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FOCUS ON

Radioiodine therapy dosimetry in benign thyroid disease and differentiated thyroid carcinoma

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"Treatments with radioiodine should be based on principles leading to the highest quality of patient care. Science is the basis for the principles and for the advances we seek in medicine" [1].
(James Sisson)

Traditionally, nuclear medicine has been regarded mainly as a diagnostic specialty in which the administration of radioactive substances yields information whose importance far outweighs any potential risk to normal tissue. Now, however, therapeutic applications of radionuclide-based approaches are at last gaining the prominence they deserve. In this field, individual patient dosimetry is essential both for optimising the administered activity through the establishment of minimum effective and maximum tolerated absorbed doses and for determining a dose-response relationship as a basis for predicting tumour response [2]. Unfortunately, the lack of comprehensive clinical trials designed to bring out the value of radionuclide dosimetry in predicting therapy outcome has fed a general belief that dosimetry methods are daunting, prone to a large degree of uncertainty, and liable to generate increased costs, and thus held back their progress. This is, indeed, why Flux and colleagues remarked "radionuclide therapy remains the Cinderella of cancer treatment modalities, under-utilised with respect to more conventional treatments" [3].

Now, however, the availability of new technologies (e.g. PET/CT) and radioisotope pairs for diagnosis and therapy (e.g. ^{124}I and ^{131}I or ^{86}Y and ^{90}Y), supported by a new generation of personal computer software for internal dose assessment, is at last leading to an increase in the use of dosimetry in clinical therapeutic applications.

To show the appreciable progress now being made in this field we here take a look at a sample of the most recent literature on dosimetry for radioiodine treatment of benign thyroid disease and differentiated thyroid carcinoma.

"Focus on…" abridgements aim to highlight papers published within the past year and draw extensively on the texts and summaries of the articles referenced. Less recent citations are also included when deemed useful to provide background information on the topic reviewed.

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Benign thyroid disease

Radioiodine treatment of hyperthyroidism and benign thyroid disease is the quintessence of nuclear medicine therapy, but after more than half a century and the treatment of hundreds of thousands of patients the question of the "optimal" radioiodine activity to administer still lacks a definitive answer [4]. Reassuringly, however, a significant number of papers are published each year on dosimetry-based radioiodine treatment of hyperthyroidism and benign non-toxic multinodular goitre (MNG), demonstrating a sustained level of interest in this topic.

Methods, protocols and strategies for the treatment of hyperthyroidism

What is the optimal method for determining ^{131}I activity in the treatment of hyperthyroidism? To answer this question, a Dutch group recently conducted a systematic review and meta-analysis of the literature in order to establish the relative value, based on clinical outcome, of the two main methods currently used: estimation and calculation (the first

fixed or based on thyroid weight, the second based on radioiodine uptake measurement) [5]. Outcome was measured by the frequency of treatment success (defined as persistent euthyroidism) and the cure rates of hyperthyroidism (defined as euthyroidism or hypothyroidism) at the end of follow-up. The weighted mean relative frequency of successful treatment outcome was 1.03 [95% confidence interval (CI): 0.91–1.16] for estimated versus calculated activity; the weighted mean relative frequency of cure of hyperthyroidism was 1.03 (95% CI: 0.96–1.10). The authors thus concluded that treatment outcome is equally successful with the two methods. However, methodological limitations (heterogeneity of the included studies, different causes of hyperthyroidism, follow-up period limited to 12 months) preclude the drawing of a definitive conclusion from this meta-analysis. For the ultimate verdict on the optimal method for determining ^{131}I activity, a large prospective, randomised trial is needed.

