxic nodular thyroid disease has been reviewed in two recent publications.[3,6]

Toxic adenoma (TA) and toxic multinodular goiter (TMNG) are often viewed as distinct and separate entities, but they represent a spectrum of thyroid tissue disorders that are characterized by nodular growth and autonomous hyperfunction.[1,7,8] After the first clinical observations by Plummer (1913) and Goetsch (1918) and the later histopathologic studies by Studer,[4] recent advances in molecular biology have had a considerable impact on several aspects of thyroidology. Studies of ras proto-oncogene expression have shown that micronodules develop from bursts of follicular cell growth.[3] The identification and functional characterization of mutations in the TSH receptor gene which activate the TSH receptor in the absence of its ligand provide an explanation for the molecular mechanism which is most likely responsible for the majority of the hyperfunctioning thyroid adenomas.[9,10] Somatic gain of function mutations in the TSH receptor itself or in the Gsα protein linked to it result in the accumulation of cyclic adenosine monophosphate (cAMP).[11] cAMP stimulates the growth and differentiated thyroid function of the thyroid gland. Activating TSH receptor mutations were identified in 20-80% of thyrotoxic nodules and multinodular goiters.[12]

Therapeutic options

Antithyroid drugs (ATD) are capable of normalizing FT_4, FT_3 and TSH concentrations in both TA and TMNG, but thyrotoxicosis recurrence after cessation of therapy is greater than 95%.[13-15] The alternative, life-long antithyroid drug (ATD) or combined ATD and levothyroxine (LT_4) medication, bears the risk of serious side effects.[16-18] Rational use can be made of ATD to render the patient euthyroid

before more definitive therapy. This reduces the risk of acerbations of hyperthyroidism after radioiodine therapy or surgery.[6,19,20] TA is different from TMNG because of its singular occurrence, which offers a better target for therapeutic interventions. Subtotal thyroidectomy provides fast results. There is a recurrence rate of only 10-20%, but a hypothyroidism rate of about 90% at one year follow-up.[21,22] Surgical hazards are infrequent, but potentially serious. They have contributed to the continuing shift from surgery towards radioiodine as the treatment of choice for toxic nodular thyroid disorders, as well as for other benign thyroid disorders.[23] For the treatment of a solitary TA in young patients many physicians prefer unilateral lobectomy over radioiodine therapy because of the reportedly increased risk of nodular disease developing after ^{131}I.[24] An alternative therapeutic approach for solitary TA is ultrasound-guided percutaneous ethanol injection, which has a cure rate of about 66% one year after treatment.[25] It induces coagulative necrosis of the follicular cells, resulting in a reduction of the nodule size. The experience with this treatment form is limited.

Patients with TA and TMNG now represent about 20-25% of all referrals for radioiodine treatment in The Netherlands. Theoretically TA forms a very good indication for radioiodine therapy. The mass of the adenoma rather than that of the thyroid as a whole determine the amount of radioiodine. Relatively large amounts of radioiodine can be used for the ablation of the target tissue (the adenoma) while the functioning of the surrounding tissue can be relatively spared in the process. However, in a recent report it was indicated that the radiation absorbed dose to the normal thyroid tissue is higher than has generally been assumed.[26] In toxic multinodular goiter the ^{131}I uptake throughout the thyroid gland is inhomogeneous. If the normally functioning thyroid tissue is to be spared, very high radioiodine dosages should not be administered. With an amount of 3.7 MBq (100 μCi) per gram functioning thyroid tissue, normalization of the thyroid function is common, and the risk of hypothyroidism is low.[19,20,27-31] As the multinodular goiter itself remains,[5] other nodules may become toxic when endogenous TSH increases following radioiodine therapy. For this reason repeat dosages of ^{131}I may be required years after the first treatment.[5]

The aim of this study was to assess the functional thyroid status after standardized radioiodine treatment in patients with toxic adenoma or toxic multinodular goiter.

2.2 Patients and methods

Patients

A retrospective follow-up study was done in 44 (31 female/13 male) patients with toxic adenoma and 63 (56 female/7 male) patients with toxic multinodular goiter who had been referred for radioiodine treatment, and for whom follow-up data at least one year after radioiodine treatment were available. The diagnosis at 1-year follow-up was based on the physician's clinical impression and on serum TSH (normal concentration 0.35-6.0 mIU/l). Extended clinical follow-up data was available for all patients (see table 2.1), except 6 patients with TA and 29 patients with TMNG who were all interviewed by telephone. In these cases the diagnosis was based on the patient history and the use of thyroid medication. One-year follow-up data were not available for 9 patients with TA and for 17 patients with TMNG (26/133, or 20% of total).

ATD had been prescribed to 7 patients (16%) with toxic adenoma, ATD + LT_4 to 1 patient (2%), no medication to 36 patients (82%). All medication had been discontinued at least 3 days before radioiodine treatment. ATD medication was not reinstalled after ^{131}I therapy unless persistent hyperthyroidism had been diagnosed. LT_4 was prescribed only to those patients who became hypothyroid after radioiodine treatment. Of all patients with TMNG 29 (46%) had no thyroid medication at all before radioiodine treatment. 34 (54%) had received some form of medication, for a mean period of 2.9 years (2 months-18 years); 15 patients (24%) received ATD only, 16 (25%) had ATD + LT_4, and 2 (3%) had LT_4 monotherapy. One patient had received symptomatic treatment with β-adrenergic blocking drugs only.

Methods

Before radioiodine therapy, hyperthyroidism had been confirmed by biochemical assays of TSH, T_3 and FT_4. All patients had also suffered from clinical symptoms of hyperthyroidism. A diagnosis of uninodular or multinodular goiter had been confirmed by palpation and by ^{99m}Tc-pertechnetate thyroid scintigraphy. Thyroid scintigraphy was also used for estimations of the size of the adenoma or goiter. In patients with TA an estimation was made of the degree of suppression of the normal extranodular thyroid tissue; scintigrams were scored as (near) total suppression (uptake in the adenoma > 5 × that in normal thyroid; present in 76% of all cases), moderate suppression (uptake in the adenoma 2-5 × that in normal thyroid; present in 21%), or slight suppression (uptake in the adenoma < 2 × that in normal thyroid; present in 3%).

The therapeutic ^{131}I dosage was standardized by using the formula:

$$D = W \times [100\%/U] \times C,$$

where D is the administered ^{131}I dosage (in MBq), W is the thyroid weight (in grams), U is the 24-h ^{131}I uptake (in %) and C is a constant (equaling 3.7 MBq per gram functioning thyroid tissue for patients with multinodular goiter and 7.4 MBq per gram adenomatous tissue for patients with toxic adenoma).

The descriptive statistics concerning age, 5-h and 24-h radioiodine uptake, weight of the adenoma or the goiter, the administered radioiodine dose, the

Table 2.1 Patient data.

toxic adenoma (n = 44)

	n	mean ± sd	range
female	34		
male	10		
age		56.0 ± 15.3	15-81
administered dose ^{131}I (MBq)		349.5 ± 224.0	84-950
follow-up (yrs)		3.2 ± 1.8	1.5-8.0
5-h ^{131}I uptake (%)		25.6 ± 11.5	11-69
24-h ^{131}I uptake (%)		41.6 ± 12.4	22-66
weight of adenoma		16.1 ± 11.2	4-44
presence of nodule (yrs)		(?)	(?)
presence of hyperthyroidism (yrs)		2.2 ± 3.7	0.1-17.0

toxic multinodular goiter (n = 63)

	n	mean ± sd	range
female	56		
male	7		
age		65.2 ± 12.4	36.6-84.0
administered dose ^{131}I (MBq)		892.4 ± 667.1	174-3772
follow-up (yrs)		3.5 ± 1.7	1.7-8.7
5-h ^{131}I uptake (%)		37.0 ± 21.2	8-92
24-h ^{131}I uptake (%)		50.7 ± 18.1	20-87
weight of goiter		117.3 ± 73.4	27-272
presence of goiter (yrs)		10.9 ± 11.7	1-50
presence of hyperthyroidism (yrs)		3.9 ± 5.7	0.3-26.0

duration of the follow-up, the duration of the presence of the adenoma or goiter and the duration of the hyperthyroidism for all patients are summarized in table 2.1.

2.3 Results

Toxic adenoma

Euthyroidism was reached in 33/44 patients (75%) one year after treatment, 5 patients (11%) became permanently hypothyroid, and 6 patients (14%) suffered a relapse of thyrotoxicosis.

For all patients an extended follow-up was available (see table 2.1). During this follow-up period, no change was noted in any of the patients who had become euthyroid nor in those who had become hypothyroid. 4 of the 6 patients with a relapse of hyperthyroidism had had repeat radioiodine treatment, and all four had regained euthyroidism. In the remaining two patients ATD had been reinstalled (since 22 months and 36 months, respectively). No side effects of the radioiodine treatment during the follow-up period had been reported by the referring physicians in the correspondence, or by the patients during the telephone interviews.

The degree of suppression on thyroid scintigraphy had no bearing on the clinical outcome. (Near) total suppression was in proportion of the clinical outcome (13% in patients who later became hypothyroid, 16% in those who became hyperthyroid). Moderate or slight suppression was seen only in those patients who later became euthyroid. Of all patients who regained euthyroidism, 67% had (near) total, 30% moderate and 3% slight suppression on thyroid scintigraphy. No statistically significant relations were found between the clinical outcome and the radioiodine uptake, the size of the nodule, the patients' age or gender, the administered ^{131}I dosage, or the duration of the nodule or of the hyperthyroidism.

Toxic multinodular goiter

One year after radioiodine treatment, euthyroidism was reached in 44 patients (70%), hyperthyroidism persisted in 14 patients (22%), and 5 patients (8%) became hypothyroid. For all patients extended follow-up was available (see table 2.1). During this follow-up 3 of the patients who had initially become euthyroid (5%) suffered a relapse of hyperthyroidism, 1 (2%) became hypothyroid after 2.5 years, and 40 (63%) remained euthyroid. In 3/6 patients with a hypothyroid outcome, the hypothyroidism was only transient. 11/14 patients with persist-

ent hyperthyroidism had repeat ^{131}I treatment, and euthyroidism was regained in all of them; in the other 3 ATD had apparently been reinstalled (for 1.5-2.5 yrs since radioiodine treatment). At long-term follow-up, the results were: 54 (86%) euthyroidism, 3 (5%) hypothyroidism, and 6 (9%) hyperthyroidism. Three of the latter were biochemically hyperthyroid but had no longer any clinical symptoms. No side effects from the radioiodine treatment during the follow-up were reported by the referring physicians or by the patients themselves. There were no statistically significant relations between the clinical outcome and the radioiodine uptake, the size of the goiter, the patients' age or gender, the administered ^{131}I dosage, or the duration of the goiter or of the hyperthyroidism.

2.4 Discussion

With a single radioiodine dosage good clinical results were obtained in patients with toxic adenoma (75% euthyroidism, 11% hypothyroidism, 14% relapse) over a follow-up period varying from 1 to 8 years. In patients with toxic multinodular goiter, 70% became euthyroid, 8% became hypothyroid and 22% suffered a relapse. Repeat radioiodine therapy (3 for TA, 11 for TMNG) was successful in all patients with a relapse. The retrospective nature of this study is a disadvantage because of incomplete data retrieval and the inability to set uniform end-points. Although the risk of patient selection bias cannot be denied, a relatively high percentage of patients who had dropped out of the regular clinical follow-up but who could be reached for telephone interviews appeared to have regained euthyroidism (90**%** of TA patients, 85% of TMNG patients). This may have induced these patients' discontinuing their regular check-up visits. It seems fair to assume that the missing data in 20% of the patients constitutes a selection bias in the same direction.

The present results are in fair agreement with those of others, although most authors find somewhat fewer relapses and higher hypothyroidism rates for toxic multinodular goiter.[19,20,27-32] In a number of studies, all with different methods of dosage calculation, the recurrence rate for TMNG varied between 2% and 52%.[32-38] The lowest failure rate was obtained with a fixed dosage of 740 MBq (20 mCi).[32] It seems contradictory that with this regimen the hypothyroidism rate (6%) was also slightly lower than what we found.

More accurate measurements of the autonomously functioning thyroid volume may be worthwhile both in TA and in TMNG.[39] Scintigraphic estimations of the volume of adenomas are difficult because of the very high uptake; these measurements may be too inaccurate to allow their use for dosage calculation

purposes. Ultrasonography is probably the most appropriate modality for such measurements. Inaccuracy of our volume estimations may be one of the reasons that a fixed dosage schema outperformed our individualized dosage regimen. Whatever the cause may be, at this stage a fixed dosage regimen seems preferable over individualized regimens.

Effective ways to determine the autonomously functioning volume of the thyroid facilitate estimations of the radiation dose.[39] Large differences in the effective half-life of thyroidal radioiodine, varying from 1.7 to 106.5 days, have recently been demonstrated in patients with toxic adenoma (data for toxic multinodular goiter are unknown).[26] This is bound to have a bearing on the effect of a given amount of ^{131}I. Accounting for the effective half-life leads to a better definition of the delivered radiation absorbed dose in these patients.

In patients with toxic adenoma the autonomy of the hyperfunctioning tissue can easily be demonstrated by 'suppression imaging', i.e. thyroid scintigraphy after administration of T_3 which reduces the uptake by the normal thyroid tissue through suppression of TSH. There is evidence that this intervention also improves the precision of the calculations of required therapy dosages.[28] This procedure must however be carried out with caution, because it may provoke atrial fibrillation or 'thyroid storm' in elderly patients.[3]

Lithium medication before and during radioiodine therapy may be considered, especially in patients with large goiters. The overall net effect of lithium is a prolonged retention of thyroidal (radio)iodine.[40-42] Consequently the effect of a given radioiodine dosage is increased, or inversely a lower dosage will suffice to obtain the same effect. However, it is unclear whether a quantitative relationship exists between lithium serum concentration and the increase of the thyroidal radioiodine retention. The risk of increased hypothyroidism rates may be greater than the potential profit of lower dosages. Therefore, at this stage no rational use can be made of adjuvant lithium treatment.

It is remarkable that many patients with TA or TMNG are still being treated with antithyroid drugs, as thyrotoxicosis recurrence after cessation of therapy is almost certain to occur.[13-15]

2.5 Acknowledgements

The authors gratefully acknowledge the persistence of Bart de Keizer, B.Sc., Diane Helmink, B.Sc. and Dr. Miriam Boteanu in gathering the patients' follow-up data. They thank Ms. Sally Collyer for scrutinizing the English text and for her valuable critical remarks.

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Chapter Three

Iodine-131 therapy in sporadic nontoxic goiter

John M.H. de Klerk, Johannes W. van Isselt, Aalt van Dijk, Marc E. Hakman, Frank A. Pameijer, Hans P.F. Koppeschaar, Pierre M.J. Zelissen, Jan P.J. van Schaik, Peter P. van Rijk

Published in the Journal of Nuclear Medicine 1997; 38: 372-376

Summary

The effect of radioiodine in the treatment of nontoxic goiter is seldom evaluated quantitatively. The aim of this study was threefold: (i) to assess the effect of ^{131}I on goiter volume, (ii) to establish a relationship between CT volume reduction and the amount of radioactivity taken up by the thyroid and (iii) to assess the precision of scintigraphic thyroid volume measurements.

In 27 patients with sporadic nontoxic goiter, the thyroid volume was estimated from a ^{99m}Tc-pertechnetate scintigram. Two different models (cylinder model and surface model) were applied. The ^{131}I dosage varied between 507 and 3700 MBq. In all patients, noncontrast CT scanning of the neck was performed before therapy and 1 year after therapy.

The mean CT thyroid volume before therapy was 194 ± 138 ml. A reduction was obtained in all patients and averaged 34% ± 17%. The volume reduction measured by CT correlated well with the amount of ^{131}I in the thyroid ($R = 0.70$). In thyroids larger than 200 ml, both scintigraphic volume estimation methods were imprecise. For smaller volumes, the surface model was superior. Hypothyroidism developed in 14% of the patients. No other side effects occurred.

Iodine-131 therapy for volume reduction in nontoxic goiter is a safe and effective treatment. For scintigraphic estimation of thyroid gland volumes smaller than 200 ml, the surface model is preferred.

3.1 Introduction

The term nontoxic goiter refers to thyroid gland enlargement unassociated with hyperthyroidism. It is the most common thyroid problem encountered in clinical practice. Thyroid nodules are detected in less than 1% of the male population but occur in 5% of all females. There is an increase in frequency after the age of 45 to 9% in women aged 75 or older.[1] Nontoxic goiter increases 20% in volume every 9 months.[2] Obstructive symptoms and cosmetic problems are usually predominant in the clinical picture, and volume reduction is frequently necessary.

Thyroid hormones have been used to shrink goiters and to arrest further growth.[2] In a double-blind controlled study, it has been shown that levothyroxine (LT_4) suppressive therapy is not effective in shrinking goiters.[3] Furthermore, lifelong suppressive LT_4 therapy is associated with side effects such as decreased bone mineral density and cardiac arrhythmias. Surgical treatment is effective but carries the risk of recurrent laryngeal nerve damage and permanent hypoparathyroidism.[4] Transient voice disabilities and hypothyroidism are relatively frequent complications (20% and 10%, respectively).[5] Moreover, after subtotal thyroidectomy, a recurrence of the goiter has been found in almost 20% of the patients.[5] For these patients, as well as for those with high surgical risk, a nonoperative reduction of the thyroid volume would be desirable.

Over decades, radioiodine (^{131}I) has proved to be effective in the treatment of hyperthyroidism with diffuse or nodular goiters. ^{131}I also has been used to shrink the goiter in nontoxic patients.[6-10] In most studies, volume reduction was measured by ultrasonography (US). The use of US for thyroid volume estimations has been studied chiefly in normal thyroids and diffuse goiters. For large multinodular goiters, however, ultrasound becomes less reliable because of frequent intrathoracic extension. Furthermore, US is observer-dependent, especially in large goiters in which it is not possible to visualize the whole gland in one view. Thyroid gland volume reduction by ^{131}I has rarely been evaluated by more reliable methods such as CT or MRI. The aims of this study were to determine thyroid gland volume reduction by therapeutic dosages of ^{131}I in patients with nontoxic goiter using CT as a gold standard; to relate this volume reduction to ^{131}I uptake by the thyroid gland; and to determine the reliability of scintigraphic volume measurements in patients with nontoxic goiter.

3.2 Methods

Patients

Twenty-seven patients with sporadic nontoxic goiter were included in the study. The group consisted of 22 women (mean age 57 yr, range 36-78 yr) and 5 men (mean age 62 yr, range 50-81 yr). Patient characteristics are summarized in table 3.1. Inclusion criteria for ^{131}I treatment were growth of the goiter, obstructive or cosmetic symptoms, clinical euthyroidism and a preference of the patient for ^{131}I therapy over surgery. Those having had previous partial thyroidectomy or use of LT_4 suppressive therapy were not excluded. None of the patients had

Table 3.1 Patient characteristics.

patient no.	sex	age (year)	24-h uptake* (%)	dosage (MBq)
1	F	49	29	630
2	M	50	48	1245
3	M	71	32	740
4	F	78	37	1480
5	M	58	39	1850
6	F	48	40	555
7	F	50	38	555
8	F	60	41	925
9	F	66	31	1480
10	F	69	83	600
11	F	36	40	900
12	F	68	35	740
13	F	48	42	518
14	F	51	32	1900
15	F	62	21	925
16	F	64	66	507
17	F	43	60	1850
18	F	55	39	1295
19	F	62	37	2750
20	F	55	40	1295
21	F	66	45	800
22	F	57	34	1480
23	F	59	27	1850
24	F	42	64	1480
25	M	51	41	3700
26	F	65	44	1600
27	M	81	37	1160

* Normal value for 24-h uptake: < 30%.

previously undergone ^{131}I therapy. Before treatment, the plasma TSH concentration was within the normal range (0.35-6.0 mU/l) in 11 patients and subnormal in 15 patients (< 0.35 mU/l). In one patient, the plasma TSH concentration was not available. In all patients, plasma total T_4 (TT_4) and free T_4 (FT_4) concentrations were in the normal range (60-140 nmole/l and 6-23 nmol/l, respectively). Two patients could not be evaluated for thyroid volume reduction, as they had undergone partial thyroidectomy or a second ^{131}I treatment within the 1-year follow-up period.

Imaging protocol

CT and thyroid scintigraphy were performed and ^{131}I uptake was measured within 4 weeks before radioiodine treatment. Thyroid scintigraphy was performed after intravenous administration of 80 MBq ^{99m}Tc-pertechnetate on a round field of view or rectangular gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator. Two different scintigraphy-based methods were used to estimate thyroid volume.

In the first, the cylinder formula (Vcyl) is applied to both thyroid lobes:

$$Vcyl = L \times (0.5W)^2 \times \pi,$$

where V represents the volume of each lobe, L is maximum length in centimeters, and W is maximum width in centimeters (figure 3.1).

In the second method, the surface formula (Vsurf) by Himanka and Larsson[11] is applied:

$$Vsurf = 0.33 \times A^{1.5},$$

where A equals the thyroid projection area. This formula was derived experimentally through determination of volumes of surgical thyroid specimens by fluid replacement. Several of these specimens were of irregularly shaped thyroids. For scintigraphic estimation of thyroid surface, regions were drawn automatically using a 30% threshold of the maximum counts per pixel. In cases of very poor thyroid uptake, regions were drawn manually (figure 3.1).

The 5-h and 24-h ^{131}I uptakes were measured after ingestion of 0.37 MBq Na ^{131}I tracer (Canberra 7350-PE collimator with a 2×2-inch NaI crystal). The collimator crystal was centered at the trachea or at the ^{131}I standard placed in a neck phantom at a distance of 25 cm. Thyroid uptake was measured using the formula:[12]

$$^{131}\text{I uptake} = \frac{\text{neck counts} - \text{thigh background counts}}{\text{standard counts} - \text{room background counts}} \times 100\%$$

Calculation of the therapeutic ^{131}I dosage included corrections for thyroid weight and 24-h radioiodine uptake, according to the formula:

$$D = (100/U) \times Vcyl \times C,$$

where D is the administered dose of ^{131}I (in MBq), U equals the 24-h uptake (%), Vcyl (which was used routinely for dosage calculations) represents the thyroid volume (in ml) and C was set at 3.7 MBq/ml. Nine patients received a lower dosage. Corrections were made: (a) for scintigraphically active thyroid volume, (b) in case D exceeded 3700 MBq or (c) if the estimated period of mandatory hospitalization in an isolated room was considered unacceptable. The dosage in these nine patients was 2.1 ± 0.6 MBq/ml. Before ^{131}I therapy, patients on LT_4 had discontinued this medication for at least 4 weeks.

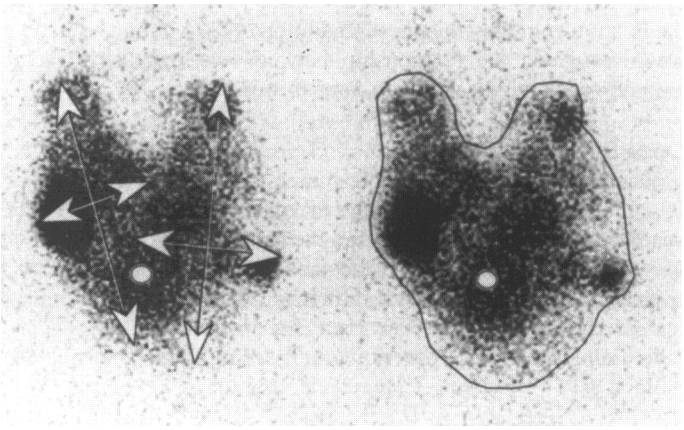

Figure 3.1 Examples of scintigraphic volume estimation with the cylinder (left) and volume models (right) in patient 9.

CT was used as the gold standard for measurement of thyroid volume before treatment (CT_{pre}). The use of CT for measuring thyroid volume is both accurate and reproducible.[13] Noncontrast CT of the thyroid gland was performed using 5-mm contiguous sections. Volume measurements were performed using the summation-of-areas technique. At 12 ± 1 month(s) after treatment, CT (CT_{post}) was repeated. $CT_{pre} - CT_{post}$ provides the absolute volume reduction, while $[(CT_{pre} - CT_{post})/CT_{pre}] \times 100\%$ represents the relative volume reduction. In addition to CT volume reduction, we investigated the relationship between the two scintigraphic methods of volume estimation used in this study.

Dose effect relationship

The amount of ^{131}I per ml CT volume corrected for 24-h uptake (C_{CT}) is related to the percentage of volume reduction (ΔCT). To describe this relationship, we used the sigmoid E_{max} model, which is the simplest model for the adequate description of drug effects over the whole range of concentrations.[14] It is also a mathematical description of the S-shaped curve, known from radiobiological models describing cell-killing.[15] The model is defined as:

$$E = \frac{E_{max} \times C^N}{C^N + EC_{50}^N},$$

where E is effect, C is concentration, N is a number influencing the slope of the curve, E_{max} is the maximum effect attributable to the drug and EC_{50} is the concentration producing 50% of E_{max}.

For this study, the formula can be rearranged into:

$$\Delta CT = \frac{100 \times C_{CT}^N}{C_{CT}^N + EC_{CT50}^N},$$

where ΔCT is the percentage of volume reduction as measured by CT, 100 is the maximum effect and EC_{CT5O} is the concentration per MBq/ml CT volume (uptake corrected), producing 50% volume reduction.

For comparison, the relationship between C_{CT} and ΔCT was also tested by linear regression.

Statistical analysis

Data were analyzed with the SYSTAT 5.2.1 program (SYSTAT, Inc., Evanston, IL). To describe the predictive performance of the scintigraphic volumes, the mean squared prediction error (precision) and mean prediction error (bias) were evaluated.[16] To assess the dose effect relationship, statistical tests were used as mentioned previously.

3.3 Results

Pretreatment thyroid volume measurements by CT and scintigraphy

The results of CT and scintigraphic measurements are summarized in table 3.2. As illustrated in figure 3.2, both scintigraphic volume estimations show a better relationship with CT measurements for smaller goiters (< 200 ml). Table 3.3 shows the performance evaluation of Vcyl and Vsurf.