Zakavi et al. also compared fixed and calculated activities of ^{131}I, this time in the treatment of patients with hyperthyroidism and a single hot thyroid nodule. But these authors added a further dimension, namely the question of whether high- or low-activity protocols are to be preferred [6]. In their randomised prospective trial, 97 patients were treated with one of the four following protocols: fixed low activity [FLD (481 MBq, 13 mCi)], fixed high activity [FHD (832 MBq, 22.5 mCi)], calculated low activity [CLD (3.33–3.70 MBq/g, 90–100 μCi)] and calculated high activity [CHD (6.66–7.4 MBq/g, 180–200 μCi)]. A curative effect was defined as absence of thyroid-stimulating hormone (TSH) suppression, and an analysis of variance test was used for comparison of the groups, which showed no significant demographic or clinical differences. About 10 months after therapy, cure of hyperthyroidism was higher in the CHD group than in the other three groups. Hypothyroidism was significantly higher in the CHD and FHD groups than in the CLD and FLD groups. No significant difference was noted in the cure of hyperthyroidism between the CLD and FLD groups. Mean administered radioiodine activity was significantly less in the calculated groups than the fixed activity groups. The results of this study suggested that hyperthyroidism could be successfully managed with ^{131}I therapy in most of the patients with toxic thyroid nodule after 1 year, regardless of the activity of radioiodine. However, if a prompt response is desired, e.g. in elderly patients, high-activity protocols may be more appropriate, while young patients may be treated with lower activities of radioiodine in an attempt to prevent long-term hypothyroidism.

In both high- and low-activity radioiodine therapy, antithyroid drugs are liable to have detrimental effects. These effects may be avoided by withdrawing the antithyroid drug or increasing the radioiodine target doses, although it is not clear which of these strategies is to be preferred. Walter et al. explored this question, using continuous dose-effect models to evaluate the effects of carbimazole on 1-year post-radioiodine success rates in a series of 228 patients; success was defined as elimination of hyperthyroidism [7]. Euthyroidism rates with and without carbimazole were calculated by numerical integration of the area between the success and hypothyroidism curves. Target dose amplification factors for equal chance of success with and without carbimazole were calculated using logistic regression. Radioiodine target doses between 33 and 839 Gy were applied. Overall, the "euthyroidism rates" were 16.5 and 64.8%, while the hypothyroidism rates were 37.6 and 14.8% in Graves' disease and toxic nodular goitre, respectively. The success rate with simultaneous carbimazole [median dose: 15 mg day (−1); range: 2.5–60 mg day (−1)] was reduced over the entire target dose range in Graves' disease and toxic nodular goitre. The areas between curves for euthyroidism without and with simultaneous carbimazole were 127 and 43 Gy in Graves' disease and 178 and 128 Gy in toxic nodular goitre. The estimated radioiodine target dose amplification factor was 5.5 for Graves' disease and 3.0 for toxic nodular goitre. These findings suggest that antithyroid drug discontinuation should be preferred in low-activity radioiodine therapy, while escalation of the target dose should be preferred in high-activity radioiodine therapy.

Other authors have considered the question of strategies that might promote the use of dosimetry-based radioiodine treatment in benign thyroid disease. Traino and Xhafa [8], for example, remarking that the development of a reasonably fast, simple and cost-effective method to measure thyroid ^{131}I kinetics could lead to greater use of individualised, dosimetry-based radioiodine treatment in Graves' disease, recorded the maximum thyroid uptake (U_0) and the thyroid absorbed doses calculated by two simple methods (based on one and on two measurements, respectively, 4 h and 4 and 24 h after diagnostic ^{131}I administration). These values were compared with a "reference value" calculated using a more detailed radioiodine kinetics evaluation based on seven thyroid uptake measurements obtained at various times after ^{131}I therapy. The authors observed significant differences between the thyroid absorbed doses calculated by each of the two simpler methods and the "reference value" and concluded that although the one- and two-measurement approaches were faster and more convenient than treatment based on measurement of "complete" thyroid kinetics of radioiodine, they did not appear to be as accurate and reproducible. Methods based on three or more measurements (one done at least 120 h after radioiodine administration) yield not only the U_0, but also the effective half-life of the radionuclide in the gland: two kinetic parameters crucial in the calculation of the thyroid absorbed dose.