Table 3.2 CT and scintigraphic* measurements.

patient no.	Vcyl pretherapy	Vsurf pretherapy	CT volume pretherapy	CT volume posttherapy	volume reduction
1	52	51	52	33	37
2	161	153	175	108	38
3	49	58	48	19	61
4	500	254	491	403	18
5	400	305	454	273	40
6	60	50	42	18	57
7	100	80	64	51	20
8	160	120	134	119	11
9	350	222	259	215	17
10	134	142	140	135	3
11	100	97	123	82	33
12	63	91	95	71	19
13	58	63	56	36	35
14	165	307	434	317	27
15	50	44	43	15	65
16	90	84	76	31	59
17	300	287	269	118	56
18	254	233	339	306	10
19	378	293	424	305	28
20	140	143	205		
21	75	94	90	53	41
22	135	82	94	50	47
23	213	161	162	113	30
24	250	173	188	118	37
25	326	282	313	168	46
26	240	190	208	166	20
27	117	176	271		

* All numbers in milliliters, except volume reduction measured by CT (%).

Table 3.3 Performance evaluation of predictors Vcyl and Vsurf using mean error (me), mean squared error (mse) and root mean squared error (rmse) for thyroid gland volumes < 200 ml and > 200 ml.

precision	Vcyl (< 200 ml)	Vsurf (< 200 ml)	Vcyl (> 200 ml)	Vsurf (> 200 ml)
mse (ml^2)	798.6	142.3	11185.3	12577.2
rmse (ml)	28.3	12	106	112
bias me (ml)	10.6	–2.3	–45.0	–88.4

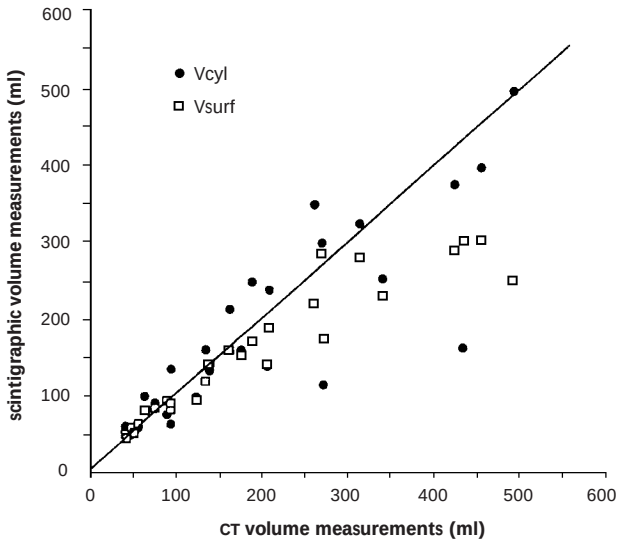

Figure 3.2 Relation between scintigraphic and CT volume measurements of the thyroid before ^{131}I therapy. The line through the origin is the line of identity.

The mean squared error (mse) of the Vsurf method is considerably smaller than the mse of the Vcyl method for thyroid gland volumes smaller than 200 ml, indicating a greater precision of the Vsurf method. In thyroid gland volumes exceeding 200 ml, both methods are inadequate as demonstrated by the magnitude of the mean error.

Iodine-131 dosage versus thyroid volume reduction

The administered dose of ^{131}I ranged from 507 to 3700 MBq (1289 ± 733 MBq, mean ± sd). For the whole group, the mean administered dose corrected for Vcyl and 24-h uptake was 3.3 ± 1.0 MBq/ml Vcyl (range: 1.1-4.8 MBq/ml Vcyl). As mentioned previously, nine patients received a lower dosage. In these patients, the administered dose ranged from 1.1 MBq/ml Vcyl to 2.9 MBq/ml Vcyl (mean: 2.1 ± 0.6 MBq/ml). For the remaining group (18 patients), the dosage was 3.9 ± 0.4 MBq/ml Vcyl (range: 3.5-4.8 MBq/ml Vcyl). Complete CT data were available for 25 patients. All statements about absolute and relative volume reduction are based on CT measurements unless indicated otherwise. Volume reduction was obtained in all patients. The mean volume reduction was 58 ± 48 ml (range: 5-180 ml), and the relative volume reduction was 34% ± 17% (range: 3%-65%).

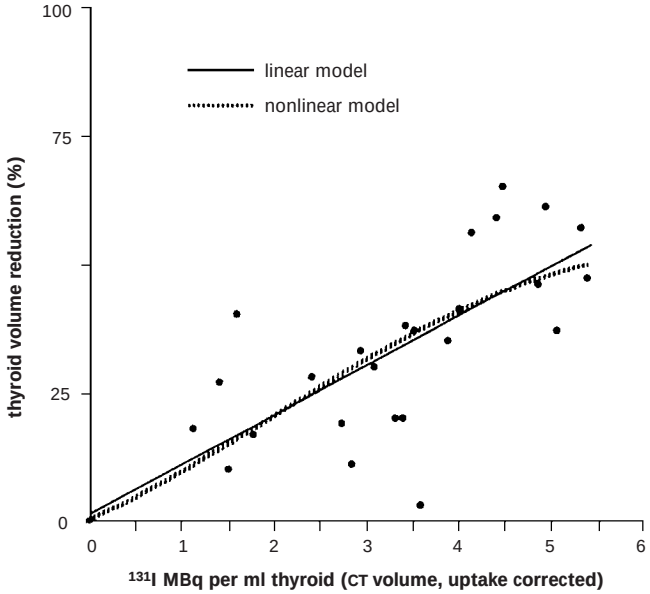

Figure 3.3 Relation between the percentage of volume reduction measured by CT and the amount of ^{131}I uptake per ml CT volume, corrected for 24-h uptake, using linear and nonlinear models.

Dose effect relationship

The relationship between the percentage of volume reduction as measured by CT (ΔCT), and the amount of ^{131}I per ml CT volume corrected for 24-h uptake (C_{CT}) is described by the following formula:

$$\Delta CT = \frac{100 \times C_{CT}^{1.4}}{C_{CT}^{1.4} + 5.3^{1.4}}.$$

Statistical parameters are correlation coefficient (R) = 0.70; F-value = 92; confidence interval of EC_{CT50} = 3.8-6.9 MBq/ml. Linear regression analysis results in a correlation coefficient of the same order of magnitude (R = 0.72, F-value = 26), but from a dosimetric point of view, the sigmoid E_{max} model is preferred. Figure 3.3 depicts the relationship between ΔCT and C_{CT}.

Side effects

In 21 patients, TSH values were available 1 year after treatment. Hypothyroidism (TSH level > 6.0 mU/I) occurred in 3 of 21 patients (14%) (patients 1, 6 and 17).

No other side effects occurred, and in particular, no clinically detectable increase of goiter or exacerbation of obstructive symptoms were noted.

Clinical response

Four (15%) of the 27 patients (patients 1, 12, 20 and 27) were dissatisfied with the volume reduction results, although the objective volume reduction was satisfactory in patients 1 and 12 (37% and 19%, respectively). Within the 1-year follow-up period, patient 20 had a partial thyroidectomy and patient 27 received a second ^{131}I treatment. All other patients reported substantial improvement or complete relief of their complaints.

3.4 Discussion

This study shows ^{131}I to be an effective therapeutic option for the reduction of thyroid volume in patients with sporadic nontoxic goiter, with a relatively small risk of hypothyroidism. Volume reduction was obtained in all patients. With a dosage of 3.3 ± 1.0 MBq/ml, the mean volume reduction was 34% ± 17%, which is of the same order as that reported by other investigators.[8-9]

By using the sigmoid E_{max} mode, and CT-based measurements, we have found a good relationship between thyroid volume reduction and the amount of ^{131}I taken up per ml thyroid volume.

In our patient series, we found a wide range of thyroid volume reduction (3%-65%). No doubt, individual differences in ^{131}I uptake and biological half-life of ^{131}I in the thyroid are responsible for some of the varying responses. However, we propose that inappropriate estimation of thyroid volume, used for dosage calculations, is generally an underestimated factor. Accurate volume estimations are the basis of reliable dosimetric calculations.

It is obvious that if individual dosages can be optimized, benefits can be expected in terms of increased therapeutic effect, minimal risk of hypothyroidism and reduced radiation burden to the patient and the environment.

Thyroid gland volume can be estimated by several methods, of which the CT has a documented high rate of accuracy. Up to 40 years ago, palpation was the only way to estimate the thyroid volume.[11] Afterwards, scintigraphy became the only reliable method. In more recent literature, there are numerous reports confirming the accuracy of CT volume measurements.[17-20] In general, CT volume measurements of thyroid specimens are within 5-10% of direct volume measurements. In an earlier study, our group reported a 5% intra- and inter-observer variability for CT.[13] Some investigators have used MRI.[8,9,21-23] However, no references are available for either CT or MRI measurements for ^{131}I therapy

dosage calculation. Ultrasonography also is recognized as a reliable modality for volume measurements, but only two groups have described the use of this modality for dosage calculation.[6,10] In those series, no thyroid volumes over 300 ml were reported. It is possible that one specific problem with US, i.e. imaging of retrosternally located tissue, is the reason for this. CT and MRI apparently do not have this drawback.

Scintigraphic estimates of thyroid volume using the ellipsoid method are reliable in the case of normal or slightly enlarged thyroid glands with homogeneous iodine uptake. For nontoxic goiter, this is not self-evident. In particular, estimation of actual functioning volume is hampered by physical difficulties, especially the classic problems of contour detection in the presence of high background activity and the effects of finite spatial resolution. Possibly SPECT or PET (using ^{124}I-NaI) measurements are more accurate for dosage calculation purposes than planar scintigraphy.[24-26] This needs to be confirmed by larger studies.

In a scintigraphic study of largely varying thyroid sizes and conditions, Himanka and Larsson found that the area of the frontal projection was the sole variable determining thyroid volume.[11] This study confirms that their surface method (Vsurf) is more accurate than the cylinder method (Vcyl) but only in thyroid gland volumes smaller than 200 ml. For volumes greater than 200 ml, the mse was relatively large both for Vsurf and Vcyl, indicating that scintigraphic volume measurements are unreliable in larger thyroids. In this subgroup, CT is recommended for therapeutic ^{131}I dosage calculations.

3.5 Conclusion

Radioiodine is a safe and effective treatment for volume reduction of nontoxic goiters, leading to a mean volume reduction of 34% ± 17% as measured by CT. For scintigraphic thyroid volume estimation, the surface method (Vsurf) is to be preferred in glands smaller than 200 ml.

3.6 Acknowledgements

We thank the following physicians for patient referrals and for providing follow-up data: M. van Berkel and H.L. van Zijll Langhout, Beatrix Ziekenhuis Gorinchem; R. Colthoff, Ziekenhuis Zonnegloren Soest; R.A. Geerdink, Elisabeth Ziekenhuis Amersfoort; M.H. Helsloot, Diakonessenhuis Utrecht; P. Hengeveld, Overvecht Ziekenhuis Utrecht; F. Kuipers and S.G.L. van der Vegt, Ziekenhuis

Oudenrijn Utrecht; H.G. van Riet, P.L.M. Thunnissen and H.R. de Vries, Lorentz Ziekenhuis Zeist; R.J.M. Croughs, D.W. Erkelens and E.J.K. Zweers, Academisch Ziekenhuis Utrecht. We also thank Ron Jonk for technical assistance and Jan de Groot for photographic assistance.

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Chapter Four

Standardized radioiodine therapy in Graves' disease: the persistent effect of thyroid weight and radioiodine uptake on outcome

Tjerk W.A. de Bruin, Carine D.L. Croon, John M.H. de Klerk,
Johannes W. van Isselt

Published in Journal of Internal Medicine 1994; 236: 507-513

Summary

A single-center prospective follow-up study was conducted to assess the incidence of hypothyroidism, euthyroidism, and recurrent hyperthyroidism following a standard dose of ^{131}I-NaI per gram thyroid tissue, adjusted for radioiodine tracer uptake.

Newly diagnosed patients with Graves' disease (n = 148) received radioiodine treatment at a standard dose of 3.7 MBq (100 μCi) per gram thyroid tissue. Confidence interval testing was done of the resulting thyroid status, defined by biochemical criteria.

The overall cure rate was 70% (103 of 148 subjects), 95% confidence interval 62-77%. A 90% incidence of hypothyroidism was found in patients with a small thyroid (less than 20 grams). Recurrent hyperthyroidism was found significantly more often in subjects with a thyroid weight exceeding 60 grams compared to those who had a thyroid of 9-59 grams. More recurrences were found in subjects in the highest tertile of a 24-h radioiodine uptake test (> 80% uptake) compared to those in the lowest tertile (< 60% uptake).

No uniform treatment results expressed per thyroid weight category were obtained, in spite of standardizing the treatment ^{131}I-NaI dose (3.7 MBq per gram thyroid). Graves' disease patients with a thyroid smaller than 20 grams and those with less than 60% 24-h radioiodine uptake have a 50-90% chance of hypothyroidism at the 12-month follow-up.

4.1 Introduction

Graves' disease is an autoimmune disease characterized by a course of remission and relapse. The hyperfunctioning of the thyroid is initiated by stimulatory autoantibodies directed to the thyrotropin (TSH) receptor protein on thyrocytes.[1,2] Graves' disease is more common in young adults (15-35 years) with an estimated incidence of between two and five cases per 1000 and is 4 times more frequent in women.[3] Three not entirely satisfactory therapeutic options exist: thionamide drug therapy, subtotal thyroidectomy and radioiodine.[4-7]

Analysis of prospective studies and follow-up studies in the UK and European countries[2,8-10] have shown that drug treatment results in euthyroidism in 50 ± 7% of cases, 12 months after therapy.[10] In areas where the diet contains efficient iodine like the USA,11 to 54% of cases are still euthyroid 1 year after drug treatment [reviewed in 2, 10-12]. Subtotal thyroidectomy is an immediate and effective form of treatment; however, it is associated with direct complications such as hypoparathyroidism, laryngeal nerve palsy, bleeding and infections.[8,13] Radioiodine has been recommended as the best option with which to treat patients with Graves' disease because of its ease, low cost and low rate of serious complications.[5-7,14,15] The principle of radioiodine treatment is based on the unique ability of the thyroid follicular cells to trap and organify iodine.[16,17] After intracellular uptake, radioiodine causes sterilization and destruction of a number of these cells; the effect is to a large extent dependent on the dose of ^{131}I radiation absorbed.[14,18] The accumulated incidence of late hypothyroidism after radioiodine treatment is 40-70%,[6,7,14,18,19] whilst late hypothyroidism is found in 20-40% of cases with Graves' disease who had surgery.[7,14] However, no exact mathematical relationship has been found between ^{131}I dose and the appearance of hypothyroidism [reviewed in 6, 7], as this also depends on the autoimmune nature of the disease or the effectiveness of a given ^{131}I dose to prevent a recurrence.[5,6,16,19] For instance, administration of 50 µCi (1.85 MBq) per g thyroid weight has been considered to be too low a dose because of the unacceptably high relapse rate of 54% after 1 year of follow-up,[20] whereas 150 µCi (5.55 MBq) per g thyroid has been associated with a high incidence of hypothyroidism.[6,7] The present report evaluates the short-term outcome of an intermediate dose of radioiodine therapy in Dutch patients with Graves' disease in a prospective follow-up study. Radioiodine was administered in a moderate dose of 3.7 MBq (= 100 µCi) ^{131}I per g thyroid tissue, after adjusting for 24-h radioiodine uptake.

4.2 Patients and methods

Patients

A follow-up study was conducted on 207 subjects who had radioiodine treatment for newly diagnosed Graves' disease between January 1990 and December 1992 at the Academic Hospital Utrecht, The Netherlands. Criteria for Graves' disease were as follows: (i) signs and symptoms of thyrotoxicosis with elevated plasma concentrations of thyroid hormones and a suppressed TSH (< 0.1 mU/l); (ii) a diffuse goiter by palpation; (iii) anti-thyroid peroxidase antibodies in a titer greater than 1:100; (iv) increased 24-h ^{131}I uptake (normal range < 30%) in combination with a homogeneous ^{131}I uptake on thyroid scintigraphy; and (v) if present, endocrine ophthalmopathy.[1-3]

Questionnaires were mailed to referring internists with the request for data on patients treated before June 1992 regarding clinical outcome and thyroid status, as determined from plasma concentrations of levothyroxine (LT_4), T_4 uptake, free T_4 index (FTI), TSH and T_3. Data on medication (antithyroid drugs or T_4 supplementation) as well as duration of treatment were also supplied. Individual values of 5-h and 24-h thyroid radioiodine uptake and the thyroid weight estimation had already been determined before the ^{131}I-NaI (Benelux Isotope Service, Baarle-Nassau, The Netherlands) treatment. All patients used antithyroid drugs (ATD) in combination with LT_4 (usually 100 µg/day) before therapy.[21] All thyroid medication was stopped at least 72 h before uptake measurements and administration of the therapeutic dose ^{131}I-NaI. After radioiodine therapy, 73 subjects remained untreated, and 75 subjects had resumed their medication 48 h after radioiodine administration, for a period of 3 months. The decision to treat with ATD after radioiodine was made by the referring internist. In 59 subjects, data collection remained incomplete and these patients were not included in this report. Age and gender distribution in these 59 subjects was identical (48 women, 11 men; 45.7 ± 12.1 years) to the group of 148 subjects reported here, that consisted of 121 women (44.8 ± 14.6 years) and 27 men (43.7 ± 16.1 years).

To evaluate the effect of radioiodine therapy on thyroid status, the following definitions were used. Patients were considered euthyroid when 3 months after the radioiodine therapy no medication had been used for at least 4 weeks, in combination with normal plasma concentrations of TSH (0.3 to 5.0 mU/l), T_4 (70 to 160 nmol/l) and T_3 (1.0 to 3.0 nmol/l). Recurrent hyperthyroidism was defined by the presence of plasma concentrations of TSH < 0.1 mU/ml, T_4 > 170 nmol/l and/or T_3 > 3.5 nmol/l in combination with clinical symptoms of thyrotoxicosis, necessitating reinstitution of ATD treatment [either PTU (propylthiouracil), MMI (methimazole) or CMI (carbimazole)]. Hypothyroidism was defined

by plasma concentrations of TSH > 8 mU/ml and T_4 < 60 nmol/l or T_3 < 0.8 nmol/l in untreated subjects, at least 3 months after radioiodine. Subjects who received *de novo* LT_4 treatment after radioiodine were also classified as hypothyroid. Patients visited their physician 2 to 3 times during the first 4 months after radioiodine treatment and biochemical tests were done at each visit.

Radioiodine therapy

Calculation of the therapeutic ^{131}I-NaI dose included corrections for thyroid weight and 24-h radioiodine uptake, according to the formula:

$$D = W \times (100/U) \times C,$$

where D is the ^{131}I dose (in MBq) to be administered, W represents thyroid gland weight (in g), U equals the 24-h ^{131}I uptake (%), and C equals 3.7 MBq/g. The average dose given in this study is 4.7 ± 3.3 mCi or 173 ± 111 MBq. The 5-h and 24-h ^{131}I-NaI uptakes were measured following ingestion of 0.37 MBq ^{131}I-NaI tracer (Canberra 7350-PE collimator with 2×2 inch NaI crystal). The collimator crystal was centered for 4 min at the trachea or at the ^{131}I-NaI standard placed in a neck phantom at a distance of 25 cm. Thyroid uptake is calculated using the formula:

$$^{131}\text{I uptake} = \frac{\text{neck counts} - \text{background counts}}{\text{standard counts} - \text{background counts}} \times 100\%$$

The background count was measured in the room for 4 min.

Thyroid weight was estimated from the scintigraphic image by applying the cylinder formula for each lobe:

$$V = L\,(0.5\,W)^2 \times \pi,$$

where V represents the volume of each lobe, L is length in cm, and W is width in cm. Thyroid volume was assumed to represent thyroid weight (1 ml equals 1 g). Normal thyroid weight in adults is 20 g.[23] Thyroid scintigraphy was performed after intravenous administration of 80 MBq technetium-99m-pertechnetate using an Elscint 409 round-field gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator.

Other methods

Both T_4 and T_3 plasma concentrations were determined by fluorescent polarization immunoassays (Abbot Diagnostics, Chicago, IL, USA).[24,25] The FTI is the product of total T_4 and resin uptake (RU): FTI = $T_4 \times$ RU. TSH (normal 0.3-5.0 mU/l) was measured by immuno-enzymometric assay (Boehringer Mannheim, Mannheim,

Table 4.1 Outcome in relation to thyroid weight following ^{131}I-NaI therapy.

thyroid weight[#]	subjects (n)	recurrent hyperthyroidism [n (%)]	euthyroidism [n (%)]	hypothyroidism [n (%)]	cure rate[+] (%)
9-19	13	1 (8%)	0 (0%)	12 (92%)*	92%*
20-29	24	5 (21%)	11 (46%)	8 (33%)	79%
30-39	37	11 (30%)	13 (35%)	13 (35%)	70%
40-49	26	9 (35%)	9 (35%)	8 (30%)	65%
50-59	16	3 (19%)	6 (37%)	7 (44%)	81%
combined 9-59 g	116	29 (25%)	39 (34%)	48 (41%)	75%
95% confidence interval		16.9-34.7%*	24.7-44.2%	31.2-51.3%	65.3-83.1%
combined 60-150 g	32	16 (50%)	7 (22%)	9 (28%)*	50%*
95% confidence interval		37.4-74.5%*	12.3-45.9	14.7-49.4	37.4-74.5
total outcome	148	45 (30%)	46 (31%)	57 (39%)	70%
95% confidence interval		22.8-38.0%	23.4-41.5%	30.9-46.5%	62.0-77.2%

* $P < 0.05$ versus corresponding category.

[#] Thyroid weight was estimated from the thyroid scintigraphic image (see *Patients and methods*).

[+] The 'cure rate' is defined as the number of hypothyroid plus euthyroid subjects divided by the total number of all patients treated.

Germany).[24,25] Autoantibodies to thyroid peroxidase were determined by a commercial kit (FujiZoki, Tokyo, Japan). Statistical analysis was performed using confidence interval (C.I.) testing.[26] Subjects were divided into tertiles according to their 24-h radioiodine uptake values or into categories of thyroid weight. Student's *t*-tests or ANOVA were used to compare variables (SPSS/PC + version 5.0). Data are reported as 95% C.I. or as mean ± sd. The two-sided level of significance was $P < 0.05$.

4.3 Results

Of the 148 patients with Graves' disease, 46 patients remained euthyroid (31%; 38 women and 8 men), 57 patients became hypothyroid (39%; 47 women and 10 men), and recurrent hyperthyroidism was observed in 45 patients (30%; 36 women and 9 men) (table 4.1). The follow-up was for 12 ± 6 months.

Thyroid weight and outcome

Hypothyroidism developed in 12 of 13 patients with a thyroid weight under 20 g (92%; C.I. 76.8-99.8%). By contrast, recurrent hyperthyroidism was observed in 50% of the subjects with a thyroid weight exceeding 60 g (i.e. three times enlarged). This is a significantly higher incidence compared with the group of subjects who had a thyroid weight under 60 g ($P < 0.05$; table 4.1). In subjects with thyroid weights exceeding 110 g, recurrent hyperthyroidism was found in 7 of the 9 individuals.

In general, thyroid weight was significantly higher in patients who relapsed (57.6 ± 35.9 g) compared to subjects who became hypothyroid (38.9 ± 23.0 g; $P < 0.01$) or remained euthyroid (44.8 ± 27.5 g; $P < 0.05$).

24-h ^{131}I uptake and outcome

Subjects were divided into tertiles of 24-h radioiodine uptake (figure 4.1). Individuals with a 24-h radioiodine uptake value under 60% showed significantly more hypothyroidism (30 of 56 subjects, or 54%; C.I. 40-66%) than relapse (n = 12, 21%; C.I. 14-40%; $P < 0.05$). To this group of 56 subjects belonged the 12 subjects with a thyroid weight under 20 g. By contrast, patients with a 24-h iodine uptake exceeding 80% had a lower incidence of hypothyroidism (14%; C.I. 2.5-31.2%; $P < 0.05$) and a higher relapse rate (59%; C.I. 31.3-72.2%; $P < 0.05$). Only 10 of 22 subjects with uptake values exceeding 80% had a thyroid weight exceeding 60 g. No linear relationship was present between 24-h uptake and gland weight, and therefore a high thyroid weight (> 60 g) did not necessarily imply a high 24-h uptake (figure 4.2).

In general terms, radioiodine uptake was significantly higher in patients who suffered a relapse compared with subjects who became hypothyroid. The average 24-h uptake in all 148 subjects with Graves' disease was 64.8 ± 14.5% (normal range, < 30%). Subjects who relapsed had an average 24-h uptake of 70.4 ± 15.3% ($P < 0.001$ versus the hypothyroid group: 60.7 ± 12.4%).

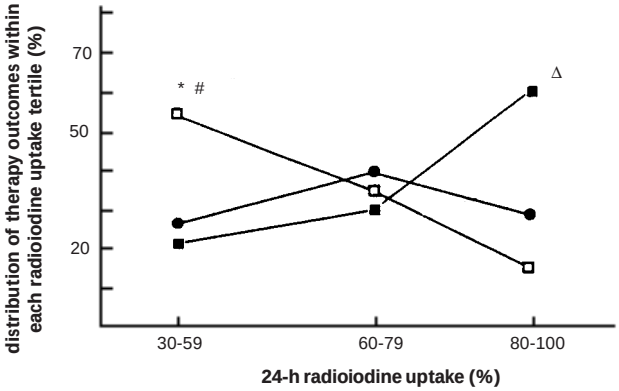

Figure 4.1 Relation between 24-h radioiodine uptake values and thyroid status following radioiodine therapy (3.7 MBq per g thyroid). *: $P < 0.01$ versus euthyroid and hyperthyroid subjects in this category; #: $P < 0.01$ versus proportion of hypothyroid subjects in category with higher 24-h uptake values; Δ: $P < 0.05$ versus hypothyroid subjects in this category. ■ hyperthyroidism; □ hypothyroidism; ● euthyroidism.

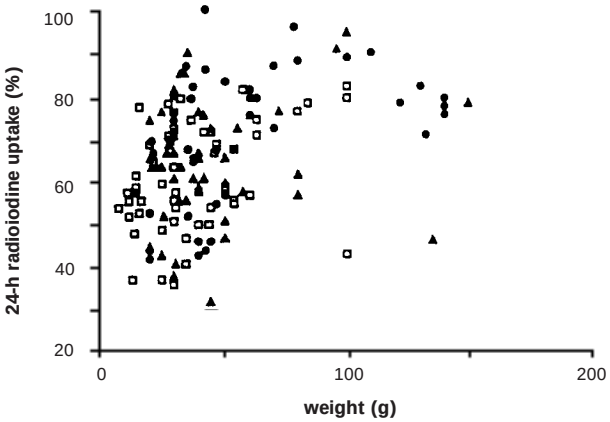

Figure 4.2 Thyroid weight compared with 24-h radioiodine uptake values. The thyroid status resulting from ^{131}I therapy is indicated: euthyroidism (▲), hypothyroidism (□), and recurrent hyperthyroidism (●).

Outcome and other variables

No differences in short-term outcome were observed between male and female patients. Hypothyroidism developed in 37 subjects within 6 months and in 20 subjects within 7 months after therapy; no new cases developed during 12 months follow-up. Twenty-six patients had a recurrence within 3 months, 13 patients relapsed between 7 and 9 months after radioiodine, and 6 patients relapsed within 10 months. No differences in clinical outcome were found between the 75 patients who resumed ATD medication plus levothyroxine immediately after radioiodine (23 subjects remained euthyroid, 24 relapsed and 28 became hypothyroid) and the 73 subjects who used no ATD after radioiodine (23 remained euthyroid, 21 relapsed and 29 became hypothyroid). Also, no significant differences were found with regard to age: 45.3 ± 15.8 years in the hypothyroid group, 46.0 ± 14.8 years in the euthyroid group, and 42.7 ± 12.4 years in the hyperthyroid group. No patient older than 70 years (n = 7) suffered a relapse.

4.4 Discussion

Administration of a standard dose of 3.7 MBq ^{131}I per g thyroid tissue, adjusted for 24-h radioiodine uptake, did not yield uniform treatment results when expressed per thyroid weight category. The present study showed a 90% incidence of hypothyroidism within 3 months of follow-up in patients who had a small thyroid gland of less than 20 g. The cure rate is conventionally defined as the number of hypothyroid plus euthyroid subjects. The highest cure rate (75%; C.I. 65-83%) was obtained in the thyroid weight range of 9-59 gram. Significantly lower success rates were found in subjects with a thyroid greater than 60 g and in subjects with a higher than 80% radioiodine uptake, the latter with a 41% cure rate. The overall cure rate in the present study was 70% (C.I. 60-78%) which is significantly better ($P < 0.01$) than the cure rate (49.8 ± 7.0%) calculated by meta-analysis in 10 prospective studies on ATD treatment conducted between 1975 and 1991 and comprising a total of 937 patients with Graves' disease.[10,21]

Variability in the effectiveness of radioiodine in Graves' disease is related to factors that influence the biological half-life of ^{131}I and therefore the actual radiation effect on the thyroid, and to clinical factors.[17,22,27-29] Factors that determine the actual radiation effect of ^{131}I are thyroid size, 24-h radioiodine uptake (representing the avidity of the thyroid for iodine), the effective half-life of ^{131}I in the thyroid gland [estimated at 5.4 days in ref. 28]. Clinical factors include ATD treatment that affects the biological half-life of iodine.[22,27,28] In practice, it is time-consuming to determine the ^{131}I biological half-life in individual

patients because it requires several visits prior to definite radioiodine treatment.[27,28] The approach taken in this study used a standardized 'μCi/g' method based on calculations of thyroid volume and radioiodine uptake. These calculations may have suffered from inherent variability as a result of inaccuracy (which may be as high as 6-20%) in the estimate of thyroid size.[22,23] However, thyroid volumes estimated by magnetic resonance imaging correlated well with estimates derived from planar thyroid scintiscanning (R = 0.94; n = 20),[30] and we ourselves found a good correlation between CT scanning estimates and scintigraphy in the range up to 175 ml (R = 0.97; n = 13) (see *Chapter Three*). These recent data suggest that variability in estimates of thyroid size may not be a sufficient explanation of the variability in outcome observed in different thyroid weight categories. With respect to the potential variability introduced by ATD treatment, a higher incidence of relapse in ATD users after radioiodine treatment has been reported[28] as well as a reduction in short-term hypothyroidism.[19,28,29] However, all patients in the present study used ATD and LT_4 prior to radioiodine therapy, and absence or presence of ATD treatment after radioiodine did not correlate with therapy outcome. The explanation for this discrepancy must be the fact that our patients received the combination of ATD treatment and LT_4 substitution instead of a titrated dose of ATD.

The reduced effectiveness of radioiodine in larger Graves' thyroids is in agreement with observations that neither a lower standard radioiodine dose per gram tissue,[6,19] nor a higher standard dose,[6] nor compensation factors for thyroid weight[20] could correct the relationship between rate of recurrence and thyroid weight. The presence of autonomous tissue with functional differences in uptake and organification of iodine may be an additional explanation for the fact that larger Graves' thyroids are less ^{131}I sensitive (figure 4.2),[8,9,31,32] similar to observations in multinodular goitre.[18,31] Recurrent hyperthyroidism after treatment is usually caused by autonomous production of thyroid hormones in autonomously functioning areas,[2,31,32] or alternatively by increased stimulation of thyrocytes by TSH receptor antibodies.[2,10] However, measurement of TSH receptor antibodies has not accurately predicted recurrences after ATD treatment,[2,8-10] although the risk of relapse was significantly reduced by 65% in the absence of TSH receptor antibodies.[10] It has been suggested that some remissions are related to depletion of the thyroid iodine pool after ATD.[2,22,27] On the other hand, some of the relapses have been related to the development of autonomous functioning tissue in large Graves' thyroids.[33] Thyroid nodules can be found in 5-15 % of patients with Graves' disease, which is at least a twofold increase compared to the normal population. Thyroid nodules and neoplasms in Graves' disease pre-

sumably result from the development of autonomous follicles in the course of this disease and do not result from ^{131}I treatment.[6,7,15,34-36]

Important recent data show that radioiodine treatment causes no increased risk of cancer in patients with Graves' disease after a follow-up of 15 to 28 years.[15] Radioiodine treatment may cause an exacerbation of already present endocrine ophthalmopathy,[37] and preventive measures have to be considered in patients at risk.[38,39] Prevention of recurrent hyperthyroidism in Graves' disease is not only the goal of immediate therapy but can be regarded as a potential method with which to reduce the observed excess long-term mortality,[15,40] which appears to depend on the severity of the hyperthyroid state.[40] The present data and current literature suggest several strategies to reach such an objective. In the thyroid weight range of 9-60 g, a satisfactory cure rate of 75% has been consistently observed.[7,14,20] Improvements can therefore be expected in the treatment of patients with large thyroids by increasing the dose of radioiodine in subjects who have high (> 80%) 24-h uptake values.[6,7] Subtotal thyroidectomy is a second-choice option in patients with Graves' disease who have a large thyroid (> 60 g).

In conclusion, treatment of patients with Graves' disease with ^{131}I-NaI, standardized to 3.7 MBq per g thyroid weight and corrected for 24-h radioiodine uptake, revealed persistent significant differences in outcome per thyroid weight category. Graves' disease patients with a thyroid of less than 20 g and those with a 24-h radioiodine uptake less than 60% have a 50-90% chance of hypothyroidism at 12 months of follow-up. In the thyroid weight range of 9-60 g, a satisfactory cure rate of 75% was observed. Aiming for improvement in the outcome in Graves' disease patients with large thyroids is a challenge because of the governing principle of radioiodine therapy to keep the administered dose as low as reasonably achievable.[15]

4.5 Acknowledgement

We thank the collaborating internists in the province of Utrecht for contributing data to this study.

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Chapter Five

Iodine-131 uptake and turnover rate vary over short intervals in Graves' disease

Johannes W. van Isselt, John M.H. de Klerk, Hans P.F. Koppeschaar,
Peter P. van Rijk

Published in Nuclear Medicine Communications 2000; 21: 609-616

Summary

From a Dutch questionnaire, it was apparent that nearly all institutions used the percentage of radioiodine uptake for the radioiodine dosage calculation in Graves' disease. Although there is a general belief that fluctuations in radioiodine uptake might occur, with few exceptions relatively long intervals were accepted between the uptake measurement and the actual therapy dosage. With the aim of optimizing the pretherapeutic work up, we evaluated the stability of iodine uptake over time in patients with Graves' disease who were referred for ^{131}I therapy.

^{131}I uptake was measured in 300 consecutive patients for the calculation of the required ^{131}I therapy dosage; data were complete in 291 patients (97%). After discontinuing thyroid medication for 3 days, standardized thyroid probe measurements were performed at 5 and 24 h after ingestion of a capsule containing 0.37 MBq ^{131}I-NaI. Measurements were performed at the time of scintigraphic diagnosis (test 1), as well as immediately before ^{131}I therapy (test 2). The time interval between test 1 and test 2 ranged from 2 to 421 (median 40) days.

A relative increase or decrease greater than 10% between tests 1 and 2 occurred in 180/291 cases (62%) at 5 h, and in 158/291 patients (54%) at 24 h. These changes were not related to the interval between the tests, or to initial uptake values, thyroid mass, gender, or age. Rapid turnover of radioiodine (5/24-h uptake ratio >1) was present in 17% of the patients during test 1 and in 15% during test 2. Rapid turnover was persistent (present in both tests 1 and 2) in only 9%.

Patients with Graves' disease show considerable changes in ^{131}I uptake over relatively short periods of time, and the turnover rate of ^{131}I in this condition is not constant.

5.1 Introduction

In Europe, patients with clinical and biochemical evidence of hyperthyroidism due to Graves' disease are usually treated with antithyroid medication, typically for 1-1.5 years. Up to 50% of all patients become euthyroid after discontinuing this medication. In patients with persisting or recurrent hyperthyroidism, little benefit can be expected from re-initiating antithyroid medication.[1] Definitive treatment may then be achieved either by subtotal thyroidectomy or by radioiodine (^{131}I) therapy. ^{131}I is recognized as the simplest, safest, cheapest and most convenient form of therapy for patients with persisting hyperthyroidism.[2-4]

In the treatment of Graves' hyperthyroidism there is no general agreement on the ^{131}I dosage or even the therapy objective.[5] Many clinicians favor a large ^{131}I dosage with the aim of inducing hypothyroidism, which is then treated by permanent levothyroxine replacement therapy.[6,7] Others consider it undesirable to replace one disease by another irreversible disease.[8,9]

Alternative options include the 'fixed dosage' regimen (with or without modifying factors for thyroid volume, iodine turnover rate, age and gender),[10] and the so-called becquerel-per-gram method.[2] With the latter method, the therapeutic ^{131}I dosage is calculated as a fixed dosage per gram functioning thyroid tissue, usually 3.7 MBq/g (100 μCi/g). The dosage calculation is given by the formula:

$$D = W \times (100/U) \times 3.7 \text{ MBq},$$

(where D is the ^{131}I dosage in MBq, W is the thyroid weight in grams, and U is the 24-h radioiodine uptake in %);[2] reliable information is required regarding thyroid volume and ^{131}I uptake. Useful estimations of the thyroid weight can be made from planar scintigraphy;[11,12] radioiodine uptake is measured with a tracer amount of ^{131}I and a scintillation probe.[13] In most euthyroid people with a sufficient iodine supply the maximum radioiodine uptake is reached between 24 and 48 h. In hyperthyroid patients, radioiodine uptake may reach a peak sooner than 24 h, and it is recommended that uptake is measured at a relatively early stage (4-6 h) as well as at 24 h.[14] If the 5/24-h uptake ratio is > 1 this is defined as 'rapid iodine turnover'.[15] Rapid turnover implies a short effective half-life (T_{eff}) of ^{131}I and a diminished therapeutic effect. Under these circumstances, increased therapeutic ^{131}I dosages are advocated to reduce the risk of recurrent disease.[15]

Most authors in their methodological descriptions of uptake measurements state the time after ingestion of the tracer dose, but not the time interval between the uptake test and the actual therapy dosage; however, there are excep-

tions.[16] Recommendations for performing the radioiodine uptake test are often solely directed towards technical quality assurance of the thyroid probe. Only very recently, the North-American and the German Societies of Nuclear Medicine have addressed the issue of the timing of uptake measurements, but without substantiating literature references.[17,18]

5.2 Dutch radioiodine therapy survey

In The Netherlands and at least five other European countries (Germany, Austria, Hungary, the Czech Republic and Slovakia) all or most patients have to be

Table 5.1 Results of the Dutch radioiodine therapy survey.

			n	%	days
number of nuclear medicine departments			70		
respondents to the questionnaire			70	100	
number of nuclear medicine departments with ^{131}I therapy facilities			32	45.7	
number of radioiodine treatments in 1998 for Graves' disease			40	85	
^{131}I uptake tests used for dosage calculation?					
	yes	(departments)	29	90.6	
		(all patients)	3910	95.7	
	no	(departments)	3	9.4	
		(all patients)	175	4.3	
interval between 24 h ^{131}I uptake test and treatment					
	typical (i.e., effectively done in most patients)				
	mean	(departments)			7.1
		(all patients)			9.8
	range				0-60
	minimum observed				
	mean	(departments)			4.2
		(all patients)			4.5
	range				0-14
	maximum observed				
	mean	(departments)			75.5
		(all patients)			88.4
	range				0-730

hospitalized for ^{131}I treatment.[19] At our department, owing to fluctuations in the waiting list and patients' preferences, the interval between the diagnostic test and the admission for the radioiodine therapy typically varied from 2 days to just over 1 month. We have conducted a survey of the practice of radioiodine uptake measurements for the calculation of therapeutic ^{131}I dosages in The Netherlands. The response to the questionnaire was 100% (for results see table 5.1). The general conclusions that can be drawn from the Dutch questionnaire are: (i) at most nuclear medicine departments, the intention is to treat patients within 4-8 days after the 24-h uptake measurement; (ii) most patients, however, receive the therapeutic radioiodine dosage about 10 days after the uptake measurement; (iii) 56% of all departments regard an interval of 1-4 weeks between uptake measurement and therapy dosage to be acceptable; one-third accept intervals of 1-24 months; (iv) in only one department is a same-day protocol for 24-h uptake measurements and therapy dosage administration maintained.

In clinical practice, there appears to be a considerable time interval between the 24-h ^{131}I uptake measurement and actual therapy.

The main aim of the present study was to define if, and to what extent, changes in 5 and 24-h ^{131}I uptake values occur over time in patients with Graves' disease.

A secondary aim was to assess changes in the radioiodine turnover rate over the same time intervals in the same patients. The study was approved by the hospital's ethics review board.

5.3 Patients and methods

Patients

Three-hundred consecutive patients with Graves' disease were enrolled in the study, all of whom had been referred for radioiodine therapy. All suffered from recurrent hyperthyroidism (TSH levels < 0.10 mU/l after 1-1.5 years of antithyroid drug medication in combination with thyroxine. Criteria for Graves' disease were: (i) signs and symptoms of thyrotoxicosis with elevated plasma concentrations of thyroid hormones and a suppressed TSH (< 0.1 mU/l); (ii) a diffuse goiter upon palpation; (iii) increased 24-h ^{131}I uptake in combination with homogeneous ^{99m}Tc-pertechnetate uptake on scintigraphy; (iv) (if available) antithyroid peroxidase antibodies in a titer greater than 1:100; and (v) (if present) endocrine ophthalmopathy.[20-22] At the time of the ^{131}I therapy all patients were clinically euthyroid.

In 291 patients (242 females, 49 males) the follow-up data were complete. The age of the females and males was comparable (females: 46.5 ± 15.9 year,

median 44.8 year; males: 47.7 ± 15.4 year, median 49.1 year). Thyroid weight ranged from 10 to 190 g (47 ± 31 g, mean ± sd).

Uptake measurements ('test 1')

Before all measurements, thyroid medication had been discontinued for 3 days. Care was taken that no iodine containing drugs (e.g., amiodarone, kelp) had been ingested and that no radiographic contrast agents had been administered in the 3 months before uptake measurement. On the first day, patients were allowed a light breakfast. Thyroid uptake measurements were carried out in a standardized manner.[13] The ^{131}I uptake ('test 1') was measured 5 and 24 h after ingestion of a capsule containing a tracer dose of 0.37 MBq ^{131}I-NaI (Mallinckrodt Medical B.V., Petten, The Netherlands). A scintillation probe (Canberra 7350-PE collimator with a 2×2" NaI crystal) was positioned at the site of the patient's thyroid area for 4 minutes, at a fixed distance of 25 cm. For the purpose of background (BKG) correction, the probe was then positioned at the patient's thigh, also for 4 minutes and at the same distance. After correction for BKG, the activity (counts per minute, cpm) over the thyroid region was compared with the activity (cpm) measured from a standard containing 0.37 MBq ^{131}I, placed in an anthropomorphic perspex thyroid/neck phantom, after correction for room BKG activity. The percent ^{131}I uptake (U) by the thyroid is:

$$U = [(cpm_{neck} - cpm_{thigh})/ (cpm_{standard} - cpm_{room\ BKG})] \times 100\%.$$

Quality assurance and regular quality controls were performed: energy peak calibration of the scintillation probe was performed before use each day and energy resolution tests were performed annually.[23]

Follow-up measurements ('test 2')

5 and 24-h ^{131}I uptake measurements were repeated shortly before ^{131}I therapy ('test 2'), using the same procedure and with the same precautions as for test 1. The therapeutic capsule was administered 48 h after the diagnostic capsule (i.e. one day after the 24-h uptake measurement). The interval between test 1 and test 2 ranged from 2 to 421 days, with a mean (± sd) of 52.3 ± 24.8, and a median of 40.0 days. In most cases (185 patients, 64%) it was between 21 and 60 days, in 40 cases (14%), it was less than 3 weeks.

We investigated changes in 5 and 24-h ^{131}I uptake values and changes in turnover state (normal or rapid) between the two tests. Statistical analysis was performed of the ^{131}I uptake changes in relation to the time interval between the first and the second test, the initial uptake values, the patients' thyroid

weight, gender and age. We also assessed the influence of the time of year on the measurements, in view of potential seasonal variations in the dietary iodine intake. The ^{131}I uptake values from 'test 2' were treated as the reference data or true values, since they were the closest possible approximation of the biological state of the thyroid at the time of treatment.

The precision of the ^{131}I content of the therapy capsules, if ordered one day before use, is 10%. Therefore only differences in 5 or 24-h ^{131}I uptake greater than 10% were considered to be relevant with regard to therapy dosage adjustment. The choice of the 10% level was supported by (i) the good reproducibility of the uptake measurements (see paragraph *Reproducibility*), and (ii) the high precision with regard to the ^{131}I content of the diagnostic capsules (see paragraph *Product specifications of ^{131}I capsules*).

Changes from normal to rapid ^{131}I turnover rate, or vice versa, were also considered to be relevant for dosage calculation purposes, because rapid iodine turnover warrants a larger therapeutic dosage.[15]

Reproducibility

The reproducibility of thyroid uptake measurements in 20 patients was assessed by three nuclear medicine technologists. The coefficient of variance (%CV) for the measurements was 1.79% for thyroid and background, and 1.00% for the ^{131}I standard in a neck phantom. The overall precision of the uptake measurement was:

$$\sqrt{(1.79)^2 + (1.00)^2} = 2.06\%.$$

Product specifications of ^{131}I capsules

In the formulation that we used, the ^{131}I is carrier-free. Radionuclide purity ≥ 99.9% and radiochemical purity ≥ 95% are guaranteed (Mallinckrodt Medical International Catalogue). The ^{131}I diagnostic capsules and the ^{131}I standard are delivered in one batch. As stated by the manufacturer, the coefficient of variance (%CV) between capsules from the same batch is not more than 1.0%. This was confirmed by spot checks.

Measurements of functioning thyroid volume

All thyroid volume estimates have been derived from standard planar thyroid scintigraphy and dedicated software. Fifteen minutes after the intravenous administration of 80 MBq ^{99m}Tc-pertechnetate a 2-min anterior view (256×256 matrix) of the thyroid was made on an Elscint 409 round-field-of-view gamma

camera, equipped with a low-energy, all-purpose collimator. A rectangular region of interest (ROI) was outlined, so that it contained the entire thyroid gland and excluded the salivary glands. This ROI typically contained about 100 kcnts. Within the thyroid, a small rectangular ROI (size 5×8 pixels) was outlined over the area of the thyroid with the highest radioactivity content per pixel. The value representing 30% of the average count density in this ROI was taken as a threshold for automatic thyroid contour delineation. The area within the contour was then converted from pixels to square centimeters. For the calculation of the functioning thyroid volume (V) we used the surface area (A) formula as described earlier by Himanka and Larson:[24]

$$V = 0.33 \times A^{3/2}.$$

In a different group of patients (with nontoxic goiter) we found that this formula had a good precision for measurement of thyroid volumes up to 200 ml.[25]

Biochemical parameters

Patients who were referred from within our own hospital had documented positive antithyroid peroxidase antibodies at the time of diagnosis. Antibodies had not been assessed in most patients referred from other hospitals. Therefore we did not analyze antibody titers versus the stability of radioiodine uptake. Serum T_3, FT_4 and TSH levels were not included in the analysis either, because the availability of biochemical data from the thirteen referring sites at specific times before and after ^{131}I treatment varied widely.

Statistical analysis

Statistical analysis was performed with the SYSTAT® 5.0 program (SYSTAT Inc., Evanston, IL). The agreement between the two sets of test results was assessed with the method described by Sheiner and Beal.[26] The precision (expressed as the root mean squared error, rmse) is a measure for the correctness of test 1 as an 'outcome predictor' of test 2 in individual cases. The method of Sheiner and Beal gives a description of systematic components of any errors in test 1 compared with test 2 in the form of the mean prediction error (bias). A parallel analysis was done with the method of Bland and Altman.[27]

The correlation coefficient and the paired *t*-test for test 1 versus test 2 were used for comparison of the grouped results. Regression analysis was applied to analyze the correlation of uptake values with gender, age, the time between the tests, or seasonal influences.

5.4 Results

5-h uptake

For the group as a whole, the mean, median and range of the 5-h uptake values remained unchanged from test 1 to test 2. The uptake values from test 1 and test 2 correlated well (R = 0.85, P < 0.01; table 5.2 and figure 5.1a). For individual patients the 5-h uptake was much less stable: changes > 10% were noted in 62% of all cases. The observed uptake changes were not related to the duration of the interval between measurements, the initial uptake value, the patients' thyroid weight, gender or age, or seasonal influences (table 5.3 and figure 5.1b). With regard to the 5-h uptake, the precision of test 1 was poor compared with test 2 (mse = 151.4, rmse = 12.3). Bias (0.83) was negligible (figure 5.1c).

24-h uptake

The mean, median and range of the 24 h uptake values from test 1 and test 2 did not differ for the group as a whole, and the two test sets correlated well (R = 0.79, P < 0.01, table 5.2 and figure 5.2a). However, individual changes greater than 10% were noted in 54%. When the 24-h uptake had increased in comparison with test 1, this increase averaged 28 ± 18%. In patients with decreased uptake, the decrease averaged 13 ± 11%. Regression analysis showed no relation

Table 5.2 Summary of the ^{131}I uptake measurement results.

	5-h ^{131}I uptake	24-h ^{131}I uptake
test 1 (mean ± sd)	54.2 ± 21.9%	62.6 ± 17.3%
test 2 (mean ± sd)	55.1 ± 22.7%	64.4 ± 18.5%
correlation	R = 0.85, P < 0.01	R = 0.79, P < 0.01
number of patients (%) with change >10%	180/291 (62%)	158/291 (54%)
increase		
number of patients (%)	100/291 (34%)	97/291 (33%)
relative increase (mean ± sd)	25 ± 14%	28 ± 18%
decrease		
number of patients (%)	80/291 (28%)	61/291 (21%)
relative decrease (mean ± sd)	17 ± 13%	13 ± 11%
rmse	12.3	11.8
radioiodine turnover		
increased at test 1	50/291 (17%)	
increased at test 2	44/291 (15%)	
increased at both test 1 and test 2	27/291 (9%)	
change from normal to increased or vice versa	40/291 (14%)	

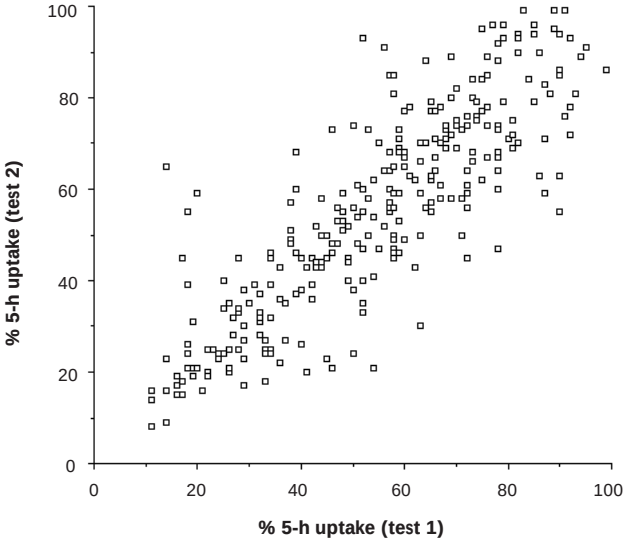

Figure 5.1a 5-h radioiodine uptake: relation between tests 1 and 2; $y = 7.343 + 0.880x$; $R^2 = 0.719$.

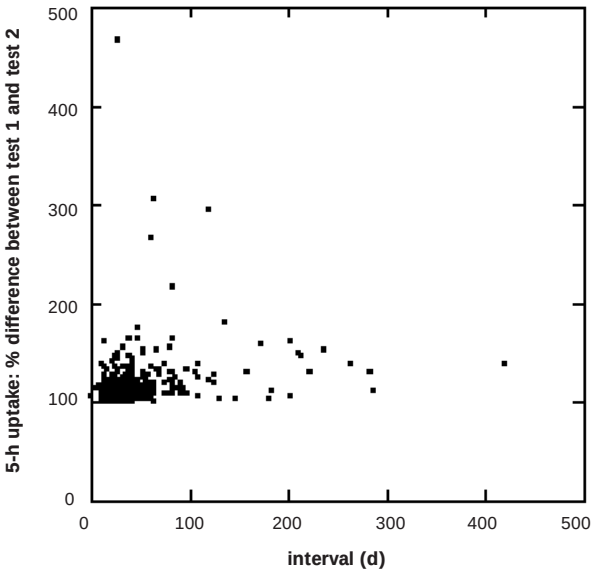

Figure 5.1b The relative changes in 5-h radioiodine uptake between tests 1 and 2 are independent of the interval between the tests; $y = 6.956 – 0.029x$; $R^2 = 0.002$.