The updating of standard reference values may be another valid strategy for promoting more effective and

widespread use of radioiodine treatment in benign thyroid disease. Kobe et al. recently remarked that a semi-quantitative approach to radioiodine therapy in this field depends on the availability of standard reference values derived from a large population. Noting that thyroid radioiodine kinetic parameters were last examined as long as 15 years ago, they suggested that updated values may be now needed (radioiodine half-life and uptake may have changed, due to an enhanced and more stable iodine supply, for example). Accordingly, the authors measured both the individual effective half-life and uptake of ^{131}I in a large number of patients with different benign thyroid disorders (Graves' disease, non-toxic goitre, toxic goitre or toxic adenoma), thereby obtaining new standard values under current conditions in Germany [9]. Control of hyperthyroidism and withdrawal of antithyroid drugs 2 days before preliminary radioiodine testing and therapy was part of the inclusion criteria. The effective half-life and the maximal uptake of ^{131}I were estimated by uptake measurements after 24 h and 5 days during the pre-therapeutic radioiodine testing, and serial measurements over 5 days during therapy. The mean effective half-life of ^{131}I measured during radioiodine therapy was found to be 5.4 days in Graves' disease, 6.4 days in non-toxic goitre, 6.6 days in toxic goitre and 5.7 days in toxic uninodular adenoma. The mean maximal uptake of ^{131}I measured during radioiodine therapy was 64% in Graves' disease, 42% in non-toxic goitre, 38% in toxic goitre and 31% in toxic unifocal adenoma. In relation to the data from 1988–1989, the authors found a lower radioiodine uptake and longer half-life, probably linked to an easing, around that time, of legal restrictions on the use of iodised salt in food industries in Germany. The status of iodine nutrition has markedly improved, with a mean current urinary iodine concentration of about 180 mg/l compared with 75 mg/l some 20 years ago. Stable iodine intake can change the intrathyroidal radioiodine kinetics and is a well-known contributory factor. The novel values calculated by these authors could be used for semi-individual calculations of the therapeutic activity when an individual approach is not possible and in areas with a comparable nutritional iodine intake.

Benign non-toxic multinodular goitre

According to a 2007 World Health Organisation (WHO) report, the prevalence of iodine deficiency is mild to moderate in 13 of 40 European countries. In Germany, 30–57% of the population is estimated to have insufficient iodine uptake (IU <100 mg/l), with an average prevalence of goitre and/or thyroid nodules of approximately 33% [10]. Treatment options for symptomatic non-toxic multinodular goitre (MNG) include long-term medication with levothyroxine or a combination of levothyroxine and iodine, surgery or radioiodine therapy. In the elderly population, in which MNG is prevalent, ^{131}I therapy has been used for more than two decades in symptomatic non-toxic MNG, resulting in a mean thyroid volume reduction of ~40% 1 year after treatment and 50–60% after 3–5 years [11].

The effect of radioiodine therapy for goitre volume reduction (GVR) was recently evaluated in a retrospective study of 88 patients receiving radioiodine therapy for toxic or non-toxic goitre (median goitre volumes: 127±38 ml) between 2001 and 2007 [10]. The administered radioiodine activities (mean: 1,721±440 MBq ^{131}I, equivalent to a mean of 14±4.2 MBq ^{131}I /g of thyroid tissue) were calculated individually through repeated uptake measurements over 5 days. The designated dose was 150 Gy for the entire thyroid volume, and post-therapeutic dosimetry revealed a mean thyroid dose of 175±45.9 Gy. The effect of treatment was evaluated by thyroid function tests in the blood and thyroid ultrasound at 6 weeks and 3, 6, 12, 24, 36, 48 and 72 months after radioiodine administration. The mean GVR was 41.9% at 3 months, rising to a highly significant 65.9% at 1 year, 70% at 2 years and nearly 75% at 3 years after therapy. No volume increase was observed in any subject during follow-up, and although many patients were lost to follow-up the authors concluded that radioiodine is an effective modality of treatment for both non-toxic and toxic goitre.