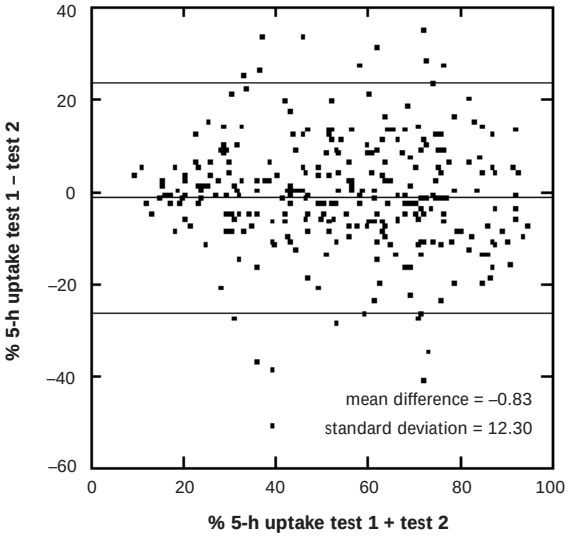

Figure 5.1c Difference versus mean for the 5-h-uptake values of test 1 and test 2.

between the changes observed in ^{131}I uptake and the interval between measurements, the initial uptake value, the patients' thyroid weight, gender or age, or seasonal influences (see table 5.3 and figure 5.2b). With regard to the 24-h uptake, the precision of test 1 compared with test 2 was no better than for the 5-h uptake (mse = 139.0, rmse = 11.8). Bias (1.75) was again negligible (figure 5.2c).

^{131}I turnover rate

The prevalence of rapid iodine turnover was similar for both tests: in 50 patients (17%) at the first measurement and in 44 patients (15%) at the second measurement. It was persistent (present in both tests) in only 27 patients (9%). Changes in iodine turnover state, from normal to rapid or from rapid to normal, were observed in 40 of 291 patients (14%). These changes were not related to the initial 5 or 24-h uptake values or to the interval between the two measurements.

Table 5.3 The observed changes in ^{131}I uptake in relation to other parameters.

	5-h uptake changes	24-h uptake changes
interval between measurements	R = 0.039; P = 0.50	R = 0.033; P = 0.57
thyroid weight	R = 0.042; P = 0.47	R = 0.112; P = 0.06
gender	R = 0.005; P = 0.94	R = 0.015; P = 0.80
age	R = 0.014; P = 0.81	R = 0.011; P = 0.86
seasonal influences	R = 0.017; P = 0.77	R = 0.031; P = 0.60

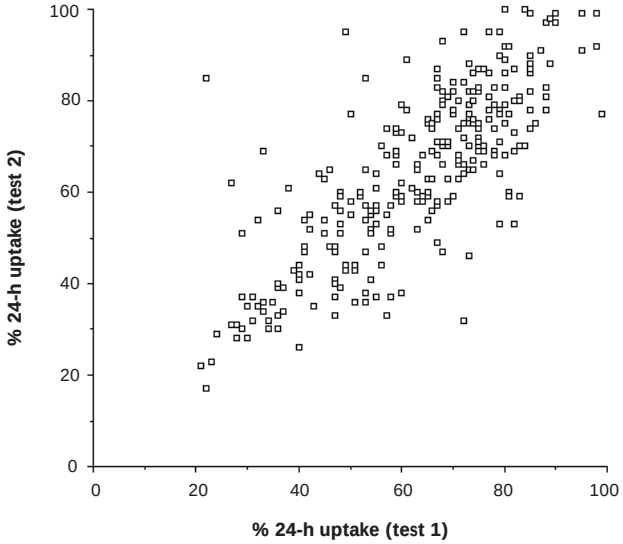

Figure 5.2a 24-h radioiodine uptake: relation between tests 1 and 2; $y = 11.635 + 0.842x$; $R^2 = 0.622$.

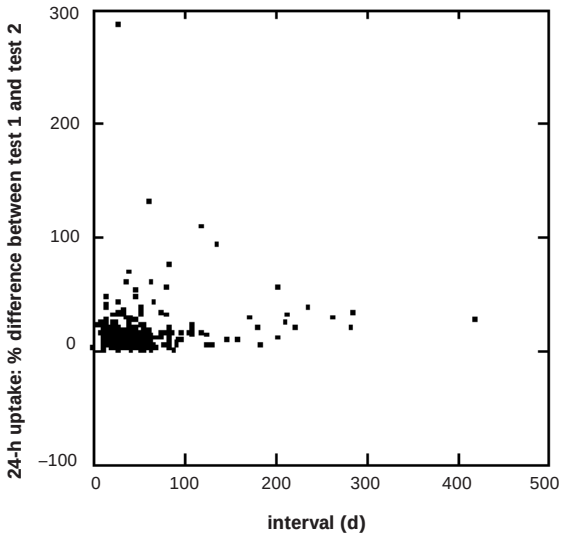

Figure 5.2b The relative changes in 24-h radioiodine uptake between tests 1 and 2 are independent of the interval between the tests; $y = 5.920 + 0.018x$; $R^2 = 0.001$.

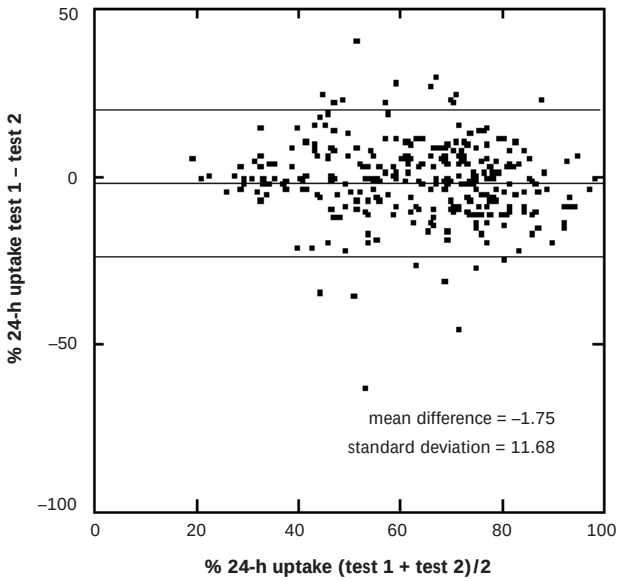

Figure 5.2c Difference versus mean for the 24-h uptake values of test 1 and test 2.

Nor were they related to seasonal influences, the patients' age, gender or thyroid weight. The correlation between the turnover rates from the first and the second test was very poor ($R = 0.311$, $P < 0.01$). There was no bias (0.01).

5.5 Discussion

Quantitative approaches towards radioiodine therapy dosing are generally aimed at reducing the risk of early hypothyroidism. From the first year after radioiodine therapy, the increase in hypothyroidism progresses at about the same rate (2-4% per year) regardless of the dosage used. Long-term cure rates are similar to those with fixed dose protocols.[2] Our own experience shows that the rate of hypothyroidism depends on thyroid weight and radioiodine uptake at the time of treatment.[28]

Reasons to strive for euthyroidism were recently reinforced by Bunevicius *et al.*, who found that an adequate supply of triiodothyronine substantially enhances the patients' well-being.[9] It may be argued that the same is true for endogenous T_3 production. Not only clinical arguments but also radiation safety considerations may lead to generally lower radioiodine dosages. Based on the ALARA principle, an individualized dosage regimen is required by law in Germany and some Eastern European countries.[16] The avoidance of an unnecessary

radiation burden alone is deemed to balance out the extra time burden. Radiation safety can be guaranteed only if optimal dosage calculations are possible. Optimization of the radioiodine uptake procedure is essential. It follows directly from the formula that the therapeutic ^{131}I dosage is inversely related to the percent of ^{131}I uptake.

We have found that in most patients with Graves' hyperthyroidism the radioiodine uptake varies greatly over time, even over relatively short periods. None of the parameters that we analyzed had a significant correlation with the variations in uptake. We have demonstrated that there is no correlation between the time between the measurements and the observed uptake changes.

The group results were moderately correlated for the 5 and 24-h uptake measurements ($R^2 = 0.72$ and 0.62, resp.), and the average uptake values varied only marginally between the two tests. At an individual level, however, significant deviations were found. Relative changes > 10% were seen in 60% of the patients. A few individuals showed extreme differences. The correctness of test 1 as an 'outcome predictor' of test 2, expressed as the precision, appeared to be unacceptable.

Whereas the prevalence of rapid turnover in our study at each measuring point (15-17%) was in line with previous research, it was persistent in only 9% of the patients. In 14%, the turnover rate had either increased or decreased significantly. This implies that, on the basis of iodine turnover alone, 1 in every 7 patients would have received inappropriate ^{131}I therapy dosages if the uptake values from test 1 had been used for the dosage calculation.

Factors that may be responsible for variations in radioiodine uptake include the activity of the immune process itself, stress factors surrounding the clinical setup, and day-to-day variations in dietary iodine intake. Geographic variations in the alimentary iodine intake are unlikely, because all patients in this study live in the same (iodine-sufficient) area in The Netherlands. We have not been able to investigate the relation between ^{131}I-uptake and serum concentrations of T_4, FT_4, T_3, and anti-TSH antibodies. However, the thyroid medication had been identical in the periods leading up to tests 1 and 2, and in all cases it had been discontinued 3 days before each of the uptake measurements.

At most institutions in The Netherlands – and elsewhere probably – radioiodine treatment takes place several days or even weeks after the radioiodine uptake test. In view of the intra-individual changes in both ^{131}I uptake and iodine turnover, this policy might well be responsible for a substantial number of inappropriate therapeutic dosages calculations. If the becquerel-per-gram method is used for therapy dosage calculation, it is our belief that ^{131}I-uptake measurements are best performed as shortly as possible before radioiodine treat-

ment. In the present study, only a small number of cases experienced an interval of less than 1 week between test and therapy. Therefore, definite conclusions are not possible at present. The predictive value of the uptake test for the actual retention of therapeutic dosages is not absolutely certain. Bockisch *et al.* have investigated this in patients with various thyroid disorders,[29] but the number of patients with Graves' disease in their series was limited.

It will be of interest to know whether the proposed adaptation leads to improved therapy results. Using the adapted protocol in a prospective study, we are now investigating the clinical outcome of radioiodine therapy in patients with Graves' disease.

5.6 Acknowledgements

For their cooperation in retrieving the patient data we are indebted to the referring physicians from the following hospitals: Academisch Ziekenhuis Utrecht; Centraal Militair Hospitaal, Utrecht; Beatrix Ziekenhuis Gorinchem; Bosch MediCentrum, 's-Hertogenbosch; Algemeen Christelijk Ziekenhuis Eemland, Amersfoort; Internistenpraktijk Berg & Bosch, Bilthoven; Lorentz Ziekenhuis, Zeist; Maatschap Internisten Gelderse Vallei, Ede/Wageningen; Medisch Centrum Molendael, Baarn/Soest; Overvecht Ziekenhuis, Utrecht; Ziekenhuis Oudenrijn, Utrecht; Ziekenhuis St. Jansdal, Harderwijk.

We greatly value the cooperation regarding the questionnaire of our colleagues from all seventy nuclear medicine departments in The Netherlands. We thank Mohamud Osman Dualeh for collecting the patient data, Aalt van Dijk for help in the statistical analysis. We express our gratitude to Prof.Dr. Cornelis J.M. Lips and to Ms. Sally Collyer for careful reading of the manuscript and for their valuable suggestions.

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Chapter Six

The outcome of radioiodine treatment in Graves' disease is determined by the ^{131}I turnover rate and by the timing of ^{131}I uptake measurements

Johannes W. van Isselt, Aalt van Dijk, Cornelis J.M. Lips, Peter P. van Rijk, M. Osman Dualeh, Herman J. Wijnne, John M.H. de Klerk

Submitted for publication

Summary

In a previous study of radioiodine therapy in patients with Graves' hyperthyroidism, we established that the clinical outcome was not linearly related to the radioiodine uptake and to the thyroid volume. Later we demonstrated that the timing of the uptake measurements influenced the measurement results. Others had found that the 5/24-h ^{131}I uptake ratio could serve as an alternative to multiple measurements of the effective half-life.

A re-evaluation of the radioiodine therapy results was made, using a protocol in which the uptake measurements immediately preceded the radioiodine treatment. With other parameters essentially unaltered, the radioiodine therapy results were compared with the results from the former protocol. The value of the 5/24-h ^{131}I uptake ratio was also assessed.

The percentage of patients with euthyroid outcome had not changed but a significant shift had occurred from hypothyroidism to persistent hyperthyroidism. This effect was most pronounced for patients in the low radioiodine uptake tertile and in patients with small thyroids. The 5/24-h ^{131}I uptake ratio (mean ± sd) was 0.74 ± 0.16 for patients with a hypothyroid outcome, 0.81 ± 0.17 for patients with a euthyroid outcome, and 0.88 ± 0.16 for patients with persistent hyperthyroidism.

Because of variations in radioiodine uptake over short periods of time, uptake measurements directly preceding the radioiodine treatment are recommended. This recommendation has a significant influence on the outcome of radioiodine therapy. The 5/24-h uptake ratio appears to be a strong predictor of the radioiodine therapy outcome.

6.1 Introduction

For radioiodine treatment of Graves' hyperthyroidism there are roughly two strategies with regard to dosage calculation, i.e. fixed and individualized schemas. Each have their own advantages and disadvantages. In several European countries, primarily for reasons of radiation safety, individualized dosage schemas are a legal requirement.[1] The most widely used is the becquerel-per-gram method,[2] necessitating measurements of the radioiodine uptake and of the thyroid volume.[3,4] Despite this additional effort the short-term cure rate is no better than with fixed dosage schemas.[4] In an earlier study of patients with Graves' disease, using the becquerel-per-gram method, we obtained a 70% cure rate (31% euthyroidism, 39% hypothyroidism) one year after treatment.[5] In that study, long intervals had been allowed between uptake measurements and radioiodine treatment. Later we demonstrated that substantial intraindividual variations in radioiodine uptake and radioiodine turnover rate occur over relatively short periods.[6] A recommendation to minimize the time between uptake measurements and radioiodine therapy was recently included in the guidelines of the American Society of Nuclear Medicine,[7] and was also mentioned in a textbook of nuclear medicine.[8] It seemed apposite to study the clinical effects of these recommendations.

A prospective investigation was conducted with a view to studying the effects of the timing of the radioiodine uptake measurement on the clinical outcome of radioiodine therapy in patients with Graves' disease. A protocol maintaining a 1-day interval between uptake measurements and therapy was compared with the protocol used in a historic control group in which arbitrary intervals had been allowed. The investigation was approved by the hospital's ethics committee.

6.2 Patients and methods

Patients

A follow-up study was conducted on 204 patients with Graves' hyperthyroidism who had been referred for radioiodine therapy by internists from 16 regional hospital sites. Patients who were referred for retreatment were not accepted for inclusion in this study. In 17 patients, a double radioiodine dosage was administered because an increased radioiodine turnover rate had been established at the first uptake test (see *Radioiodine uptake measurements*); these patients were excluded from the analysis. Also excluded were 22 patients who had been lost to follow-up. A total of 165 evaluable patients remained. The classic criteria for

Graves' disease,[5] used in the historic control group, were also applied here. All patients had used antithyroid drugs (ATD) in combination with levothyroxine (LT_4) for 1-1.5 years before radioiodine therapy, and all had had a relapse after discontinuation of the medication. In all cases, ATD and LT_4 were withheld for 3 days before the radioiodine uptake measurements; without exception the patients were clinically euthyroid at the time of radioiodine treatment. The medication was not resumed until the fourth day after radioiodine therapy.

Radioiodine uptake measurements

As part of a study of the stability of radioiodine uptake values,[6] the 5-h and 24-h radioiodine uptake measurements had been performed twice: first at the time of referral for diagnosis ('test 1') and second immediately preceding the radioiodine treatment ('test 2'). A scintillation probe (Canberra 7350-PE collimator with a 2×2" NaI crystal) was used for the radioiodine uptake measurements. Quality assurance and regular quality controls of the probe were procured.[1,9] The ^{131}I uptake was measured 5 h and 24 h after ingestion of a capsule containing a tracer dose of 0.37 MBq ^{131}I-NaI (Mallinckrodt Medical bv, Petten, The Netherlands). On the first day patients were allowed a light breakfast only.[10] The probe was positioned at the patient's thyroid region for 4 min, at a fixed distance of 25 cm. To allow background (BKG) correction, the probe was then positioned at the patient's thigh, also for 4 min and at the same distance. After correction for BKG, the activity in the thyroid was compared with the activity measured from a standard containing 0.37 MBq ^{131}I, placed in an anthropomorphic perspex thyroid/neck phantom, after correction for room BKG that was measured for four minutes. In terms of percentage the ^{131}I uptake by the thyroid is:

$$^{131}\text{I uptake} = [(\text{cpm}_{\text{neck}} - \text{cpm}_{\text{thigh}})/(\text{cpm}_{\text{standard}} - \text{cpm}_{\text{room BKG}})] \times 100\%.$$

Thyroid volume measurement

Immediately after the 24-h uptake measurement, an estimation of the thyroid volume was made from planar thyroid scintigraphy. The acquisition was done on an Elscint Apex 609 gamma camera with LEHR collimator, 20 min after intravenous administration of 80 MBq ^{99m}Tc-pertechnetate. The patient was in a supine position, with the neck slightly extended. Acquisition parameters: anterior view, 128×128×16 matrix, pixel size 4.42×4.42 mm (19.54 mm^2), zoom factor 1, acquisition time 300 s. The volume calculation was exercised with the surface model instead of the cylinder model. These two methods correlate well for thyroid volumes up to 200 g.[11] The surface model, a semi-automated com-

puter algorithm, was preferred as it eliminates observer variations. This model is based on the empirical formula:

$$V = 0.33 \times A^{3/2},$$

where V is the thyroid volume and A is the thyroid's surface which is derived from the frontal projection area.[12] After applying a 30% threshold to the scintigraphic image, the thyroid's surface was measured automatically.

Therapeutic dosage

The therapeutic ^{131}I dosage was based on the standard formula:

$$D = V \times (100\%/U) \times C,$$

where D is the therapeutic ^{131}I-NaI dosage (MBq), V is the thyroid volume (ml), U is the 24-h uptake (%), and the constant C equals 3.7 MBq/ml.[4] The dosage was corrected for changes in the 5-h uptake value between tests 1 and 2. The actual amount of ^{131}I administered per gram thyroid tissue varied from 2.7 to 5.3 MBq/ml (at 24 h). The therapeutic ^{131}I dosage was administered on the day following the final measurements. All diagnostic and therapeutic dosages were administered as capsules (Mallinckrodt Medical bv, Petten, The Netherlands).

Clinical evaluation

In order to assess the influence of the timing of the radioiodine uptake procedure, all methods had been essentially unaltered in comparison with that of the historic control study.[5] Subjects were divided in tertiles according to the 24-h uptake (< 60%, 60-79%, and 80-100%) or in two categories of thyroid volume (< 60 ml and ≥ 60 ml). The clinical outcome was evaluated after a follow-up period of 13.9 ± 8.3 months (mean ± sd). A diagnosis of euthyroidism, hypothyroidism or persistent hyperthyroidism was based on clinical presentation, TSH levels (normal 0.35-5.0 mIU/l) and use of medication. In addition, we investigated the relation between the clinical outcome and biological parameters such as radioiodine turnover, age and gender.

Statistical analysis

The results from the two studies were compared using the chi-square test, the one-way ANOVA test and linear regression analysis. P = 0.05 was maintained as the limit of statistical significance. Statistical calculations were executed with SPSS v6.1 for Macintosh (SPSS Inc., Chicago, IL).

6.3 Results

Overall outcome

In comparison with the former treatment protocol the overall incidence of early hypothyroidism was reduced from 39% to 27%, while persisting hyperthyroidism had increased from 30% to 40% (Pearson's chi-square = 5.30, P = 0.021); these differences were just below the level of significance when euthyroid outcomes were also included in the analysis (P = 0.069). The number of euthyroid outcomes was unaltered (31% versus 33%, n.s.).

Age and gender

The female-to-male ratio in this study was 5:1 (see table 6.1). There were no age differences between the sexes (P = 0.64). The clinical outcome was affected neither by age (P = 0.97), nor by gender (P = 0.36), see table 6.2.

Table 6.1 Patient data for female, male, and all patients with regard to thyroid volume, ^{131}I uptake, ^{131}I turnover rate, ^{131}I dosage per gram, and age.

	137 female patients (mean ± sd)	28 male patients (mean ± sd)	all patients (mean ± sd)
thyroid volume (ml)	45.6 ± 28.9	48.9 ± 22.1	46.2 ± 27.8
5-h uptake (%)	55.5 ± 22.3	60.1 ± 22.2	56.3 ± 22.3
24-h uptake (%)	65.2 ± 18.6	70.9 ± 16.6	66.2 ± 18.4
5/24-h uptake ratio	0.82 ± 0.18	0.82 ± 0.17	0.82 ± 0.17
dosage/ml at 24h (MBq)	3.8 ± 0.5	4.0 ± 0.5	3.8 ± 0.5
age (years)	45.8 ± 15.0	47.3 ± 14.3	46.0 ± 14.8

Table 6.2 Clinical outcome in relation to thyroid volume, ^{131}I uptake, ^{131}I turnover rate, ^{131}I dosage per gram, and age by gender.

	hypothyroid (mean ± sd)	euthyroid (mean ± sd)	hyperthyroid (mean ± sd)
thyroid volume (ml)	38.7 ± 22.3	43.9 ± 23.7	52.9 ± 32.4
5-h uptake 'test 2' (%)	46.5 ± 23.2	54.9 ± 20.0	63.8 ± 20.8
24-h uptake 'test 2' (%)	59.5 ± 19.9	65.8 ± 16.6	70.8 ± 17.5
5/24-h uptake ratio	0.74 ± 0.16	0.81 ± 0.17	0.88 ± 0.16
dosage/ml at 24h (MBq)	3.9 ± 0.6	3.8 ± 0.5	3.8 ± 0.5
age (years)			
all patients	44.3 ± 14.9	47.9 ± 15.5	45.7 ± 14.3
female patients	44.1 ± 14.5	47.3 ± 15.8	45.6 ± 14.8
male patients	44.7 ± 17.0	50.9 ± 14.4	46.4 ± 11.3

Table 6.3 Clinical outcome in the former and the present study protocols (percentages between brackets).

overall results

	former		present	
hypothyroidism	56	(39)	44	(27)
euthyroidism	47	(31)	54	(33)
hyperthyroidism	45	(30)	67	(40)
total	148		165	

thyroid volume

	< 60 ml				> 60 ml			
	former		present		former		present	
hypothyroidism	48	(41.4)	39	(30.2)	9	(28.1)	5	(13.9)
euthyroidism	39	(33.6)	43	(33.3)	7	(21.9)	11	(30.6)
hyperthyroidism	29	(25.0)	47	(36.4)	16	(50.0)	20	(55.6)
total	116		129		32		36	

24-h uptake

	< 60%				60-80%				> 80%			
	former		present		former		present		former		present	
hypothyroidism	30	(53.6)	22	(39.3)	23	(32.9)	14	(19.7)	3	(13.6)	8	(21.0)
euthyroidism	15	(27.8)	17	(30.4)	26	(37.1)	29	(40.8)	6	(27.3)	8	(21.0)
hyperthyroidism	11	(19.6)	17	(30.4)	21	(30.0)	28	(39.4)	13	(59.1)	22	(57.9)
total	56		56		70		71		22		38	

Thyroid volume and outcome

The mean thyroid volume for female and male patients is given in table 6.1. As in the historic control group, the thyroid volume had a pertinent influence on the outcome of radioiodine therapy (P = 0.03). In comparison with the historic controls there was a significant decrease of hypothyroidism accompanied by an increase of persistent hyperthyroidism in patients with a thyroid volume < 60 ml (chi-square = 4.7, P = 0.02); the percentage of euthyroidism remained unchanged. In patients with thyroids ≥ 60 ml the same tendency was observed, but the changes in this relatively small group were not significant (chi-square = 1.6, P = 0.21; see table 6.2). A comparison of the results from the two studies is represented in table 6.3.

^{131}I-uptake and outcome

The mean 5-h and 24-h uptake percentages (of test 2) for female and male patients are given in table 6.1. The relation between the radioiodine uptake and the clinical outcome which had been observed in the historic control group was confirmed in the present study (see table 6.2). The relation with the clinical outcome was somewhat clearer for the 5-h uptake than for the 24-h uptake. In comparison with the former protocol there was a nonsignificant decrease of hypothyroidism and a concurrent increase of hyperthyroidism in the lower uptake tertiles (uptake < 60%: chi-square = 2.5, P = 0.12; uptake 60-80%: chi-square = 3.14, P = 0.08; see also tables 1, 2 and 3).

Radioiodine turnover rate and outcome

The turnover rate (mean ± sd, 95% confidence interval between brackets) was 0.74 ± 0.16 (0.69-0.79) for patients with a hypothyroid outcome, 0.81 ± 0.17 (0.76-0.84) for those who became euthyroid, and 0.88 ± 0.16 (0.84-0.92) for those with persistent hyperthyroidism (see figure 6.1). The mean turnover rate in the group of patients with persisting hyperthyroidism differed significantly from the others (P < 0.05). The correlation between the radioiodine turnover rate and the 5-h uptake (R^2 = 0.69, P < 0.0001) as well as the 24-h uptake (R^2 = 0.32, P < 0.0001) was not strong, but highly significant. As the radioiodine turnover rate had not been taken into account in the historic control group, a comparison of this parameter could not be made.

^{131}I dosage per ml (corrected for uptake) and outcome

The amount of ^{131}I administered per ml thyroid tissue corrected for 24-h uptake ranged from 2.7 to 5.3 MBq/ml (70-140 μCi/ml). The mean and standard devia-

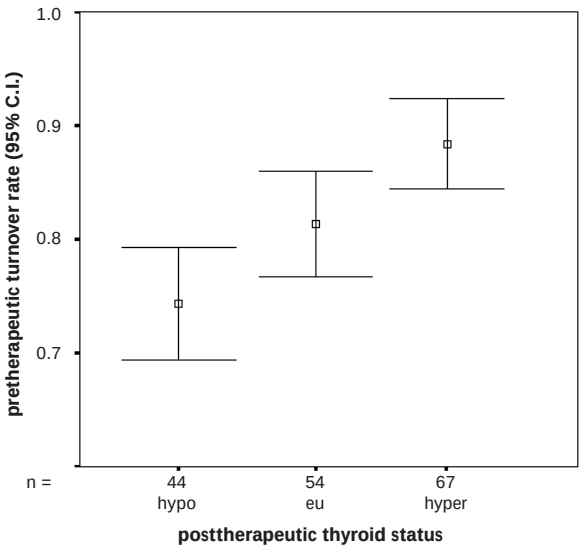

Figure 6.1 The posttherapeutic thyroid status as a function of the pretherapeutic ^{131}I turnover rate.

tion of the ^{131}I dosages was significantly different in the three outcome groups. Most patients who had received dosages > 3.9 MBq/ml (105 µCi/ml) became hypothyroid (see table 6.1).

6.4 Discussion

The importance of standardized methodology can hardly be overemphasized. In the area that was presently investigated – standardization of the timing of the uptake measurements before radioiodine therapy – a significant shift was observed in the clinical outcome from hypothyroidism to persistent hyperthyroidism (or more likely from hypothyroidism to euthyroidism, and from euthyroidism to hyperthyroidism) in comparison with our earlier study. As the net percentage of euthyroid outcomes remained unaltered, the 'cure rate' (defined as the number of patients with euthyroid or hypothyroid outcome divided by the total number of patients treated) had dropped from 70% to 60%. We and others regard euthyroidism as the only true cures and hypothyroidism as a relatively undesirable outcome. The prevention of hypothyroidism after radioiodine therapy may have greater clinical implications than is usually acknowledged. In a recent study it was stated that the functioning and the well-being of hypothyroid patients is better with combined T_3/T_4 medication than with T_4 alone.[13] We

argue that the same advantages may be expected from the preservation of normal thyroid function. In another study, a patient valuation study of radioiodine treatment of Graves' disease, 33% of patients who were biochemically well adjusted to thyroxine still had problems with mood, weight, and fatigue.[14]

It is not certain whether the time-standardized uptake measurements truly reflect the functional state of the thyroid gland at the time of radioiodine treatment, but a shorter interval is not feasible. A comparison of pretherapeutic uptake measurements with posttherapeutic measurements such as was done by Bockisch *et al*. in a small number of patients with Graves' disease,[15] could possibly elucidate this matter but methodological problems should not be underestimated.

The relation between thyroid volume and clinical outcome, also demonstrated by others,[2,16] was again confirmed. It has been proposed that the deviant response of large Graves' thyroids to radioiodine therapy may result from the presence of autonomous tissue with functional differences in uptake and organification of iodine, or from increased stimulation of thyrocytes by TSH receptor antibodies;[17-19] such changes are unpredictable and therefore difficult to account for. Interestingly, the clinical outcome after medical treatment of Graves' disease shows a similar relation with goiter size: relapse is seen significantly more often in patients with larger goiters.[20] In the present study (as well as in the historic control study) all patients who were referred for radioiodine treatment had persisting hyperthyroidism after medical treatment. It seems reasonable to presume that larger goiters were overrepresented in our study; it is inferred that such a selection bias would have a negative influence on the cure rate. Earlier we have argued that the correlation between thyroid volume and clinical outcome may be in part the result of inaccurate volume measurements.[5] The accuracy of planar scintigraphy in measuring the functional thyroid volume as such is questionable.[21-26] Planar scintigraphy and alternative modalities such as SPECT and ultrasonography need critical validation.

The 5-h uptake value appeared to be a better indicator of the clinical outcome than the 24-h uptake value; this was also reported by Hayes *et al*.[27] This finding may be secondary to the fact that the correlation with the 5/24-h uptake ratio is substantially better for the 5-h than for the 24-h uptake value.

As in the previous study, there was no relation between the clinical outcome and the patients' gender or age. The fact that other researchers did find such a relation might be explained by the clear association that they observed between age, gender, and higher thyroid volumes.[28]

The radiation absorbed dose delivered to the thyroid gland is the most important factor concerning the clinical outcome of radioiodine therapy in patients with Graves' hyperthyroidism. Accurate dosimetry, however, is very complex.[29] Several factors contribute positively or negatively to the radiation absorbed dose. Thyroid volume, ^{131}I uptake, ^{131}I turnover rate and administered ^{131}I dosage per volume thyroid tissue were the most pertinent in our study. Antithyroid medication has a strong influence on the outcome of radioiodine therapy.[30] ATD had been invariant in all patients in this study and its influence could therefore not be studied.

One of the drawbacks of the classic dosage formula, $D = V \times (100\%/U) \times C$, is that it does not account for the effective half-life (T_{eff}) of thyroidal radioiodine. T_{eff} varies with the biological half-life (T_{biol}), which may be 24-100 days in euthyroid individuals, about 6 days in most hyperthyroid patients, and as little as 3 days in hyperthyroid patients with rapid turnover ('small iodine pool').[2,31,32] Assessment of the T_{eff} is often regarded as cumbersome, because it entails multiple measurements over a 5-7 day period. T_{eff} is a function of T_{biol}, and the radioiodine turnover rate has a nonlinear inverse relation to T_{biol}.[33] Aktay *et al.* had already established a relation between the radioiodine turnover rate (defined as the 5/24-h radioiodine uptake ratio) and the therapy outcome;[31] by their definition the turnover rate was 'rapid' when it was greater than 1. In the present study we found relatively clear cut-off points at 0.75 and 0.85 for the radioiodine turnover rate with respect to posttreatment outcome (even after exclusion of patients with a turnover rate > 1 at 'test 1'). A combination of risk factors accentuated the differences in clinical outcome: hypothyroidism occurred in 44% of patients who had a thyroid volume < 60 ml combined with an ^{131}I turnover rate < 0.75, whereas only 12% hypothyroidism occurred in patients with a combination of thyroid volume > 60 ml and ^{131}I turnover rate > 0.85.

We support the opinion that the turnover rate is a useful alternative to multiple uptake measurements over several days.[31] Identification of patients with increased risk of hypothyroidism or persistent hyperthyroidism could possibly lead to quantifiable adjustments to the standard dosage formula.

6.5 Acknowledgements

We express our gratitude to the internists from the following hospitals for referral of the patients and for supplying the follow-up data: Beatrix Ziekenhuis, Gorinchem; Bosch Medicentrum, 's-Hertogenbosch; Centraal Militair Hospitaal,

Utrecht; Eemland Ziekenhuis (locations St. Elisabeth Gasthuis, De Lichtenberg); Internistenpraktijk Berg & Bosch, Bilthoven; Lorentz Ziekenhuis, Zeist; Medisch Centrum Molendael (locations Baarn, Soest); Mesos Ziekenhuis (locations Oudenrijn Ziekenhuis and Ziekenhuis Overvecht), Utrecht; St. Jansdal Ziekenhuis, Harderwijk; Ziekenhuis Gelderse Vallei (locations Veenendaal, Bennekom, Ede, Wageningen); University Medical Center Utrecht.

We are grateful to Ms. Sally Collyer for critical reading of the English text and for her most valuable suggestions.

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Chapter Seven

Computer tomography is not suited for thyroid volume measurements in patients with Graves' disease before radioiodine therapy

Johannes W. van Isselt, Eric Tetteroo, Adrianus P.G. van Gils, Peter P. van Rijk, John M.H. de Klerk

Submitted for publication

Summary

A pilot study was done to investigate the feasibility of native CT for thyroid volume measurements in patients with Graves' disease. In 4 out of 5 patient studies, the interface between the thyroid and its surroundings could not be adequately defined in a majority of the cross-sections, due to a lack of soft-tissue contrast. Contrast enhanced CT is no option in the work up for ^{131}I treatment because iodinated contrast agents may block the thyroid's radioiodine uptake capacity for several weeks. It was concluded that CT is not suited for thyroid volume measurements in patients with Graves' disease who are referred for radioiodine therapy.

7.1 Introduction

Accurate thyroid volume data are indispensable for individualized dosage calculations in patients who are referred for radioiodine therapy.[1-4] In clinical circumstances, the thyroid volume is usually measured with planar scintigraphy or with ultrasonography.[5,6] A good correlation has been demonstrated between scintigraphic or ultrasonographic data and surgical thyroid specimens.[7,8] For these comparisons, however, equipment had been used (*viz*., rectilinear scanners for scintigraphy, and static B-scanners for ultrasonography) that is no longer regarded as state of the art. In individual patients, the accuracy of modern gamma cameras or real-time ultrasound scanners for thyroid volume measurements has not been assessed with a gold standard.

The aim of the present study was to assess the feasibility of thyroid volume measurements with native computer tomography (CT) in patients with Graves' disease. Radiographic contrast media are contra-indicated in patients who are scheduled for radioiodine therapy, as the relatively small content of free iodine (contamination) in these agents is enough to block the thyroidal radioiodine uptake for weeks or even months.[1,4,9,10] Generally speaking, CT is a reliable standard for organ volumetry.[11,12] The value of native CT for thyroid volume measurements has earlier been demonstrated in patients with nontoxic nodular goiter.[13]

7.2 Patients and methods

Native CT-scanning was performed in addition to the standard pretherapeutic work up (^{131}I uptake test and ^{99m}Tc-pertechnetate thyroid scintigraphy) in 5 patients with Graves' disease who had been referred for radioiodine therapy. Written informed consent had been obtained from all patients. The study was approved by the hospital's ethics committee.

Acquisition

Spiral CT without contrast enhancement was performed with a commercially available scanner (Tomoscan SR 7000, Philips Medical Systems, Best, The Netherlands). A volume acquisition was performed with the following protocol: 120 kV at 250 mA (± 40 seconds continuous exposure); 5 mm collimation (slice thickness); 5 mm/s table speed with a reconstruction index of 3 mm. Patients were in a supine position and were requested not to swallow. Scanning was performed in descending order over approximately 20 cm (mandibular angle to aortic root) with a field of view of 200 mm, a 512×512 matrix, and the plane of

section perpendicular to the cervical spine. All studies were reviewed independently by two readers.

Image processing

For analysis of thyroid volumes the summation-of-areas technique was used, a method of volume calculation from sequential CT images. This method required manual outlining of the thyroid gland with a mouse on all thyroid-containing CT cross-sections on screen, using the volume measurement function on an Easyvision® workstation (Philips Medical Systems). For each cross-section this function calculates the volume in cubic centimeters within the region of interest, taking into account magnification factor, slice thickness and reconstruction index. The thyroid volume was determined by adding up the volumes calculated from the separate slices.

7.3 Results

In 4 out of 5 studies, accurate manual segmentation of the entire thyroid gland was not feasible. In a majority of the cross-sections, the interface between the thyroid gland and the surrounding tissues (dermal structures, fat, muscles) could only partially be identified. This is illustrated in figures 7.1a-d. In the one remaining study (figure 7.1e) the thyroid contour could be identified in most cross-sections, enabling a reliable volume measurement of the thyroid gland.

7.4 Discussion

In patients with Graves' disease, the delineation and manual segmentation of the thyroid gland was not feasible with native CT. This is contrary to findings in patients with nontoxic nodular goiter.[13] The discordant results with CT-scanning in different thyroid disorders lead to some speculation.

Iodine is stored in the thyroid gland in the form of colloidal tri- and tetraiodothyronine. In euthyroid subjects the iodine content approximates 500 µg per gram thyroid tissue.[14,15] In hyperthyroid patients the iodine turnover is increased,[16] which is reflected in a reduction of the thyroidal iodine pool.[17,18] We argue that the lower (endogenous) thyroidal iodide content in Graves' disease patients causes a lower signal intensity on CT, which in turn leads to a diminished contrast between the thyroid gland and the surrounding tissues in comparison with euthyroid subjects.

With concern to contrast, the properties of newer developments such as multi-array CT are no different from standard or spiral CT.

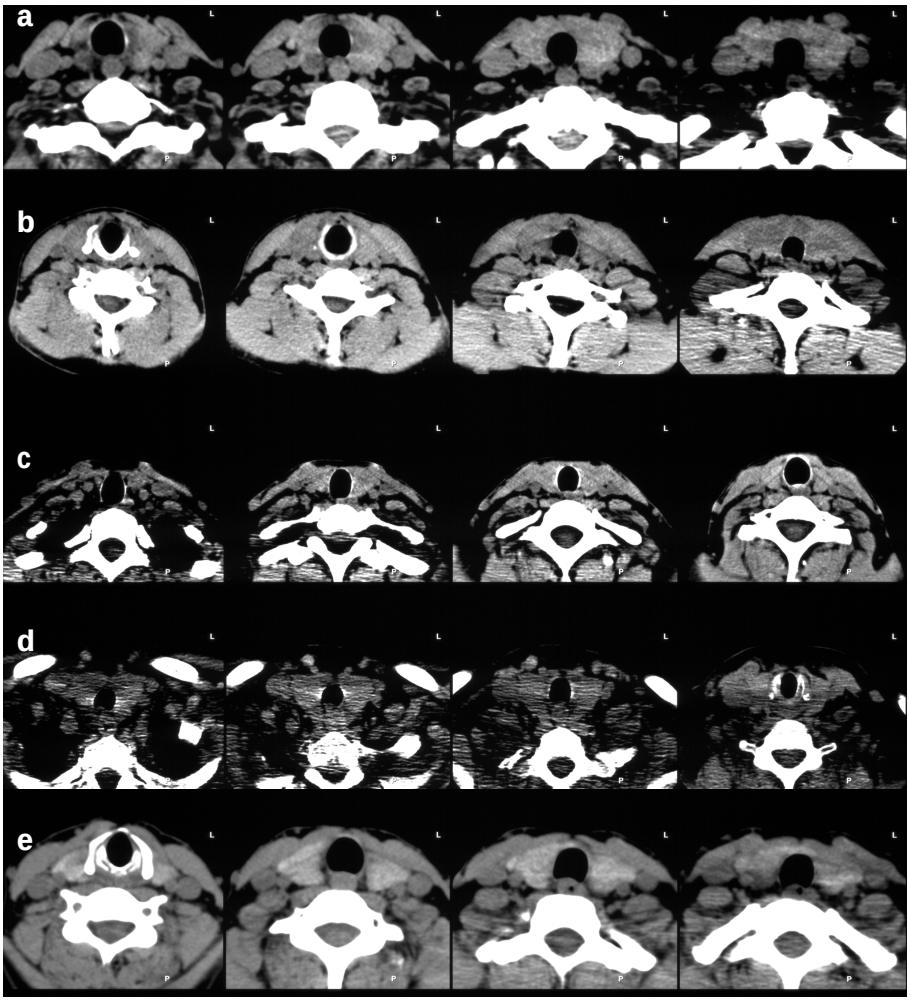

Figure 7.1 CT images of 5 patients (a-e), at the level of the thyroid gland. Four cross-sections with interslice gaps of approximately 1.5 cm are shown for each patient study.

With native CT, proper segmentation of the thyroid gland is problematic in most patients with Graves' disease. Contrast enhancement with radiographic contrast media is contraindicated if radioiodine treatment is considered. In conclusion, CT-scanning is not suited for thyroid volume measurements in patients with Graves' disease who are referred for radioiodine therapy.

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Chapter Eight

A comparison of methods for thyroid volume determination in patients with Graves' disease

Johannes W. van Isselt, Freek J. Beekman, Chris Kamphuis, John M.H. de Klerk, Lambertus J. Polman, Adrianus P.G. van Gils, Koen Vincken, Peter P. van Rijk

Submitted for publication

Summary

The measurement of the thyroid volume is one of the cornerstones of the calculation of individualized radioiodine therapy dosages for patients with Graves' hyperthyroidism. Thyroid volume determinations are usually made with ultrasonography or with thyroid scintigraphy, although the accuracy of these techniques is not well known. The aim of this study was to assess the accuracy of three modalities for the determination of the thyroid volume in patients with Graves' disease: ultrasonography (US), planar scintigraphy (PS) and single photon emission computer tomography (SPECT) with attenuation correction and scatter correction.

A comparison was made of these three modalities versus magnetic resonance imaging (MRI) as the gold standard. Thyroid volume measurements were done in 25 patients with Graves' disease. Thyroid segmentation was performed manually in gadolinium enhanced T1-weighted MRI images and a summation-of-areas technique was used for the volume measurements. With US, the volumes were calculated using the ellipsoid volume model for two-dimensional measurements. After filtering and thresholding, a standard volume formula was applied to the PS images. The SPECT data were filtered, and after applying a threshold method, an automatic segmentation algorithm was used for the volume determinations.

The thyroid volumes as they were calculated with MRI were 25.0 ± 13.8 ml (mean ± sd, range: 7.0-56.3 ml). PS correlated poorly with MRI (R^2 = 0.61), and showed a relatively large bias (–4.0 ± 17.6 ml, mean ± 2 sd). The correlation with MRI was appreciably better for SPECT (R^2 = 0.84) than for planar scintigraphy, with a small bias but a large standard deviation (1.8 ± 11.9 ml). US had an excellent correlation with MRI (R^2 = 0.96), but it had the largest bias (–6.6 ± 8.8 ml). Functional imaging (PS or SPECT) remains a requirement for choosing the proper dosage regimen.

Substantial improvement over currently used methods for measuring the thyroid volume may be obtained with one of three options: MRI + PS, SPECT, or US (if a correction factor is applied) + PS. A definitive choice in the clinical environment will be based on clinical, logistic and financial considerations.

8.1 Introduction

Individualized treatment protocols for radioiodine (^{131}I) therapy in patients with Graves' disease are based on measurements of thyroid volume and radioiodine uptake.[1-3] This is expressed in the formula:

$$D = V \times (100\%/U) \times 3.7 \text{ MBq},$$

where D equals the ^{131}I therapy dosage (MBq), V is the thyroid volume (ml), U is the 24-h thyroidal radioiodine uptake (%) and 3.7 is a constant (MBq/g).[4] From this formula it follows that the accuracy of the therapy dosage is directly dependent from the accuracy of thyroid volume measurements and radioiodine uptake measurements. The importance of further standardization of the latter has recently been described.[5] Validation of the most frequently applied modalities for thyroid volume measurements – ultrasonography and scintigraphy – is lacking.

Worldwide, ultrasonography (US) is probably the most frequently used modality for thyroid measurements in the routine clinical setting. It is a relatively inexpensive and easily accessible technique. In the past, validation studies for volume measurements have been conducted with static B-scanners, using a summation-of-areas technique.[6,7] For real-time US scanners operated with hand-held transducers, volume estimations are generally made from measurements of the largest dimensions along the three principal axes, using an ellipsoid model.[8]

Scintigraphy is the second most frequently applied modality for thyroid volume measurements, as thyroid scintigraphy is also used for a functional diagnosis in the work up for radioiodine therapy. Different mathematical models (ellipsoid, cylinder and surface models) coexist for the calculation of the thyroid volume from two-dimensional scintigraphic data.[9,10] Validation studies have been conducted with rectilinear scanners,[9] but rarely with gamma cameras.[11]

Single photon emission computer tomography (SPECT) has been advocated for thyroid volume measurements. Although reportedly SPECT is more precise than planar imaging for such measurements,[12-16] most of the described methods are not applicable with 'off-the-shelf' hardware and software, which hinders their clinical implementation. Substantial improvement of standard SPECT results has been reported with attenuation correction and scatter correction.[17] Currently such corrections can be applied with commercially available equipment.

^{124}I PET has great research potential,[18-21] but this modality has far too limited accessibility and is too expensive to be considered for clinical use.

Native CT is not suitable for thyroid volume measurements in patients with

Graves' disease.[22] Radiographic contrast media are no option in this patient group, as they may block the thyroid's radioiodine uptake for weeks or even months.[3,4,23,24]

Magnetic resonance imaging (MRI) has a documented place in thyroid imaging.[25-31] MRI provides excellent delineation of the thyroid from the surrounding tissues, either with or without gadolinium contrast enhancement.[30-32] The summation-of-areas technique has been well standardized and validated, and its reproducibility (with an error of about 1-2%) is very good.[27,28]

Ultrasonography and thyroid scintigraphy have become standard clinical practice for measurements of the thyroid volume. The aim of this study was to assess the accuracy of these modalities.

8.2 Patients and methods

Patients

Twenty-five consecutive patients with Graves' hyperthyroidism who had been referred for radioiodine therapy were accrued. The study was approved by the hospital's ethics committee. Written informed consent was obtained from all patients. One patient suspended her participation with only the SPECT study lacking. In one patient, the MRI scan was incomplete at the caudal end, and consequently MRI volume measurements could not be done in this patient. Due to computer failures one SPECT study and one US study were lost after acquisition.

MRI

In all patients, the volume of the thyroid gland was measured on a Philips Gyroscan™ ACS-NT 1.5 T Powertrak 6000 (Philips Medical Systems, Best, The Netherlands). T1-weighted scans were acquired before and after intravenous administration of dimegluminegadopentetate, 469.01 mg/ml (Magnevist®, Schering AG, Germany) (TR/TE: 552/20 msec; FOV 25 cm; 16 transverse slices, thickness 6 mm/interslice gap 0.6 mm; NSA 2; total scanning time 3.47 min). A typical example of an MRI study is given in figure 8.1.

The images were processed on a Gyroview™ workstation (Philips Medical Systems, Best, The Netherlands). The circumferences of the thyroid gland were depicted and segmented manually with a mouse, and the area was calculated on each slice. The thyroid volume was then calculated with a summation-of-areas technique, using a multiplication factor of 1.1 to correct for the interslice gaps.

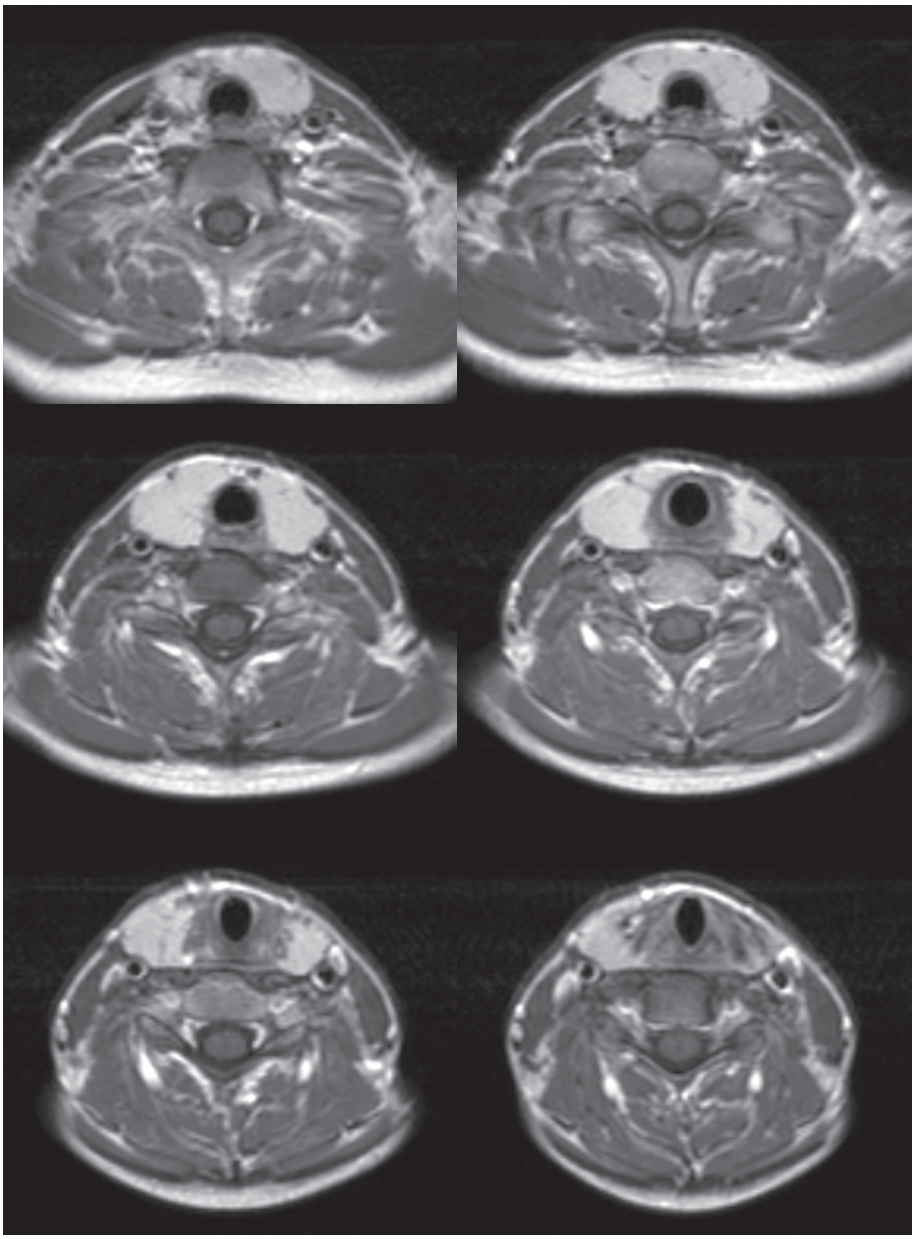

Figure 8.1 T1-weighted gadolinium enhanced thyroid MRI study in patient #6 (only 6 cross-sections shown).

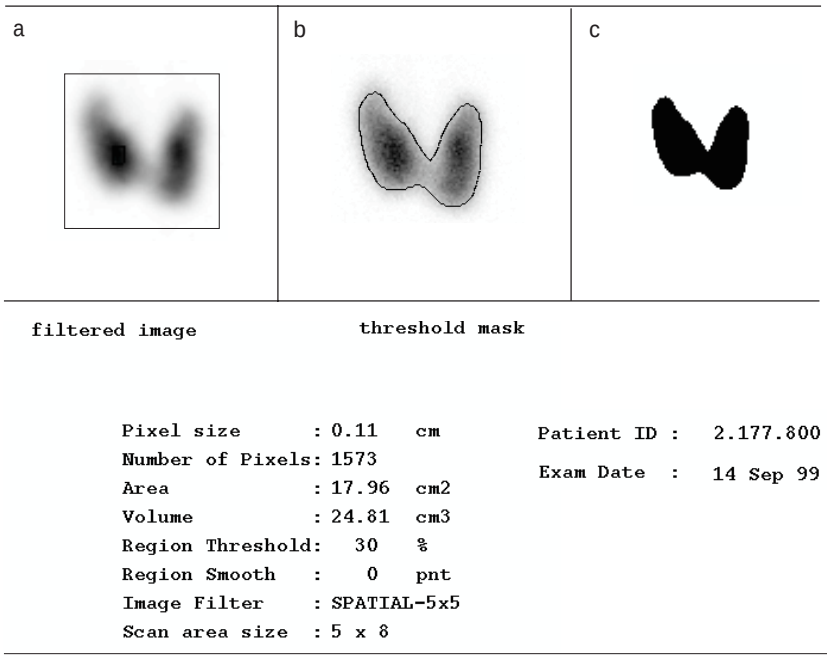

Figure 8.2 Thyroid scintigraphy in patient #6; a: box ROI around the thyroid; b: automatic contour detection with a 30% threshold; c: image after segmentation.