Since higher activities of ^{131}I are often employed when treating non-toxic than when treating toxic MNG, there has been reluctance in many countries to use "conventional" radioiodine therapy as an effective and safe alternative to surgery in the treatment of symptomatic non-toxic MNG. However, the recent advent of recombinant human TSH (rhTSH) has opened up new avenues for ^{131}I therapy of MNG on the theoretical basis that augmented ^{131}I therapy allows increased radioactive iodine uptake (RAIU), leading to increased retained thyroid dose and irradiation. Fast et al. reviewed more than 30 papers dealing with the effects of rhTSH in healthy individuals and patients with benign non-toxic MNG [11]. Although the optimal dose of rhTSH to stimulate thyroid RAIU remains to be established, 0.1 mg or lower is probably effective, since doses down to 0.01 mg have proven useful for enhancing RAIU and higher doses could aggravate underlying thyroid autonomy. It is unclear whether large goitres require higher doses of rhTSH for an optimal increase in RAIU, despite the existence of an inverse correlation between RAIU increase and initial RAIU. A 24-h interval between rhTSH injection and subsequent ^{131}I therapy seems to be the most suitable for obtaining an approximate doubling of RAIU in MNG patients, largely independent of the rhTSH dose. rhTSH-augmented ^{131}I therapy increases GVR in MNG patients by 35–56% at the expense of an up to fivefold higher rate of permanent hypothyroidism. This effect was documented in three randomised controlled trials, while the remaining non-

controlled studies also demonstrated considerable GVR, between 35 and 53%. rhTSH-aided ^{131}I therapy, compared with ^{131}I therapy alone, resulted in greatly improved inspiratory function due to diminished tracheal compression. Several studies using conventional non-rhTSH-stimulated ^{131}I therapy reported a negative correlation between initial goitre size and GVR, this correlation not seeming to emerge in rhTSH-augmented ^{131}I therapy. Pre-treatment with rhTSH may improve GVR by causing a more homogeneous distribution of radioiodine within the thyroid, especially increasing the uptake of ^{131}I in scintigraphically relatively cold areas. This observation may well explain the more pronounced gain in GVR observed in large goitres (above 100 ml), since the degree of both morphological and functional changes within a goitre evolves with increasing goitre size. The authors remark that while surgery remains the first-line treatment for large compressive goitres, rhTSH-augmented ^{131}I therapy is a promising new strategy in these patients.

In an open-label study, Braverman et al. assessed rhTSH-enhanced RAIU in patients with MNG using a range of administered activities, and also considered the tolerability adverse effects of the procedure [12]. Euthyroid patients with small non-toxic MNGs (median size 20 ml) and normal thyrotropin concentrations underwent baseline assessments including thyroid function tests, electrocardiography, Holter monitoring, use of a hyperthyroid symptom scale, flow-volume loop, and measurement of thyroglobulin and thyroperoxidase antibodies. They had a baseline 24-h scan, and thyroid ^{123}I uptake was evaluated at 6, 24 and 48 h after rhTSH administration. Each patient received a single intramuscular injection of 0.03, 0.1 or 0.3 mg rhTSH followed 24 h later by 400 μCi ^{123}I orally. Thyroid ^{123}I uptake was again measured 6, 24 and 48 h later, and a scintigram was acquired after 24 h. Twenty-eight patients were studied. After each rhTSH dose, the RAIU approximately doubled at each time point compared with baseline. Small rises in serum thyroxine and triiodothyronine were seen in some patients, especially after 0.3 mg rhTSH, and mild symptoms of hyperthyroidism developed in several patients. The flow-volume loop showed transient, mild asymptomatic worsening in one patient with a 35-ml goitre, although thyroid volume measurements were unchanged. Minor electrocardiographic and/or Holter changes were seen in several patients. The data presented by these authors suggest that a flat dose-response curve exists over the range of rhTSH doses tested, with an approximate doubling of thyroid RAIU. All the patients tolerated rhTSH well, although theoretically the rise in thyroid hormone levels and adverse effects after rhTSH doses of 0.1 mg or higher may not be well tolerated in older or sicker patients and appear unjustified given the lack of a greater rise in RAIU than with the 0.03 mg dose. Future studies evaluating rhTSH doses of less than 0.1 mg in MNG patients are called for.