Planar scintigraphy

On the day before therapy, 2-13 days after the MRI scan, thyroid scintigraphy was done in all patients 20 min after intravenous administration of 120 MBq ^{99m}Tc-pertechnetate. The acquisition was done with a rectangular field-of-view gamma camera (ADAC Argus™, ADAC Laboratories, Milpitas, CA) with LEHR collimation and with the patient in a supine position. Acquisition parameters: anterior view, 128×128×16 matrix, zoom factor × 1, pixel size 4.2 mm, acquisition time 300 s.

A 5×5-point median filter was applied to reduce image noise.[33] A rectangular region of interest (ROI 1) was drawn including the entire thyroid gland and leaving out all nonthyroidal radioactivity concentrations, most notably the salivary glands. Within ROI 1, an area of 5×8 pixels with maximum count density was computed automatically. Using a lower threshold of 30% of this maximum value, an isocontour was created automatically around the thyroid (ROI 2). The 30% threshold level had been derived from phantom studies with volumes ranging from 10 to 40 ml. The thyroid surface was the number of pixels in ROI 2

multiplied by the pixel size (4.2×4.2 mm). The thyroid volume was calculated with the empirical formula:

$$V = 0.33 \times A^{3/2},$$

where V equals the thyroid volume (in cm^3), and A the thyroid surface projection area (in cm^2).[9] In figure 8.2, the PS images are displayed for the same patient as in figure 8.1.

SPECT

One intravenous administration of 120 MBq ^{99m}Tc-pertechnetate was used for both the planar scintigraphy and the SPECT acquisition. Zoom factor (× 1) and matrix size (128×128×16) for SPECT were the same as for planar scintigraphy.

An ADAC Vertex™ dual-detector rectangular FOV SPECT camera with Vantage™ transmission hardware and software was used, with the two detectors (with Vantage™ extra high-resolution collimators) in a perpendicular position. With the patient in the supine position, a 180° anterior rotation, starting from the 270° position, was completed with 32 azimuths at 25 s/azimuth. A matrix size of 128×128 was chosen for both SPECT and planar scintigraphy as a compromise between partial volume effect and acquisition time. Using a ^{153}Gd transmission line source (containing approximately 175 MBq), transmission scanning was done during 24 s/azimuth simultaneously with the emission scan. Total scanning time was 26 min. A scatter window (111-125 keV) was set between the ^{153}Gd transmission source peak (100 keV) and the ^{99m}Tc photopeak (140 keV).

The reconstruction of the transmission scan was done with filtered backprojection, attenuation correction and correction for down-scatter of ^{99m}Tc into the ^{153}Gd window. For the emission scan an iterative maximum likelihood reconstruction algorithm with attenuation correction and scatter correction and resolution recovery was used (ADAC EXSPECT™). Post-processing measurements were done on a Silicon Graphics™ workstation (MIPS 10000 processor) (Silicon Graphics, Mountain View, CA), using standard software. For noise reduction, an edge-preserving filter was applied.[33] Within the largest transaxial cross-section of the thyroid a ROI of 4×4 pixels was placed in the center of the largest thyroid lobe. If both lobes appeared equally large, the right lobe was chosen. Within this ROI the average maximum pixel value was calculated. A threshold of 45% of this value was applied for the segmentation of the thyroid gland. This threshold value had been established with a least-squares method in experiments using different thresholds with 5% increments. In figure 8.3, the SPECT reconstructions are displayed for the same patient as in figure 8.1.

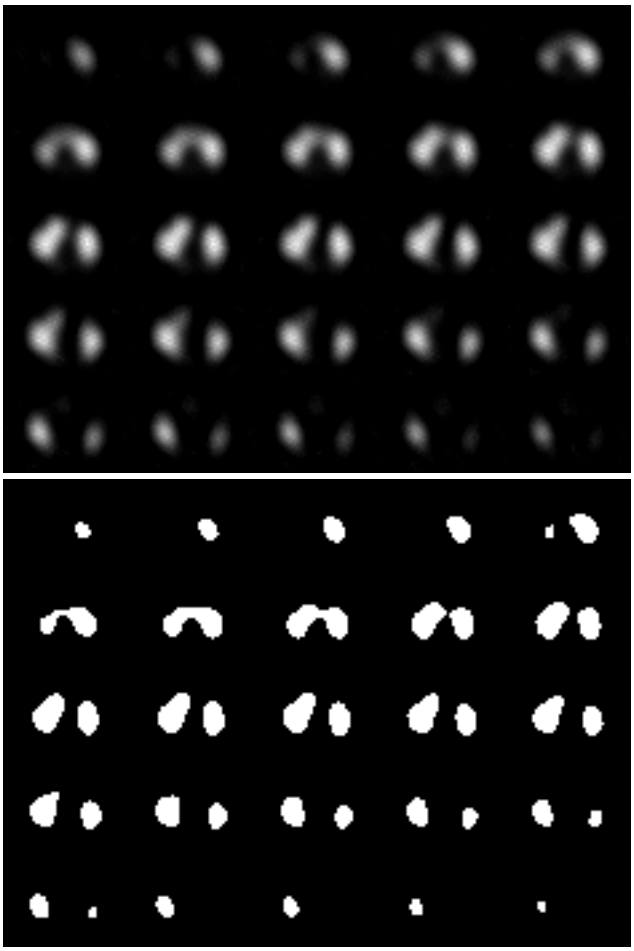

Figure 8.3 Thyroid SPECT in patient #6; a: transaxial cross-sections, and b: the same cross-sections segmented with a 45% threshold.

Ultrasonography

A real-time ultrasound scanner (Pie Medical Scanner 350, Pie Medical, Maastricht, The Netherlands) was used with a 7.5 MHz linear array transducer (width 3.8 cm). With the patient in a supine position and the neck slightly overextended, the thyroid lobes were scanned separately, and measurements were done in the three largest dimensions along the principal axes. In figure 8.4, transaxial US cross-sections are displayed for the same patient as in figure 8.1.

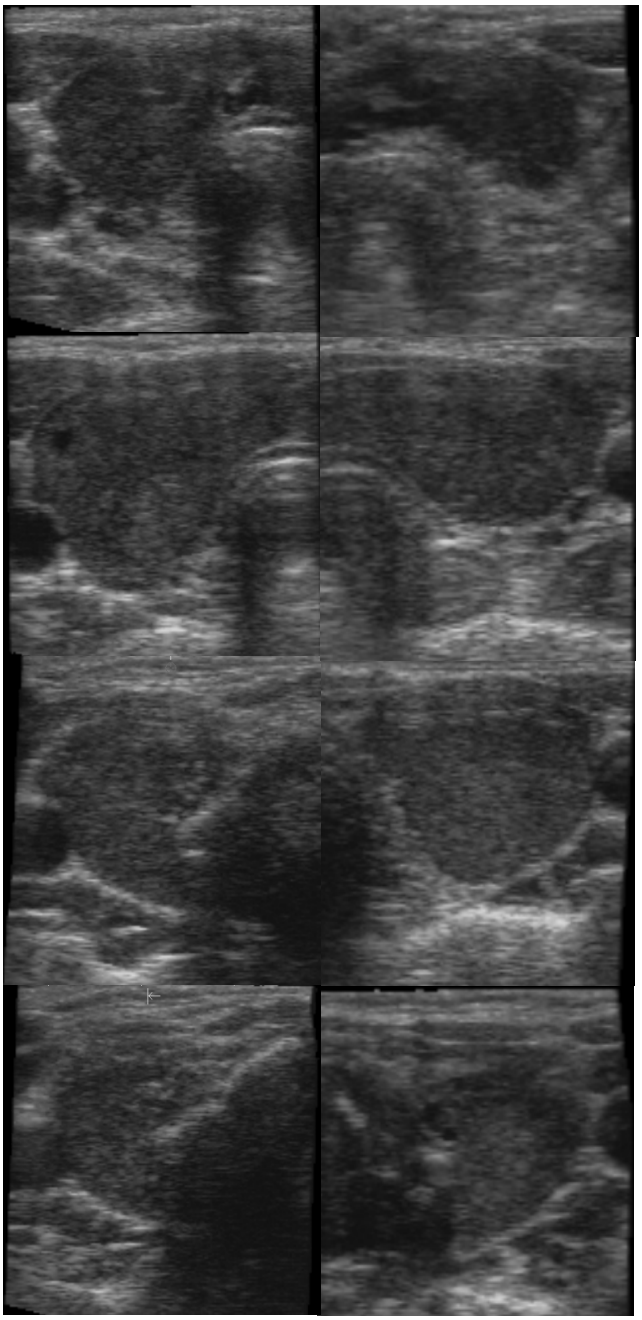

Figure 8.4 Thyroid US in patient #6: transaxial cross-sections with approximately 1.5 cm interslice gaps.

The volume of each lobe was calculated with the formula for ellipsoid volumes:

$$V = \pi/6 \times L \times W \times D,$$

where L is the maximum length, W the maximum width and D the maximum depth, measured along the three principal axes of the thyroid lobes. The thyroid volume was the sum of the volumes of the two lobes.

Statistical analysis

All quantitative results from the PS, SPECT and US studies were compared with MRI as the gold standard. The statistical analysis was done with linear regression

Table 8.1 Results of thyroid volume measurements with all four modalities.

patient #	MRI (ml)	SPECT (ml)	PS (ml)	US (ml)
25	–	43.9	89.4	61.3
4	7.0	9.9	10.7	6.3
5	7.9	15.9	26.0	4.3
8	10.9	11.2	11.0	7.9
22	12.2	17.7	22.0	8.6
18	12.5	11.5	19.6	9.1
17	12.9	15.2	16.9	9.6
23	13.2	13.7	22.2	8.1
15	13.8	13.2	29.6	8.5
12	15.1	17.4	24.0	11.5
24	18.9	15.8	21.2	12.1
1	20.8	22.5	39.0	20.0
11	21.1	20.4	22.8	11.3
13	21.4	–	24.0	–
9	24.8	22.3	23.4	14.4
7	28.1	21.9	19.2	23.8
3	29.1	21.9	38.0	21.4
6	31.2	29.5	24.8	20.7
14	34.3	42.0	43.1	20.2
2	34.5	27.7	46.0	30.0
21	41.0	–	38.2	39.1
20	41.1	25.4	26.7	26.8
10	41.8	31.1	52.7	31.5
19	49.5	41.2	43.7	34.3
16	56.3	49.3	57.5	45.8

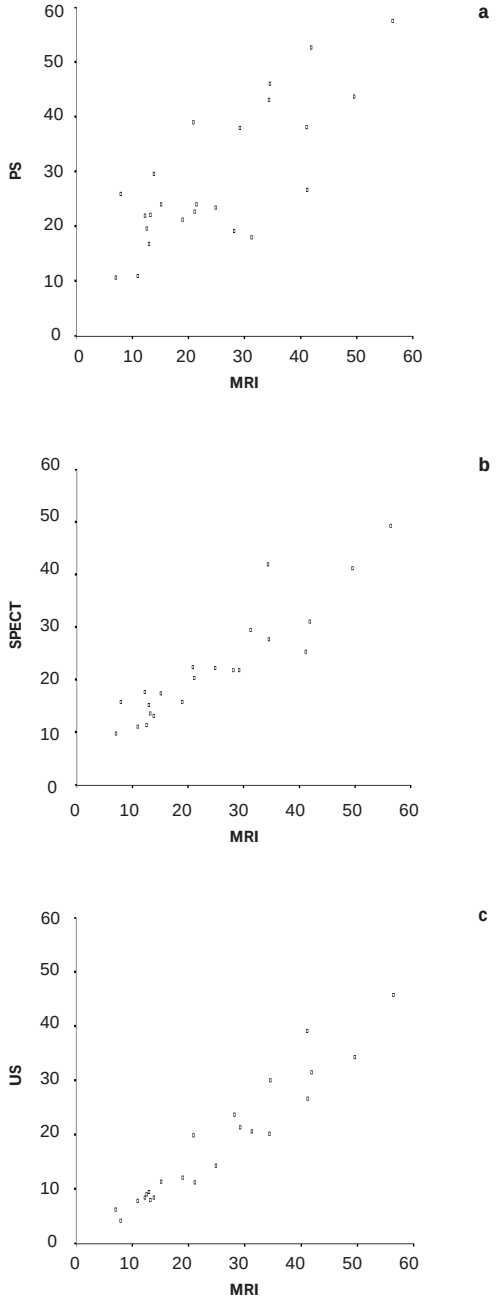

Figure 8.5 Linear regression analysis. Scatter plots for thyroid volumes measured with MRI versus (a) planar scintigraphy, (b) SPECT, and (c) ultrasound.

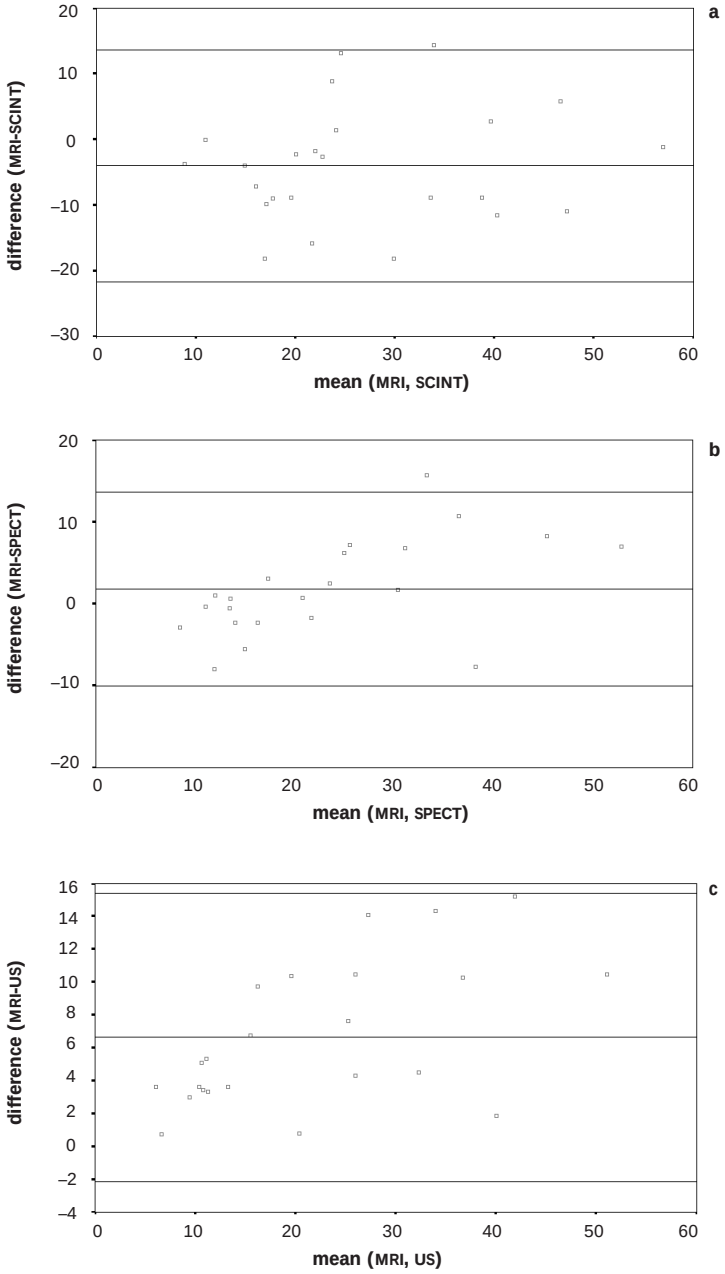

Figure 8.6 Difference versus mean. Bland and Altman plots for thyroid volumes measured with MRI versus (a) planar scintigraphy, (b) SPECT, and (c) ultrasound. Reference lines indicate +2 sd and –2 sd.

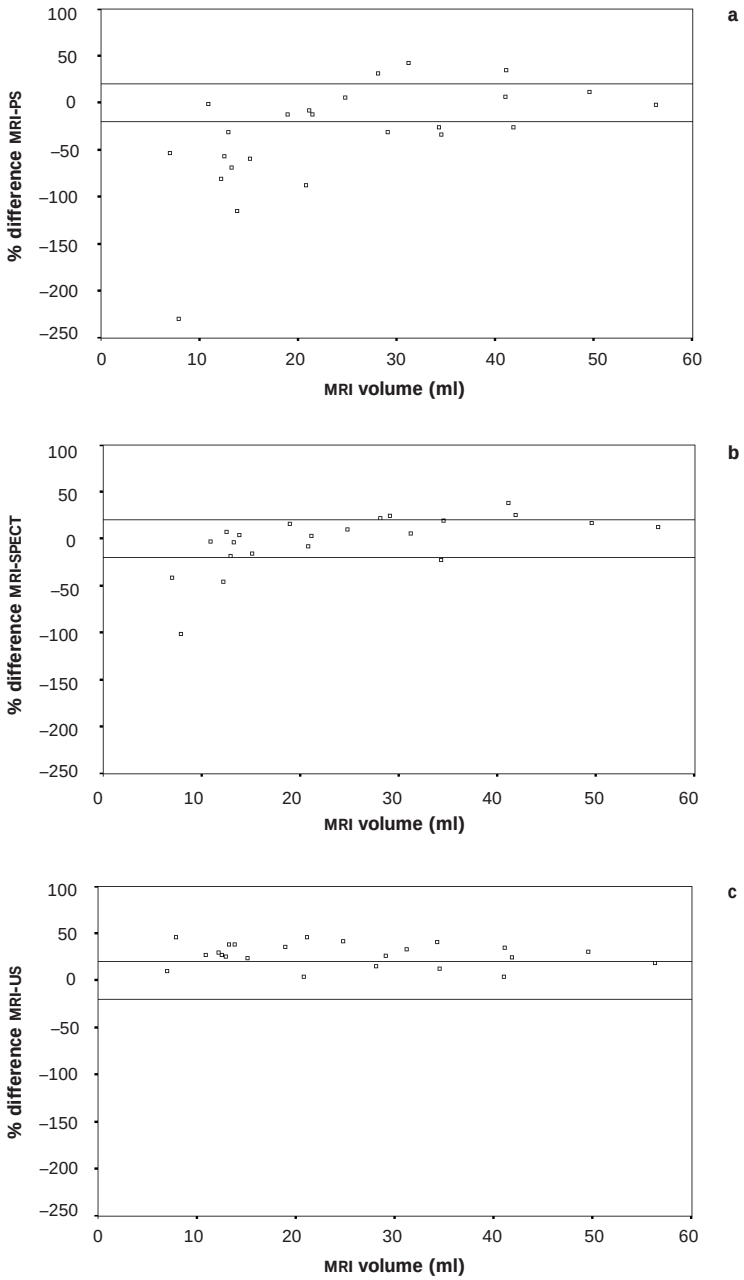

Figure 8.7 Thyroid volumes measured with MRI versus (a) planar scintigraphy, (b) SPECT, and (c) ultrasound. Y-axis: difference with MRI, expressed as a percentage of the MRI volume. Reference lines indicate deviations of +20% and –20%, respectivley, from MRI measurements.

analysis, and with a method for the comparison of measurements as proposed by Bland and Altman,[35] describing the accuracy of measurements in terms of bias and precision.

8.3 Results

Either with or without gadolinium contrast enhancement, MRI images showed excellent contrast between the thyroid and the surrounding soft tissues in all 25 patients. Both readers found it easier to do the segmentation on the gadolinium images, but no difficulties were experienced in the native images. The mean ± sd for the thyroid volumes measured with MRI was 25.0 ± 13.8 ml (range 7.0-56.3 ml). The results of the volume measurements with the four modalities are presented in table 8.1.

Comparisons of PS and MRI were available in 24 cases. The scintigraphic measurements had a low precision and a considerable bias, as illustrated in table 8.2 and figure 8.5a. The differences between planar scintigraphy and MRI were essentially independent of the thyroid size (figure 8.6a). The percentual difference (mean ± sd) between PS and MRI was –33.2 ± 57.6 (figure 8.7a).

SPECT and MRI data were compared in 22 cases. The differences between the volume estimations with these modalities were essentially independent of the thyroid size. The precision and bias were substantially better than for planar scintigraphy (see table 8.2 and figures 8.5b and 8.6b). The percentual difference (mean ± sd) between SPECT and MRI was –2.3 ± 30.5 (figure 8.7b).

A comparison between US and MRI could be made in 23 cases. Although the bias was large, the precision was good, and there was an excellent correlation with MRI (see table 8.2 and figure 8.5c). Larger differences were found in patients with larger thyroid volumes (figure 8.6c). The percentual difference (mean ± sd) between US and MRI was 27.8 ± 12.3 (figure 8.7c).

Table 8.2 Correlation, bias and precision for planar scintigraphy, SPECT and US versus MRI.

	linear regression	R^2	bias	precision
planar scintigraphy (PS)	PS = 0.73 × MRI + 10.87	0.61	–4.00	17.64
SPECT	SPECT = 0.70 × MRI + 5.47	0.84	1.83	11.86
ultrasonography (US)	US = 0.77 × MRI – 1.12	0.97	6.79	7.46

8.4 Discussion

MRI is recognized as a gold standard for volume measurements in general. Gadolinium enhanced MR imaging does not interfere with radioiodine therapy, as gadolinium chelates do not influence the iodide uptake or organification by the thyroid gland.[26,29] In spite of the excellent imaging capabilities of MRI in several thyroid disorders,[31,32] the limited availability and capacity as well as the relatively high cost have restrained its clinical application for thyroid volume measurements in patients with Graves' disease. Even research in this field is scarce.[30] In an adjacent clinical area – volume measurements of large multinodular goiters – excellent inter- and intraobserver agreement were found.[31]

The correlation of PS measurements with MRI was poor. Another indicator of the disappointing performance of scintigraphy is the percentual difference from MRI measurements, as displayed in figure 8.7a. At an acceptance level of 20% difference from the MRI results, untoward volume estimations were obtained in two-thirds of all planar scintigraphic studies. The mean error was 33%; large overestimations and large underestimations were encountered. Similar problems were reported in other studies on Graves' disease. Igl *et al*. found that thyroid volumes measured with scintigraphy were 33% larger than measured with US.[36] Veen *et al*. demonstrated a moderate correlation ($R^2 = 0.72$) in a direct comparison of presurgical scintigraphic measurements and surgical thyroid specimens in 13 patients with Graves' disease.[11] Especially larger thyroid volumes were severely underestimated with scintigraphy.

Somewhat better results have been reported in patients with thyroid disorders other than Graves' disease. Using a rectilinear scanner for their scintigraphic measurements in patients with large nodular goiters, Huysmans *et al*. found observer variations of 17% in comparison with MRI.[28] Wesche *et al*. compared scintigraphic volume measurements with US (using a static B-scanner), also in patients with large nodular goiters.[37] With a 20% threshold, they found smaller differences with a surface model than with an ellipsoid model, but in small diffuse goiters the discrepancies appeared to be larger with the surface model.

The relative imprecision of the surface model (with an average error of about 20%, maximum about 40%) was already stipulated by Himanka *et al*. at the introduction in 1955.[9] This model was originally tested with a rectilinear scanner; it has never been properly validated for use with a gamma camera. Nevertheless, Himanka's formula has enjoyed great popularity for over forty years. It should be noted that other mathematical approaches (including ellipsoid models) thus far have not yielded better results.[10]

The point spread function for collimated gamma camera systems of about 1-1.5 cm and the need for background subtraction result in less favorable spatial resolution and in less accurate measurements of small objects.[38,39] The accuracy of scintigraphic thyroid volume measurements is too low to justify their use for therapy dosage calculations in patients with Graves' disease. On the other hand, thyroid scintigraphy is still considered by most physicians as essential for a functional diagnosis in the work up for radioiodine therapy.

In the present investigation, SPECT with attenuation correction and scatter correction yielded a seizable improvement over PS. In comparison with the gold standard, both the mean difference and the range were smaller than those of PS, and so were the percentual differences with MRI. However, at an acceptance level of 20% deviation from the MRI measurements, untoward volume estimations were still observed in one-third of all cases. The largest errors occurred in the lower volume range (< 10 ml). The semi-automatic SPECT segmentation procedure that we propose is fast, easy to perform, and not liable to observer variations. It can be performed with standard commercial hardware and software. Others have indicated that more accurate volume determinations with SPECT are feasible with customized hardware and dedicated algorithms.[12-17] It has been shown that the optimal threshold value depends on object size and contrast.[16] The small size of the thyroid gland in combination with the limited system resolution makes this a challenging research area.

Thyroid SPECT may be a more cost-effective tool for thyroid volume measurements if it is substituted for, rather than added to, planar scintigraphy. This is a realistic option, as the differentiation of diffuse goiter from uni- or multinodular goiter is easily made with SPECT.

The large percentual differences between MRI and US are presented in figure 7c. At an acceptance level of 20% deviation from the MRI measurements, all US studies resulted in untoward volume estimations. This was caused by a substantial bias, *viz*. a large underestimation by US. The discrepancies were most pronounced for larger thyroid glands. The correlation of US with MRI, however, was near perfect ($R^2 = 0.96$) and from figure 7c it is apparent that a large percentage of US results could be quite acceptable if a correction factor were applied.

More accurate results had been obtained with static B-scanners.[6,7,40,41] This type of US equipment provides a set of spatially well-defined cross-sections that can be accurately computed to a three-dimensional volume, with a summation-of areas technique similar to those used in CT and MRI. The manufacturing of static B-scanners, however, has ceased a number of years ago. The ellipsoid models that are generally used for volume estimations with modern real-time scanners

are principally different; these models do not account for irregular organ shapes such as present in the thyroid.

The cost of US (which has to be added to that of scintigraphy) is moderate. This is one of the reasons for its widespread availability in clinics all over the world. 3D-US scanners are now being developed in which the transducer's position signal and the 2D-image signal are integrated into a 3D-volume set. When this modality becomes commercially available, a controlled study of its accuracy in measuring thyroid volumes is warranted.

At present scintigraphy is frequently used for thyroid volume measurements. In view of the large errors, this practice may be responsible for a substantial number of inadequate radioiodine therapy dosages. Thyroid scintigraphy is still considered as indispensable for a functional diagnosis. For this purpose, SPECT may be a good alternative. US is precise, but the accuracy may vary for specific scanners. Calibration of real-time US scanners is highly recommended before their implementation for volume measurements. We conclude that one of three options may be pursued for thyroid volume measurements: MRI + scintigraphy, ultrasound + scintigraphy, or SPECT. In a clinical environment the accuracy, the availability, the capacity and the cost of the various imaging modalities ultimately determine the physician's choice.

8.5 Acknowledgements

We thank Rudy Meijer, B.Sc. and Bas Klein, M.Sc. for collecting the ultrasonography data, and Herman J. Wijnne, Ph.D. for his guidance in the statistical analysis. The fruitful comments of Prof.Dr. W.P.Th.M. Mali and Prof.Dr.Ir. M.A. Viergever are gratefully acknowledged. We appreciate Ms. Sally Collyer's critical reading of the English text. Pie Medical bv (Maastricht, The Netherlands), is acknowledged for kindly supplying the ultrasound equipment for the duration of the study.

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Chapter Nine

General discussion: towards patient-tailored radioiodine therapy

Johannes W. van Isselt

9.1 Towards patient-tailored radioiodine therapy

After half a century of radioiodine therapy the questions "Where do we stand?" and "What have we learned?" are still being asked in leading medical journals.[1,2] Although several issues are no longer controversial, others still divide the ranks. The therapy aim and the preferred dosage strategy of radioiodine treatment evidently vary not only with the thyroid disorders that are to be cured, but also from country to country or even from clinic to clinic. We argue that individualized treatment protocols are the most appropriate way to improve the success of radioiodine therapy. As a general rule, medical interventions should be tailored to meet the patient's needs. On the other hand, patients should be made aware of the limitations of medical knowledge. In the following we describe our efforts to identify the parameters that influence the clinical outcome of radioiodine therapy in benign thyroid disorders, and we discuss the clinical consequences thereof. In the final paragraph proposals are made for future research.

9.2 Toxic adenoma and toxic multinodular goiter

In toxic adenoma and toxic multinodular goiter the primary therapeutic aim, the restoration of normal thyroid function, is widely acknowledged. With the decline in numbers of subtotal thyroidectomies performed, radioiodine has become the first treatment option.[3,4] Antithyroid drugs (ATD) do not constitute a rational treatment form. Thyrotoxicosis recurrence after cessation of therapy is greater than 95%.[5,6] The alternative, lifetime medication with ATD and levothyroxine (LT_4), is associated with serious side effects.[3,6] In this perspective it is remarkable that many patients with toxic nodular goiter are still being treated with ATD for several years. In patients with toxic adenoma, thyrotoxicosis is caused by autonomously hyperfunctioning adenomatous tissue, usually present in one nodule with increased iodine uptake. The thyroid hormone production is high (most pronouncedly the T_3 production), therefore the TSH concentrations are low, and the function of the extranodular thyroid tissue is suppressed.

In the present study, it was confirmed that in most patients the normal thyroid function is not compromised by radioiodine therapy, even if the ^{131}I dosage is high enough for ablation of the adenoma. With a ^{131}I dosage of 7.4 MBq per gram adenomatous tissue at 24 h, the administered amount was 349 ± 224 MBq (mean ± sd, equaling 9.4 ± 6.1 mCi). Euthyroidism was reached in 75% of all patients, hypothyroidism occurred in 11%, and hyperthyroidism persisted in 14%. Euthyroidism was restored in all patients with a relapse who received a second treatment with radioiodine. After a follow-up of 2-7 years, no new cases

of hypothyroidism or recurrences of hyperthyroidism were seen. In a number of other studies, all with different methods of dosage calculation, the recurrence rate varied between 2% and 52%.[7-13] The lowest failure rate was obtained with a fixed dosage of 740 MBq (20 mCi).[10] It seems contradictory that with this regimen the hypothyroidism rate (6%) was also lower than what we found.

In toxic multinodular goiter, the circumstances are different because the iodine uptake by the thyroid is much more heterogeneous. Therefore, the therapy dosage for toxic multinodular goiter should be lower than for toxic adenoma. With a standard dosage of 3.7 MBq/g thyroid tissue at 24 h, euthyroidism was reached in 74% of the patients, hypothyroidism occurred in only 7%, but hyperthyroidism persisted in 19%. These results concur with those of others, although some authors find fewer relapses and higher hypothyroidism rates for toxic multinodular goiter.[10,14-20] They indicate that standardized radioiodine therapy yields good functional results in a large majority of patients with toxic nodular thyroid disease.

Further optimization studies may be limited to a few issues. It has been put forward that further improvement of the measurements of the autonomously functioning thyroid volume may be worthwhile.[21] In order to prevent the uptake of radioiodine by the normal thyroid tissue, suppression therapy with triiodothyronine (T_3) may be useful in preparing patients with these disorders for radioiodine therapy.[16] Thereby with the same amount of ^{131}I an increased and better targeted effect might be obtained. Lithium enhances the retention of radioiodine in the thyroid and thus increases the effect of radioiodine therapy.[22,23] To date there are no large clinical studies of the quantitative aspects of the increased efficacy of these adjuvant medical approaches.

9.3 Nontoxic goiter

Many patients with large nontoxic goiters are still being treated with levothyroxine, although (as in toxic nodular thyroid disease) it has been demonstrated that medication constitutes no meaningful treatment, with the exception of small goiters.[24,25] A discrete disadvantage of medical treatment is that is has to be life-long, with concomitant cardiac complications and loss of bone mineral.[26-28] The proper treatment for nontoxic goiter used to be surgical debulking. Surgery is a fast and effective treatment form but it is associated with a small but not negligible morbidity and mortality. Until less than a decade ago nontoxic goiter was not seen as a good indication for radioiodine treatment. Results from small patient series indicated a poor clinical effect. More recent research has revealed that with a standardized radioiodine dosage regimen very

satisfying results can be obtained.[25,29-31] Hypothyroidism after radioiodine treatment is a relatively infrequent occurrence (5-15%). The subsequent development of autoimmune hyperthyroidism in seen in response to radioiodine therapy in 3-4% of all patients.[32]

The effect of radioiodine in nontoxic goiter has been evaluated quantitatively with ultrasonography in a few studies.[9,24,25] In the present investigation we have objectified the effect of radioiodine treatment with computer tomography (CT). CT has an advantage over ultrasound in patients with intrathoracic extension of the thyroid gland, which is a frequent observation in nontoxic goiter.[6] The aim of the study was threefold: (i) to assess the effect of ^{131}I on goiter volume, (ii) to establish a relationship between the amount of radioactivity taken up by the thyroid and the posttherapeutic volume reduction and (iii) to assess the precision of scintigraphic thyroid volume measurements in this thyroid disorder. In 27 patients with sporadic nontoxic goiter, the thyroid volume was estimated by planar ^{99m}Tc-pertechnetate scintigraphy. Noncontrast ('native') CT scanning of the neck was performed before therapy and one year after therapy. A clinically significant reduction was obtained in all patients (34% ± 17%, mean ± sd).[33] Hypothyroidism developed in 14% of the patients, and no other side effects occurred. It was concluded that for volume reduction in nontoxic goiter radioiodine treatment is safe and effective. The correlation of the volume reduction with the amount of ^{131}I retained at 24 h per gram thyroid was weak ($R^2 = 0.49$). Scintigraphic volume estimations were imprecise in thyroids larger than 200 ml; for smaller goiters the surface model was adequate for dosage calculation purposes. In conclusion, the results of radioiodine therapy for nontoxic goiter were quite satisfying, which is in agreement with other researchers' findings.[25,29-31]

Huysmans *et al.* have shown that the homogeneity of the radioiodine uptake increases significantly after low doses of recombinant human thyrotropin (rhTSH).[34] It is reasonable to expect a positive impact of rhTSH on radioiodine treatment results. An application for registration of this drug is pending in The Netherlands, but as yet only for the diagnostic follow-up of thyroid cancer patients.

9.4 Graves' disease

In Graves' disease, the therapeutic approach is more challenging than in nodular thyroid disorders, most likely because of the variations that occur in the disease activity. Three not entirely satisfactory treatment options exist: surgery, medication, and radionuclide therapy.[5,35-37] Subtotal thyroidectomy is an im-

mediate and effective form of treatment, with a relapse rate of about 20% one year after surgery. Hypothyroidism is seen in 10-20% immediately postoperatively, and an additional 1-2% each year during follow-up.[4,37] The direct surgical risks, as in cases of nodular goiter, are infrequent but potentially serious.

Antithyroid drug (ATD) treatment is the first choice if the therapy aim is to restore normal thyroid function. Prospective studies and follow-up studies in the UK and European countries have shown that one year ATD medication results in euthyroidism in 50 ± 7%.[38,39] For the USA only 11-50% euthyroidism was reported. The remission rate is higher for patients with smaller thyroids, and lower for patients with larger goiters. Lifetime medication with methimazole and carbimazole is not favored because it is associated with infrequent but potentially serious side effects such as granulocytopenia and pancytopenia;[40] lifetime levothyroxine suppletion is associated with an increased risk of atrial fibrillation and other cardiac complications, and bone loss.[26,41] In Europe patients who are scheduled for radioiodine treatment or surgery are often pretreated with ATD. This is definitely recommended in overtly thyrotoxic patients to reduce the risk of a 'thyroid storm' – a sudden, life-threatening exacerbation of thyrotoxicosis as a result of the acute release of large amounts of thyroid hormones.[42,43]

Radioiodine therapy has nowadays become the therapy of first choice in the USA,[6] and the use of ATD is mostly restricted to adolescents and to the pretreatment of patients with overt hyperthyroidism. Radioiodine therapy is less effective after patients have been on ATD for longer periods.[44] This is often referred to as decreased radiosensitivity of the thyroid's follicular cells as a result of the medication, but evidence for this hypothesis is not abundant. The diminished response to radioiodine may be better explained by the blockage of thyroid hormone synthesis and the reduced radioiodine uptake in combination with uninhibited release of preformed thyroid hormones. These events lead to a depletion of the intrathyroidal iodine pool. A combination of smaller amounts of thyroidal radioiodine and shorter residence times thereof would certainly render radioiodine treatment less efficacious.

9.5 Considerations regarding the calculation of radioiodine therapy dosages for Graves' disease

In the standard radioiodine dosage formula,

$$D = V \times (100\%/U) \times C,$$

the thyroid volume (V) and the radioiodine uptake (U) have a prominent place.[45]

By applying this formula it is implicated that a linear relationship exists between these two factors and the required ^{131}I therapy dosage. We did a follow-up study of the results of standardized radioiodine therapy in patients with Graves' disease ('standardized' in this context means 'with a fixed amount of ^{131}I per gram thyroid tissue at 24 h after dosing'). The clinical outcome, with a success rate of 70%, was in good agreement with reports by others. Further analysis of the data revealed a persistent effect of both the radioiodine uptake and the thyroid weight on the functional thyroid status after therapy.[46]

Radioiodine uptake

With identical radioiodine dosages per gram 24 h after dosing, patients with high iodine uptake (> 80%) had a significantly greater risk of relapse and patients with low uptake (< 60%) more frequently became hypothyroid.[46] Because of the apparently nonlinear relation between the radioiodine uptake and the therapy outcome, quantitative adjustments to the standard dosage formula are recommendable. A reduction of the ^{131}I dosage by an arbitrary factor should be considered for patients with an uptake value < 60%, and likewise an increase by an arbitrary factor for patients with a 24-h uptake value > 80%. In view of our present results we suggest that – as long as the optimal corrections can not be quantified for individual patients – 25% would be a reasonable value for this 'arbitrary factor'. One should be aware of the restrictions that apply to these recommendations in view of potential differences between clinics regarding pretreatment, patient selection, uptake measurement techniques, and so forth.

From a survey of the clinical practice in The Netherlands it appeared that considerable time intervals are sometimes allowed between the radioiodine uptake measurement (for the calculation of the therapy dosage) and the treatment itself.[47] After investigating the stability of the radioiodine uptake, we found large intraindividual variations over relatively short periods. There was no apparent relation between the degree of such variations and the length of the interval. It must be noted that the prevalence of intervals shorter than one week was too low to allow a separate quantitative analysis of these cases.

Subsequently we have investigated the clinical relevance of this finding. In comparison with a treatment protocol allowing various intervals between the uptake measurement and the therapeutic dosage administration, statistically significant differences in therapy outcome were found when the dosage calculation was based on uptake measurements immediately before the ^{131}I-treatment. More specifically, there was a reduced incidence of hypothyroidism at the cost of more relapses.[48] A recommendation to keep the interval between the meas-

urements, the dosage calculation and the radioiodine treatment as short as possible (not longer than 7-10 days) was recently included in the revised guidelines for radioiodine treatment of the Dutch Society of Nuclear Medicine, NVNG.[49]

Radioiodine turnover rate

The radioiodine turnover rate was defined by Aktay *et al.* as the 5/24-h radioiodine uptake ratio.[50] A high turnover rate indicates a short biological half-life, which in turn implies a decreased therapeutic effect of ^{131}I. From the investigation described above we learned that the iodine turnover rate shows substantial intraindividual variations over time.[47] This is another strong argument to minimize the interval between the diagnostic measurements and the actual radioiodine treatment. In a follow-up study, we demonstrated that the relation between the clinical outcome and the radioiodine turnover rate was even more significant than between the outcome and the thyroid weight or the radioiodine uptake. The radioiodine turnover rate and the 5-h radioiodine uptake were also significantly related; this may be the main reason for the reduced therapy effect in patients with high radioiodine uptake.

For the assessment of the effective half-life (T_{eff}) of ^{131}I, serial measurements over a 5-7 day period are required. It has been suggested that the 5/24-h uptake ratio can be effectively substituted for T_{eff}.[50] In the present study we found evidence that 'rapid' radioiodine turnover should not be defined as a 5/24-h uptake ratio > 1. A ratio > 0.85 appeared to be a strong indicator of therapy failure; we argue that in these cases therapy dosage adaptations should be considered. As long as an accurate quantitative approach is not available, an arbitrary increase of the therapeutic ^{131}I dosage by 50-100% seems to be reasonable; for patients with a 5/24-h uptake ratio > 1.0 such increments are already customary at some institutes. Likewise for patients with a 5/24-h uptake ratio < 0.75 a dosage reduction (by 25-50%, arbitrarily) may be considered. Because of the interdependence of the radioiodine turnover rate and the radioiodine uptake, care must be taken that adaptations to the therapy dosage are not made for both factors at the same time. It is our view that if the turnover rate is available this factor should have priority.

Rapid turnover is linked to the concept of a 'small thyroidal iodine pool'. As a result of the small thyroidal iodine pool the amount of circulating protein bound iodine (PBI) is highly increased.[44] Consequently very large amounts of ^{131}I would be required for an effective treatment, whereas under such circumstances large quantities of circulating radioactive protein bound iodine (PB^{131}I) would cause excessive total body radiation absorbed doses. This problem could

possibly be circumvented by lithium co-medication, as lithium blocks the release of thyroid hormones and causes a fall of posttherapeutic serum $PB^{131}I$ levels without hampering the radioiodine uptake.[22]

Thyroid volume

The thyroid weight (often used as a synonym of thyroid volume) is another classic dosage-determining factor. In many schemas the dosages are expressed in MBq/g. The linearity between the clinical outcome and the thyroid volume which is implied by this expression was denied by the two follow-up studies in patients with Graves' disease that were described above. With identical radioiodine dosages per gram, a relapse of hyperthyroidism was seen significantly more often in patients with thyroids larger than 60 grams, and hypothyroidism occurred significantly more often in patients with thyroids smaller than 60 grams. We concluded that adaptations to currently used dosage calculation schemas are advisable. Higher dosages than the customary 3.7 MBq per gram thyroid tissue are recommended for patients with larger goiters, and lower dosages for smaller goiters. Based on empirical data, adaptations to standard dosages had already been occasionally suggested in the earlier years of radioiodine therapy.[42]

Accurate and cost-effective thyroid volume measurements are required for therapy dosage calculations. We have shown that in patients with Graves' disease CT is no option for this purpose.[51] MRI can be seen as the gold standard,[52,53] but the high cost and the limited availability and capacity of this modality have thus far prohibited its use for this indication. We did a comparative study of planar scintigraphy, SPECT (with attenuation correction and scatter correction) and ultrasonography, in comparison with MRI as the gold standard.[54] The accuracy of SPECT was much better than for planar thyroid scintigraphy. Ultrasonography (US) measurements had a high precision but low accuracy. Because of the poor accuracy of planar scintigraphy, this method should not be recommended for thyroid volume estimations in patients with Graves' disease. It is argued that inappropriate scintigraphic thyroid volume measurements may have caused a substantial number of inadequate radioiodine therapy dosage calculations in the past, and they might be partly responsible for the relative lack of success with individualized dosage regimens. New developments such as three-dimensional US and dedicated SPECT algorithms could necessitate a review of this study.

Another tentative hypothesis deals with technical matters in regard to a hitherto unexplained clinical observation, i.e. an increase of the posttherapeutic hypothyroidism rate (with dosage modeling and patient preparation unchanged) from 1951 to 1975.[55,56] This period reflects the transition from rectilinear scanning to scintigraphy with gamma cameras. A concomitant overestimation of

thyroid volumes with scintigraphic measurements, as was found in the present study, might have ensued.

Antithyroid drugs

Whereas the use of ATD in toxic adenoma, toxic multinodular goiter and non-toxic goiter could be qualified as irrational, in Graves' disease 1-1.5 years ATD medication results in permanent euthyroidism in 20-40% of patients, as the disease undergoes spontaneous remission.[43] If ATD does not result in a definitive cure of hyperthyroidism, it is still regarded as an adequate preparation for radioiodine therapy.[42] It is again stressed that the effect of radioiodine is reduced by prior ATD medication. An even greater reduction of the therapeutic effect of ^{131}I is to be anticipated if ATD are continued during radioiodine treatment. Discontinuation of these drugs at least 3 days before ^{131}I treatment is generally recommended. In the context of radioiodine treatment it is interesting that antithyroid drug treatment, too, is less effective in patients with large goiters than in those with small goiters.[57] The cause of this phenomenon is not understood, but failure of medical treatment is likely to constitute a negative selection of patients who are referred for radioiodine treatment. Following this line of thought, primary referrals for radioiodine treatment would theoretically result in higher cure rates.

Information to the patients

In a survey conducted among patients who were treated with radioiodine a majority of responders were not satisfied with the treatment result.[58] It was concluded that the patient information had not been adequate. Patients should be well informed about the uncertainties that exist in the prognosis of the outcome after radioiodine therapy. The different options (quick induction of hypothyroidism or cautiously striving for euthyroidism) should be thoroughly discussed. This is a task for both the referring internist and the nuclear medicine physician.

9.6 Recommendations for future research

Dosimetric models

A study is recommended of the clinical applicability of Monte-Carlo based methods for dosimetric measurements with thyroid SPECT. The concept of ^{131}I concentration measurements within the thyroid gland with SPECT (as a substitute for thyroid volume measurements and ^{131}I uptake measurements) as suggested by Muller *et al.*,[59] warrants further investigation.

Investigation of very-short-term variations in radioiodine uptake

Uptake measurements, order placement and delivery of therapy capsules take a minimum of 3-4 days. It is therefore relevant to study intraindividual variations in radioiodine uptake over very short periods (e.g., 1-7 days) for an assessment of the feasibility of the currently proposed radioiodine uptake protocol, and to investigate the validity of prolonged measurements (up to 7 days) for the assessment of T_{eff}. The legal aspects of radioiodine treatment form another interesting and complicating aspect. In The Netherlands in-patient treatment is required by law if the therapy dosage is > 400 MBq. This can not be predicted in most patients before testing. The patients in question will be scheduled for hospital admittance at a later date, and the physician responsible for the dosage calculation should know whether or not to repeat the radioiodine uptake test.

Dosage modifying factors for thyroid volume, radioiodine uptake and radioiodine turnover rate

The development of computerized dosage calculation algorithms with modifying factors (for thyroid volume, radioiodine uptake and radioiodine turnover rate) requires a multifactorial analysis of very large clinical databases and long-term prospective testing.

The influence of ATD on the radioioine turnover rate

Rapid iodine turnover is associated with the activity of Graves' disease and with the depletion of the thyroidal iodine pool by ATD. It is uncertain what changes may occur in the thyroid iodine pool of patients who have used ATD for prolonged periods. Serial measurements of protein bound iodine are indicated to shed more light on the causes and the effects of rapid iodine turnover.

Triiodothyronine suppression therapy in autonomous thyroid disease

Triiodothyronine (T_3) reduces the radioiodine uptake of the normal thyroid tissue in autonomously hyperfunctioning nodular thyroid disorders (toxic adenoma and toxic multinodular goiter). With T_3 co-medication, the therapeutic effect of radioiodine could possibly be targeted more effectively at the adenomatous tissue. A prospective clinical investigation both in patients with toxic adenoma and in patients with toxic multinodular goiter is warranted to establish the optimal T_3 dosage, and to see whether subgroups of patients can be identified who profit most from this treatment.

Normal thyroid function versus thyroid hormone suppletion

Recent studies by Van Houten *et al.* and Bunevicius *et al.* have indicated that T_4 monotherapy may not be the most appropriate replacement for normal endogenous thyroid function.[58,60] It seems worthwhile to do an open-label study of the physical and psychological functioning of combined T_4/T_3 medication versus T_4 alone in patients who have become hypothyroid after radioiodine therapy, and compare these with the functioning of patients who have become euthyroid.

Adjuvant lithium medication

Lithium may be effective inasmuch it enhances the retention of ^{131}I in the thyroid.[22] We propose a study of the effect of adjuvant lithium medication with radioiodine therapy for Graves' disease, toxic adenoma, toxic multinodular goiter and nontoxic goiter. Prospective randomized trials should be designed to assess whether good clinical results may indeed be obtained with lower therapeutic ^{131}I dosages. This is important from a radiation protection perspective (ALARA), and might lead to cheaper (*viz.*, fewer in-patient) treatments. The main question to be answered is whether a quantitative relationship can be established between the lithium dosage and its effect on the thyroidal retention of radioiodine.

Low-dose recombinant human thyrotropin in patients with nontoxic goiter

The use of low-dose recombinant human thyrotropin (rhTSH) in patients with nontoxic goiter should be investigated in large clinical trials. The reported ability of this drug to enhance the relative radioiodine uptake in drug-naive 'cold' thyroid areas could lead to substantially increased efficacy of radioiodine therapy in this patient category.[34]

9.7 Concluding remarks

Of all thyroid disorders that are being treated with radioiodine, Graves' disease (the one thyroid disease with a homogeneously distributed function) has the largest variations in the clinical outcome. The relative failure of individualized therapy dosage schemas in the treatment of Graves' hyperthyroidism can only in part be attributed to the use of inappropriate estimations of thyroid volume and radioiodine uptake. The dosage schemas themselves are imperfect because they do not account for the nonlinear relation between the clinical outcome and either the thyroid volume or the radioiodine uptake. The radioiodine turn-

over rate, a potential substitute for the effective half-life, may deserve a place in these schemas.

Proposals for adaptations of existing dosage protocols are useless unless they are easily implemented in a routine clinical setting. Preferably, no additional investigational modalities or multiple patient visits are introduced, and extra cost is to be avoided or minimized. We have tried to define the general directions for adequate and clinically applicable dosage adjustments supported by clinical evidence. Over the coming years adjustments will be applied and fine-tuned in prospective study protocols. No doubt, some will disappear into oblivion. If some may seem to be viable after a thorough clinical 'test-run', their reproducibility and validity shall have to be scrutinized in multicenter clinical trials before general implementation may be considered.

All recommendations that were given for radioiodine dosage adjustments have been based on our own clinical data, and their intended use is restricted to radioiodine treatment under these conditions. Some important parameters (patient selection, patient preparation, measurement techniques) may vary between clinics. Legal requirements may prohibit implementation of these recommendations in some countries.

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Summary

The general aim of this thesis was to investigate the value and the shortcomings of the becquerel-per-gram method for radioiodine therapy in various benign thyroid disorders. The history of this treatment form, which goes back to the late 1940s, is described in Chapter 1. Almost fifty years after the discovery of radioactivity, the first clinical experiences with ^{131}I-treatment were reported in the United States. A simple and effective treatment form had emerged as an alternative to surgery and antithyroid drug (ATD) therapy in Graves' disease. The efficacy of radioiodine was initially tested – and demonstrated – in patients who could not be cured with ATD medication. With increasing experience in the management of Graves' disease, it became apparent that the outcome of radioiodine treatment was difficult to predict. No more than half of all patients treated became euthyroid with one ^{131}I administration. Higher or lower dosage protocols made the difference for the outcome in the other 50%. In other words, there was the choice between a greater risk of early hypothyroidism or persistent hyperthyroidism. The development of different schools with regard to the desired therapy outcome (i.e., rapid cure of hyperthyroidism, or restoring euthyroidism) did not hamper the furthering of radioiodine therapy. By the late 1980s, radioiodine had replaced surgery as the first choice for the curation of Graves' hyperthyroidism, toxic adenoma and toxic multinodular goiter.

After this introduction, a number of items relevant to radioiodine treatment are reviewed: the physical and radiobiologic properties of iodine-131; pros and cons of different therapeutic aims; and factors influencing the outcome of radioiodine therapy. A statement of the aims of this thesis concludes Chapter 1.

In Chapter 2, we present the clinical follow-up results of radioiodine treatment in patients with toxic adenoma and in patients with toxic multinodular goiter. The prevalence of both these disorders is relatively low in comparison with diffuse toxic goiter (Graves' disease), and consequently the number of cases included in this investigation is limited. Because of their similar histopathologic and clinical profiles, they have been studied as one group. A standardized dosage of 3.7 MBq per gram thyroid tissue was applied in patients with multinodular goiter, and a dosage of 7.4 MBq per gram adenomatous tissue was used in patients with toxic adenoma. With a single radioiodine treatment good clinical results were obtained in patients with toxic adenoma (75% euthyroidism, 11% hypothyroidism, 14% relapse) over a follow-up period varying between one and eight years. In patients with toxic multinodular goiter, 70% became euthyroid,

22% suffered a relapse of thyrotoxicosis and 8% became hypothyroid. Repeat radioiodine therapy (3 for TA, 11 for TMNG) was successful in all patients with a relapse. Most other researchers have found somewhat fewer relapses and higher hypothyroidism rates for toxic multinodular goiter; the recurrence rate for TMNG varied between 2% and 52%. The lowest failure rate was obtained with a fixed dosage of 740 MBq (20 mCi). It seems contradictory that with that regimen also the hypothyroidism rate (6%) was slightly lower than what we found. At this stage, a fixed dosage regimen seems preferable over the more laborious individualized regimen. The underperformance of the individualized protocol could possibly be explained by inaccurate volume measurements, especially in toxic adenoma. Further optimization of the standardized regimen for these disorders may be expected from T_3 suppression medication and from lithium co-medication. Both may have the ability to increase the effect of a given amount of ^{131}I, although the mechanisms of action are entirely different.