Another question is whether rhTSH increases the efficacy of a fixed activity of radioiodine in the treatment of MNG. In this regard, the results of a recent study [13] showed comparable basal RAIU and thyroid volume values in all the groups considered: group A, receiving 0.1 mg rhTSH; group B, receiving 0.005 mg rhTSH; and group C, given placebo. After rhTSH or placebo, peak levels of TSH, free T_4, T_3 and Tg were higher in group A than in group B or C. Thyroid volume reduction, however, was similar in groups A and B (37.2±25.5% vs 39.3±27.9%), but different from the non-significant reduction observed in group C (15.3±28.3%). On the basis of their findings, the authors conclude that, followed by 1.11 GBq, a very low dose of 0.005 mg rhTSH was as effective as a 0.1 mg dose. Both increased the efficacy of the radioiodine treatment. Moreover, in all groups, adverse events were mild, transient and readily treatable.

Differentiated thyroid carcinoma

Sisson et al.'s recent description of a patient with a solitary iodine-avid metastasis of thyroid carcinoma to the skull that was impinging on the brain [14] provides an interesting illustration of how radioiodine dosimetry can contribute to the effective management of differentiated thyroid carcinoma (DTC). Tumour time-activity measurements from scintigraphic probe data were combined with the 3-D dose-rate distribution from a Monte Carlo-based calculation to obtain the average absorbed dose to the tumour and brain. The Dose Planning Method (DPM), a Monte Carlo electron and photon transport program, designed for radiation-absorbed dose computations in external beam radiotherapy (EBRT), was adapted and validated for applications in internal emitter therapy. In this study, the inputs to DPM were the coregistered SPECT images, CT-derived density maps and the CT-defined masks for tumour and brain regions. The output from DPM was the 3-D absorbed dose-rate distribution, the absorbed dose-rate averaged over the tumour, and the absorbed dose-rate averaged over the brain. Dosimetry indicated delivery of 1,970 and 2,870 cGy to the tumour and 35 and 42 cGy to the brain, respectively, during two ^{131}I treatments. The tumour, initially enlarged during TSH stimulation, decreased in volume after each of the two ^{131}I treatments (administered activities of 7.4 and 7.5 GBq) and the patient has survived for more than 11 years since diagnosis. This case confirms that dosimetry of the tumour and surrounding organs is feasible and accurate with SPECT/CT, and results from these measurements may determine the amount of activity necessary for a beneficial effect.

Radioiodine certainly plays an important role in the management of DTC, being used both for thyroid remnant ablation and for the treatment of metastatic disease. However, the exact activity to be administered is still debated. A "fixed activity approach" is preferred in most

centres, with the ^{131}I dosage selected empirically on the basis of local clinical experience or according to reference values reported in the literature [15]. However, a fixed dosage selected in this way fails to take into account individual patient characteristics, such as lesion size, uptake, retention, whole-body clearance and radiation dose to the remainder of the body. It thus seems reasonable to assume that a "dosimetric approach" will offer advantages over empirically prescribed fixed activity. Dosimetry in patients with DTC can provide useful information to ensure safety limits in normal tissues, to increase efficacy of tumour treatment and to identify futility of ^{131}I therapy in some patients, and it is worth considering the advantages and disadvantages of the different methods used for the calculation of the administered activity.

New calculation models and methods

In patients with DTC, therapy with the highest safe activity is desirable to maximise the tumour radiation dose yet avoid severe myelotoxicity. Recently, the European Association of Nuclear Medicine (EANM) published a standard operational procedure (SOP) for pre-therapeutic dosimetry in DTC patients incorporating a safety threshold of a 2 Gy absorbed dose to the blood as a surrogate for the red marrow [16]. In a recent evaluation of the safety and effectiveness in everyday tertiary referral centre practice of treating advanced DTC with high ^{131}I activities chosen primarily on the basis of dosimetry results obtained following this SOP [17], the authors retrospectively assessed toxicity as well as biochemical and scintigraphic response in their first ten patients receiving this "individualised" therapy. The patients received a total of 13 dosimetrically guided treatments with a median administered activity of 14.0 GBq ^{131}I. After 6 of the 13 treatments, administered in six patients, short-term side effects of ^{131}I therapy were observed, namely nausea, vomiting or transient sialadenitis. Leukocyte and platelet counts dropped significantly in the weeks after ^{131}I treatment, but returned to pre-treatment levels by 3 months post-therapy. Serum thyroglobulin levels decreased after 12 of the 13 treatments (median reduction: 58%) in nine of the ten patients. On the basis of these findings, the authors conclude that in their initial patient cohort, high-activity ^{131}I therapy for advanced DTC based on pre-therapeutic blood dosimetry performed in accordance with the EANM SOP was safe and well tolerated. Furthermore, the treatment almost always produced a partial biochemical tumour response.

A novel calculation model was recently developed as an attempt to individualise radionuclide therapy through dosimetric data [18]. Exemplarily implemented for ^{131}I therapy of metastasised DTC ("first radioiodine therapy"), the model, rather than prescribing standard activities (and thus probabilities of effects) for targets and/or organs, weighs the success (i.e. response) of therapy against the risk (i.e. side effects) and generates an optimum patient-specific relationship between the two. The model is based on dose-effect observations and acts through the definition of a target increment for the ratio between the probability of success and side effects. Its purpose is to give objective advice on appropriate increases or decreases of therapeutic activities. By means of dose-response relationships retrieved from the literature, a three-variable model was developed consisting of a target variable weighing response against risk, a measured variable representing the lesion dose per activity (LDpA, measured in Gy/GBq) and a manipulated variable constituting the therapeutic activity. Dosimetry-related radioiodine therapy along the three-variable model increases response probability in individual patients by up to >50% compared with "standard" therapy with 7 GBq. On a patient population scale, by escalating and de-escalating activity along the model, the overall response rate can be enhanced by 8% (62 vs 70%) while saving, on average, 0.9 GBq per patient (7 vs 6.1 GBq). The authors thus conclude that this model, weighing potential success against risk, makes it possible to individualise radionuclide therapy and redistribute therapeutic activities. According to a virtual comparison between model-based and standard "first radioiodine therapy" in metastasised thyroid carcinoma there are benefits to be gained from the model in terms of overall response and overall radioactivity employed. However, the authors admit that the potential impact of model-based therapy must be proven in prospective comparative studies.

Does successful ablation of thyroid remnants depend more on absorbed doses or on administered activity? Flux et al. set out to answer this question by calculating the maximum absorbed doses to residual thyroid tissue from fixed administrations of radioiodine (3,000 MBq of ^{131}I) in 23 patients who had undergone near-total thyroidectomy for DTC [19]. The calculations were made on the basis of SPECT scans acquired 24, 48, 72 and, when possible, 96 h after administration. Blood samples were collected at 24, 48, 72 and 144 h following administration to enable the calculation of absorbed doses to the blood and the red marrow and to calculate protein-bound iodine (PBI) values. Dosimetry was performed according to the Medical Internal Radiation Dosimetry (MIRD) basic scheme, and to avoid errors in the calculation of average absorbed doses due to heterogeneity of uptake and uncertainties in defining the volume of thyroid remnants, the absorbed doses were calculated for the voxel of maximum uptake. The S value for this voxel was determined using the Monte Carlo computer code EGSnrc to be 0.99 Gy/(MBq h), and cumulated activities were obtained from trapezoidal integration of the time-activity