The aim of radioiodine therapy in patients with nontoxic goiter is the reduction of goiter size, while simultaneously preserving the normal thyroid function. This item is dealt with in Chapter 3. In 27 patients with sporadic nontoxic goiter, a therapeutic dose of 3.7 MBq per gram functioning thyroid tissue led to substantial objective reduction of the goiter mass (by 34% on average). The subjective results were more than adequate: 85% of all patients reported substantial improvement or complete relief of their complaints. Hypothyroidism resulted in 3/27 (11%) of the patients. Thyroid volume measurements with ^{99m}Tc-pertechnetate scintigraphy were carried out for therapy dosage calculations as well as for follow-up measurements. For an objective assessment of the goiter reduction, CT-scanning was used as the gold standard. It was concluded that the accuracy of planar scintigraphic volume determinations in nontoxic goiter is sufficient for dosage calculation purposes if the thyroid volume does not exceed 200 ml. However, as the therapy results were no less in patients with thyroid volumes over 200 ml than in patients with smaller goiters, the accuracy of these measurements does not seem to carry much weight. Recently, other researchers have reported equally satisfying results in the reduction of goiter size. It seems that the indication for radioiodine therapy in patients with nontoxic goiter may be broader than has thus far been assumed.

In Chapter 4, a summary is given of the radioiodine therapy results using a standardized megabecquerel-per-gram dosage protocol in patients with Graves' disease. The overall results are in compliance with the results of other research

groups. We found a cure rate of 70% (including 39% hypothyroidism), and recurrent hyperthyroidism in 30%. The thyroid's radioiodine uptake capacity and the thyroid's mass appeared to be important factors with regard to the prognosis of the therapy outcome. Patients with thyroid weights > 60 g more often suffered a recurrence of hyperthyroidism, whereas those with thyroid weights < 60 g appeared to be prone to a hypothyroid therapy outcome. Likewise, patients with radioiodine uptake values < 60% had a higher risk of becoming hypothyroid than those with uptake values > 80%.

From the preceding four chapters we may conclude that the standard therapy dosage formula $D = W \times (100\%/U) \times 3.7$ MBq (where D is the therapy dosage in MBq, W is the thyroid weight in grams, and U is the 24-h radioiodine uptake percentage) is adequate for radioiodine therapy in all thyroid conditions under consideration, except in Graves' disease. It remained unclear what particular dynamics of Graves' disease make the prediction of the therapy outcome so much more difficult than in other thyroid disorders. We have looked into the technical, biologic and logistic aspects of the two cornerstones of the radioiodine dosage calculation, *viz*. the iodine uptake measurement and the scintigraphic thyroid volume measurement. Chapter 5 sets off with a survey of the clinical practice in The Netherlands, of radioiodine uptake measurements that are used for therapeutic ^{131}I dosage calculations in patients with Graves' hyperthyroidism. From the response to a nation-wide questionnaire it was concluded that at most departments the radioiodine uptake was measured (and the therapy dosage was computed) several days or even weeks before the actual therapy date. Large differences prevailed between institutions. This survey is followed by an analysis of the clinical consequences of said practice. Variations in radioiodine uptake of over 10% occurred – within a short time – in more than half the patient population (62% of all patients with regard to the 5-hr ^{131}I uptake and 51% with regard to the 24-hr uptake). The radioiodine turnover rate, too, was recognized as a relevant parameter for the dosage calculation. The incidence of increased radioiodine turnover as earlier reported in the literature (about 16%) was confirmed in our study, but in 14% of all patients the turnover rate had changed from normal to increased or vice versa during an interval of 6 weeks on average.

The results of radioiodine treatment in patients with Graves' hyperthyroidism were again reviewed; in comparison with the methods as used in Chapter 4 only one variable was altered, *viz*. the time-point of the ^{131}I uptake measurements. In the repeat study, described in Chapter 6, the uptake was measured on the day

before therapy. The results differed significantly from those in the historic controls. A significant shift occurred from hypothyroidism to persisting hyperthyroidism. The outstanding significance of the radioiodine turnover rate as a predictor of the clinical outcome was also recognized in this investigation. For patients who had become euthyroid after radioiodine therapy, the radioiodine turnover rates (i.e., 5/24-h ^{131}I uptake ratios) were 0.76-0.84 (95% confidence interval, C.I.), whereas in patients with persisting hyperthyroidism the turnover rates were 0.84-0.92 (95% C.I.). There was some overlap between patients with euthyroid and hypothyroid outcomes (rates 0.69-0.79, 95% C.I.), but the differences were still highly significant. It seems that the radioiodine turnover rate has great predictive potential with regard to the therapy outcome. On the basis of the present data, proper quantitative dosage corrections can not yet be performed, but indicatively ^{131}I therapy dosage adaptations may be realized.

The second cornerstone of 'classic' ^{131}I therapy dosage calculations, the thyroid volume, forms the center of interest in Chapters 7 and 8. Based on our earlier experience with CT-scanning in patients with nontoxic goiter, this modality was also chosen as the gold standard in a pilot study of 5 patients with Graves' disease (Chapter 7). However, adequate manual segmentation was not feasible with native CT in 4 out of 5 patient studies. As CT with contrast enhancement is contra-indicated when radioiodine treatment is scheduled, it was concluded that CT is not suited for thyroid volume measurements under these conditions. It was argued that the discrepancies between the results in patients with nontoxic goiter and in patients with Graves' disease may be caused by the relatively small thyroidal iodine pool in the latter. The lower iodine content would cause a lower signal intensity on CT, and less contrast between the thyroid gland and the surrounding tissues.

In 25 patients with Graves' disease, a direct comparison was made between planar scintigraphy, ultrasound (US), and SPECT (with attenuation correction and scatter correction, using standard commercial hardware and software), while MRI was used as the gold standard. In this investigation (Chapter 8), it was concluded that MRI, SPECT, or US may be pursued for thyroid volume measurements. Planar scintigraphy is very inaccurate, and should be discarded as a means of pretherapeutic thyroid volume measurements. SPECT can be used as an alternative to planar scintigraphy for the qualitative functional diagnosis; MRI or US should only be used as an 'add-on' to scintigraphy.

A general discussion of radioiodine therapy for benign thyroid disorders is presented in Chapter 9. In view of the good results in all nodular thyroid disorders under study, it was concluded that adjustments to the standard dosage formula are not indicated. In patients with Graves' disease, it is much harder to make an accurate prognosis of the therapy outcome. It is argued that attempts to preserve normal endogenous thyroid function through a 'patient-tailored' model is to be preferred over the quick induction of hypothyroidism and subsequent levothyroxine substitution. Generalized proposals are made for adjustments to the standard radioiodine therapy dosage formula, making use of all optimization factors that were found in the investigations described in Chapters 2-7.

This chapter is concluded by proposals for future research, primarily aimed at optimization of radioiodine dosage calculations in patients with Graves' disease. Dosimetric models and computer algorithms are needed to adjust for variations in thyroid volume, ^{131}I uptake and radioiodine turnover rate. SPECT measurements of the ^{131}I concentration within the thyroid gland, instead of the thyroid volume and the absolute amount of ^{131}I in the thyroid gland, deserve further investigation. Because of the clinical implications, we also propose a study of very-short-term variations in radioiodine uptake. The influence of antithyroid drugs on the radioiodine turnover rate warrants further study, as well as a quantification of the dose-effect relationship of lithium co-medication in prolonging the retention of radioiodine in the thyroid. Other proposed medication studies include the investigation of the clinical value of triiodothyronine (T_3) suppression therapy in autonomous thyroid disease, and of the clinical value of low-dose recombinant human thyrotropin (rhTSH) in patients with nontoxic goiter. Finally, it seems worthwhile from an endocrinologic viewpoint to do an open-label study of the merits of combined T_3/T_4 medication versus T_4 alone in patients who have become hypothyroid after radioiodine therapy.

Nederlandse samenvatting voor de leek

Behandeling met radioactief jodium (^{131}I) wordt sinds 1946 toegepast bij patiënten met goedaardige schildklieraandoeningen. De benodigde hoeveelheid ^{131}I bleek bij individuele patiënten echter moeilijk voorspelbaar te zijn. In de praktijk zijn momenteel verschillende methoden in zwang om de therapeutische ^{131}I-dosering te berekenen. Twee belangrijke 'scholen' kunnen worden onderscheiden. De eerste hanteert een *geïndividualiseerd doseringsschema* (bijvoorbeeld met de 'becquerel-per-gram' methode, waarbij gebruik wordt gemaakt van de formule $D = G \times (100\%/U) \times C$), waarin D staat voor de toe te dienen dosis ^{131}I, U de 24-uursopname van ^{131}I representeert, en C een constante is, waarvoor per ziektebeeld een andere waarde kan worden gehanteerd. De tweede gebruikt een *vaste dosering* ^{131}I voor alle patiënten (eventueel met gestandaardiseerde dosisaanpassingen voor schildkliergewicht, jodiumopname, leeftijd, enzovoort). Geïndividualiseerde schema's voor behandeling met ^{131}I zijn erop gericht om een zo hoog mogelijk percentage euthyreoïdie (dat wil zeggen normale schildklierfunctie) te bereiken. Toch leveren ze geen wezenlijk betere resultaten op dan de vaste doseringsschema's. Dit is moeilijk te begrijpen op grond van de ons bekende relaties tussen gegeven hoeveelheden straling en de effecten daarvan op menselijke weefsels. Het leek daarom zinvol om de mogelijke oorzaken van dit fenomeen verder te onderzoeken. Bovendien zijn er redelijk sterke aanwijzingen dat een normale endogene productie van schildklierhormoon een betere kwaliteit van leven geeft dan suppletiebehandeling met schildklierhormoontabletten (levothyroxine) bij patiënten met een te lage schildklierfunctie.

Allereerst werd het resultaat nagegaan van ^{131}I-behandeling met hantering van bovenvermelde standaarddoseringsformule. Bij de nodulaire schildklierafwijkingen (het toxische adenoom, de toxische multinodulaire struma en de euthyreotische multinodulaire struma) blijken met deze benadering goede resultaten bereikt te kunnen worden. Bij patiënten met een toxisch adenoom of een toxische multinodulaire struma wordt in een hoog percentage een normale schildklierfunctie bewerkstelligd. Afwijkende uitkomsten van de behandeling met ^{131}I zijn relatief gering in aantal, en bij een deel daarvan kan met een tweede behandeling met ^{131}I het gestelde doel alsnog worden bereikt. Als rationeel alternatief voor de behandeling met radioactief jodium geldt hier alleen chirurgie. Deze geeft weliswaar snel resultaat, maar de risico's van operatief ingrijpen zijn groter dan die van behandeling met ^{131}I. Behandeling met medicamenten is geen reële optie, omdat deze slechts de symptomen bestrijden en de ziekte niet genezen.

Patiënten met een euthyreotische multinodulaire struma werden tot tien jaar geleden in de regel geopereerd wanneer klachten ontstonden van obstructieve ofwel van cosmetische aard. Het betreft hier echter grote chirurgische ingrepen (veelal bij oudere patiënten) die niet zonder risico zijn. Medicamenteuze behandeling leidt in ongeveer de helft van de gevallen tot een redelijk goed resultaat, maar alleen wanneer deze in een vroeg stadium van de ziekte wordt toegepast. Bij stoppen van de medicijnen treedt weer groei van de krop op. Van behandeling met ^{131}I van patiënten met een euthyreotische multinodulaire struma-aandoening waren nog weinig resultaten bekend. Het doel van deze behandeling is om verkleining van de struma (krop) te verkrijgen, zo mogelijk met behoud van normale schildklierfunctie. Met toepassing van de standaarddoseringsformule werd bij de patiënten in ons onderzoek een subjectief en objectief goed resultaat bereikt (gemiddeld 34% volumereductie). Circa 90% van de patiënten behield daarbij een normale schildklierfunctie.

Belangrijke aanpassingen in de ^{131}I-dosering lijken bij de nodulaire schildklierziekten daarom niet noodzakelijk.

Bij de ziekte van Graves (een stoornis van het afweersysteem, die onder meer gepaard gaat met een verhoogde schildklierfunctie) leverde ons onderzoek interessante nieuwe gezichtspunten op. Het in de standaarddoseringsformule impliciet aangegeven lineaire verband tussen de optimale dosering van het ^{131}I enerzijds, en het schildkliergewicht en de jodiumopname anderzijds, kon in deze patiëntengroep niet worden bevestigd. Wanneer het schildkliergewicht groter was, bleek de kans op een succesvol behandelresultaat significant af te nemen. Dit was al in de jaren zeventig een empirisch gegeven; toch werd hiervoor in later jaren geen correctie in de formule aangebracht. Voorts werd aangetoond dat patiënten bij wie het percentage van het door de schildklier opgenomen radioactief jodium hoog is een verhoogde kans hebben op persisterende hyperthyreoïdie, terwijl bij patiënten met een lage jodiumopname het risico op het ontstaan van hypothyreoïdie na ^{131}I-behandeling relatief groot is.

In de tweede plaats werd van algemeen toegepaste technieken nagegaan of ze accuraat zijn (dat wil zeggen of ze correcte meetresultaten geven) en of ze juist worden toegepast. Het onderzoek betrof in concreto de schildklierscintigrafie voor de berekening van het schildkiergewicht en de jodiumopnamemeting van ^{131}I (ter bepaling van het door de schildklier opgenomen percentage van een oraal toegediende dosis ^{131}I).

Van de jodiumopname door de schildklier werd vastgesteld dat deze binnen één individu in de loop van dagen tot weken in sterke mate kan variëren. Omdat bovendien in een vervolgonderzoek werd aangetoond dat de uitkomsten van behandeling met radioactief jodium afhankelijk zijn van het tijdstip waarop de (voor de dosisberekening gebruikte) jodiumopnamemeting wordt uitgevoerd, is dit gegeven voor de kliniek zeer relevant. Uit een landelijke enquête bleek dat het in de praktijk gehanteerde interval tussen de meting (inclusief de berekening van de therapiedosis) en de behandeling binnen één afdeling nucleaire geneeskunde en tussen verschillende afdelingen sterk kon variëren. Mede op basis van het hier beschreven onderzoek werd de geldende landelijke aanbeveling met betrekking tot de jodiumopnamemeting aangepast.

De *'radioiodine turnover rate'* is de snelheid waarmee de schildklier het eenmaal opgenomen radioactieve jodium omzet, en in andere vorm weer afstaat aan het bloed. Deze omzettingssnelheid wordt gedefinieerd als de verhouding tussen de jodiumopnamepercentages zoals die bij de patiënt worden gemeten (5/24-uursopnameratio). In het boven beschreven onderzoek werd aangetoond dat ook deze 'turnover rate' binnen een tijdsbestek van dagen tot weken niet constant is, en dat er bovendien een sterke correlatie bestaat tussen deze parameter en de uitkomst van de behandeling met radioactief jodium. Dit is op zich begrijpelijk: hoe korter een bepaalde hoeveelheid ^{131}I in de schildklier verblijft, hoe korter het gewenste (stralings)effect kan optreden. Bij patiënten die na behandeling een normale schildklierfunctie kregen, bleek de 5/24-uurs uptake ratio 0,76-0,84 te hebben bedragen. Bij patiënten die na behandeling nog steeds een te hoge schildklierfunctie hadden, was deze ratio 0,84-0,92. Ten opzichte van patiënten die een te lage schildklierfunctie kregen, bestond enige overlap (ratio's 0,69-0,79), maar ook hier waren de verschillen significant. De 'turnover rate' lijkt dus een goede voorspellende maat te zijn voor het behandelresultaat. Een kwantificeerbare correctiefactor voor de toe te dienen therapiedosis is daarmee nog niet bepaald, maar indicatief zouden nu al doseringsaanpassingen kunnen worden gerealiseerd.

Het schildkliervolume moet exact bekend zijn om een correcte therapiedosis te kunnen berekenen bij patiënten met de ziekte van Graves die een behandeling met ^{131}I zullen ondergaan. Om de waarde van de traditioneel gebruikte meetmethode (schildklierscintigrafie) te kunnen toetsen, werd een vergelijkend onderzoek voorbereid. In eerste instantie werd als gouden standaard de CT-scan gekozen, omdat hiermee bij patiënten met een euthyreotische struma goede

ervaringen waren opgedaan. Bij patiënten met de ziekte van Graves blijkt de CT-scan zonder contrasttoediening echter niet bruikbaar te zijn. Mogelijk komt dit doordat de schildklier bij deze patiëntengroep relatief weinig jodium bevat, en daardoor op de foto slechts weinig contrast ten opzichte van de omgeving bestaat. Uit vergelijkend onderzoek van andere methoden om het schildkliervolume te meten, is ons gebleken dat de traditionele schildklierscintigrafie een onvoldoende betrouwbare techniek is voor dergelijke metingen. Modaliteiten die hiervoor wel geschikt zijn, betreffen – in volgorde van afnemende accuraatheid – MRI, echografie, en SPECT (scintigrafie met plakjesfoto's). Op dit terrein zijn momenteel veel technische ontwikkelingen gaande die over enkele jaren wellicht tot nieuwe aanbevelingen kunnen leiden.

Al met al zijn in de loop van het onderzoek drie factoren geïdentificeerd die de uitkomst van ^{131}I-therapie bij patiënten met de ziekte van Graves in hoge mate beïnvloeden: (i) de snelheid waarmee het radioactieve jodium door de schildklier wordt omgezet, (ii) het volume van de schildklier, en (iii) de hoogte van de jodiumopname. De laatstgenoemde hangt sterk samen met de eerstgenoemde, en is daarom mogelijk van mindere betekenis als onafhankelijke factor. Er bestaat geen lineaire relatie tussen de drie genoemde factoren en de uitkomsten van therapie met ^{131}I in een gestandaardiseerde dosering (3,7 MBq per gram schildklierweefsel). Voor al deze factoren dient dus gecorrigeerd te worden bij geïndividualiseerde dosisberekeningen voor ^{131}I-behandeling. Hoewel uit het huidige onderzoek nog onvoldoende gegevens bekend zijn om een exacte kwantitatieve correctie aan te kunnen geven, wordt het onderzoek voortgezet op basis van de hier (zeer voorlopig) voorgestelde aanpassingen.

Ten slotte worden aanzetten gegeven voor toekomstig onderzoek. Er worden wegen aangeduid die tot vermindering van de therapiedosis zouden kunnen leiden zonder dat daarbij voor een verminderd behandeleffect behoeft te worden gevreesd. Laatstgenoemde aanpassingen zijn niet in de eerste plaats gericht op het verbeteren van de behandelingsresultaten, maar op het verminderen van de belasting van mens en milieu door radioactieve stoffen.

Dankwoord

Om bij het begin te beginnen: ik ben iemand vergeten, maar ik weet niet meer wie. Jou dank ik daarom als eerste, met mijn oprechte excuses. Maar nu verder.

Hooggeleerde Lips, beste Kees. De afdelingen Endocrinologie en Nucleaire Geneeskunde van het Universitair Medisch Centrum Utrecht hebben bij de behandeling van schildklieraandoeningen een samenwerkingsrelatie opgebouwd waar menigeen een puntje aan kan zuigen. De 'Unit Bijzondere Verpleegkunde Nucleaire Geneeskunde' vormt hiervan een tastbaar aspect. Enkele jaren geleden hadden we dit moment desondanks geen van beiden voorzien. Jouw exemplarische wetenschappelijke instelling en ongekend positieve denktrant hebben mij in de vele vroege ochtendlijke uren door mistige dalen gegidst. Daarvoor ben ik je erg veel dank verschuldigd.

Zeergeleerde Van Rijk, beste Peter. Het spijt mij nog meer dan jou dat je mijn promotor niet kon zijn. De cultuur en de randvoorwaarden die wetenschappelijk onderzoek mogelijk maken, zijn op onze afdeling Nucleaire Geneeskunde mede door jouw inzet weer gemeengoed geworden. Jouw ideeën omtrent de jodiumuptake hebben uiteindelijk geleid tot wellicht de interessantste waarneming in ons hele onderzoek. Enthousiasmeren en faciliteren zijn je allerbeste eigenschappen. Daarvoor hulde, maar vooral mijn grote dank.

Zeergeleerde De Klerk, beste John. Je hebt een bijna ongezonde belangstelling voor mensen met schildklierziekten, en toch heb je gul een stuk van je hobby aan me afgestaan. Bovendien heb je me veel werk bespaard, want wat jij niet in je literatuurmappen hebt zitten, is de moeite van het lezen eigenlijk niet waard. En verder is er niemand met wie ik mijn werkkamer liever zou delen.

Zeergeleerde Van Gils, beste Ad. Hoewel je pas in een laat stadium bij het onderzoek betrokken raakte, heeft dat je animo niet verminderd. Ik dank je zeer voor je consciëntieuze kritiek.

Hooggeleerde De Bruin, hooggeleerde Krenning, hooggeleerde Mali, hooggeleerde Teule, hooggeleerde Viergever, hooggeleerde Wiersinga. U hebt als leden van de beoordelingscommissie een onmisbare kritische bijdrage geleverd, waarvoor ik u vanaf deze plaats welgemeend dankzeg.

Weledelgeleerde Van Dijk, beste Aalt. Je enthousiasme is grenzenloos, en je overtuigingskracht heeft iets van hypnose. Voor ieder nieuw onderzoeksaspect dat we bespraken ben je steeds weer vol vuur geraakt, en dat bleek gelukkig

besmettelijk te zijn. Niet alleen heb je me me weer enigszins wegwijs gemaakt in de statistiek, ook had ik zonder jou nooit stilgestaan bij het niet onbetekenende feit dat een brandende sigaar straffeloos in de doos teruggestopt kan worden en daarna in de jaszak.

Zeergeleerde Beekman, beste Freek. Veel dank voor je zeer kritische opstelling vanaf het allereerste begin, en meer in het bijzonder rond het SPECT-onderzoek. Rudy Meijer en Bas Kleijn bedank ik voor hun vele inspanningen rond de echografie, nu en in de toekomst. Mohamoud Osman Dualeh en Bart de Keizer, jullie waren mijn lopers, torens en paarden tegelijk. Louter dankzij jullie onbetaalbare (en dus onbetaalde) honger naar wetenschap en erkenning werden de patiëntendata uit vele medische archieven opgediept en in kaart gebracht.

Bijna iedereen op de afdeling Nucleaire Geneeskunde heeft in de afgelopen jaren 'nolens volens' bijgedragen aan het onderzoek, of heeft me het 'gewone' werk uit handen genomen. Alice, Annet, Bart, Berber, Bernard, Bert, Carolien, Carina, Chris, Don, Els, Frank, Fred, Hanny, Hans van Asselt, Hans Balink, Hans Hardeman, Henk, Hugo, Ibolya, John Buijs, Katelijne, Loes, Maarten, Maja, Margreet, Maria, Marian, Marjan, Monique Hobbelink, Monique Wienia, Oane, Pauline, Rex, Shiuw, Stephan, Ursula, Vivian en Wim: bedankt voor alles.

Mevrouw Siersema, lieve Imke. Wat zouden we moeten zonder jouw planning, met wie zouden we nog op de trap kunnen roken, en waar werd de liefde voor onze patiënten anders zo gemakkelijk in grappen vertaald? Ook Joke, Deana, Diny, Maria en Twan: ik ben trots op jullie betrokkenheid en professionalisme.

Zeergeleerde Van der Pompe, beste Willem. De eerste schreden op het nucleaire pad deed ik aan jouw hand, en je RRTI-klapper 'Therapie met open bronnen' lag aan de basis van mijn eerste interne publicatie over schildklierbehandelingen. Ik mag er overigens wel op aandringen dat je in je huidige positie de nucleaire geneeskunde wat meer voortrekt.

Zeergeleerde De Haas, beste Gerrit. Jij zag als eerste een nucleair geneeskundige in mij. Ik ben jou, mijn Nestor, nog steeds dankbaar voor de opleidingsplaats die je me indertijd in het Utrechtse bood en voor de filosofische wijze waarop je het vak en het leven wist te integreren.

Zeergeleerde De Hooge, beste Piet. Samen hebben we vijf goede jaren gehad waarin we naast de nucleaire geneeskunde ook de schoonheid van de echografie hebben geëxploreerd. Het doet me goed dat onze samenwerking op een andere manier weer vorm krijgt.

Mijn ouders Kitty en Joop kunnen dit helaas niet meer meebeleven. Met veel warmte denk ik terug aan onze lange gesprekken in de laatste dagen.

Paula lief, dank zij jou is het boekje echt een boekje geworden. En nog met plezier ook. Daarvoor bedank ik je nog wel onder vier ogen. Als we ooit weer een beetje tijd krijgen.

Curriculum Vitae

Johannes Willem (Hans) van Isselt was born on Valentine's Day in the year 1949 in the Brabant township Steenbergen en Kruisland. After completing the Gymnasium β at the Berlage Lyceum (formerly Comeniuslyceum) in Amsterdam, he started his medical studies at the University of Amsterdam. He received his medical board certification in 1979. The clinical part of his training in nuclear medicine was initiated at the Dutch National Cancer Institute Antoni van Leeuwenhoekhuis in Amsterdam. After a six-months stay at the department of Nuclear Medicine of the Rotterdamsch Radiotherapeutisch Instituut, the specialist training was completed at the departments of Nuclear Medicine of the University Hospital Utrecht and of the Diakonessenhuis Utrecht. Certification as a nuclear medicine specialist was obtained in 1984. During the following two years he was a staff member at the Department of Nuclear Medicine and Ultrasound of the Diakonessenhuis Utrecht. Since May 1986 he has been a staff member at the Department of Nuclear Medicine of the University Hospital Utrecht (now University Medical Center Utrecht). At this department the research was carried out that has been laid down in this thesis.
Hans van Isselt was married to Paula Boeijen in Venice, Italy, in 1993.

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