curve. Of the 23 patients treated, 18 had a successful ablation, while 5 were unsuccessful. The maximum voxel absorbed dose to thyroid remnants of patients that had a complete ablation was 99±128 Gy. Patients with unsuccessful ablation received absorbed doses of 25±17 Gy. All patients that received an absorbed dose to the thyroid remnant greater than 49 Gy had a successful ablation, while persistent uptake was seen in 5 of 13 patients (38%) receiving less than 49 Gy. The remaining activity at 24 h in the maximum voxel was 0.58±0.54 MBq and the effective half-life was 89±56 h. A significant difference was seen in the absorbed doses delivered to thyroid remnants, blood and red marrow between those patients that had a successful ablation and those with a failed ablation. The difference between the PBI values acquired at days 1 and 6 were also indicative of response. On the basis of their findings, the authors concluded that successful ablation is strongly dependent on the absorbed dose to the thyroid remnant. Dosimetry-based personalised treatment can prevent both sub-optimal administrations, which entail further radioiodine therapy, and excessive administration of radioactivity, which increases the potential for radiation toxicity.

A simple method for estimating the radiation absorbed dose to the blood after radioiodine administration was recently evaluated in patients with DTC [20]. Indeed, the method required only one external measurement of the whole-body retention, and blood dose was calculated by applying the MIRD formalism under the assumptions that whole-body activity decays exponentially and that 14% of the whole-body residence time can be attributed to the blood. On accuracy testing of the method the mean of the absolute deviations between estimates and actual blood doses was found to be 14%, if external whole-body counting was performed on day 1 or 2 after radioiodine administration. On the basis of their findings, the authors conclude that this simple formalism is applicable to pre-therapeutic dosimetry for remnant ablation or treatment of metastases in the context of a blood dose-based treatment approach. In addition, it is suitable for blood dose estimates after radioiodine therapy to determine radiation exposure. Above all, when combined with a measurement of the whole-body retention 1 or 2 days after radioiodine administration this single time point method closely approximates the classic, yet much more labour-intensive, multi-day dosimetry that measures both blood and whole-body activities.

^{124}I PET dosimetry

Traditional radiopharmaceuticals such as ^{123}I and ^{131}I, despite accurately quantifying radioiodine uptake in thyroid remnants and metastases, have certain limitations: ^{123}I presents problems regarding supply and has a short half-life, while ^{131}I has relatively low sensitivity and runs the risk of inducing the "stunning" phenomenon. The recent advent of ^{124}I, a PET tracer, has opened up new perspectives for PET/CT, allowing it to be used as an effective staging tool to detect recurrent/residual disease and for dosimetry of metastatic lesions.

An Italian group recently evaluated the usefulness of ^{124}I PET/CT as a tool for DTC staging immediately before ^{131}I therapy, optimising the activity for remnant ablation and individualising dosimetry in patients with multiple distant metastases [21]. A total of 69 patients underwent whole-body ^{124}I PET/CT before ^{131}I therapy and then ^{131}I whole-body scanning after therapy (TxWBS); the scans were compared in a double-blind fashion in 67 of 69 patients. In 2 of 69 patients with already diagnosed multiple distant metastases from follicular DTC (total of 21 sites of metastases) an individualised complex dosimetric study was done. The two scans matched in 58 of 67 patients (86.6%), and where there was disagreement, ^{124}I PET/CT detected more pathological foci than TxWBS in 5 of 67 patients (7.5%), mainly cases of regional lymph node involvement; conversely, TxWBS detected more pathological foci than ^{124}I PET/CT in 4 of 67 patients (5.9%). Successful ablation was obtained in 60 of 67 patients (90%), and the individualised complex dosimetry study suggested a theoretical maximum administrable activity for the patients with multiple distant metastases of 13,320 and 9,250 MBq, respectively. It is very important to underline that 16 of 21 (76%) of the lesions received an absorbed dose of less than 80 Gy due to the limiting dose to the bone marrow. The authors' conclusion on the basis of their findings is that ^{124}I PET/CT is a powerful diagnostic tool to perform excellent pre-^{131}I therapy staging, superimposable on the highly sensitive TxWBS. ^{124}I PET/CT could be routinely performed in order to obtain reliable dosimetry studies in patients with multiple metastases or to evaluate the usefulness of alternative therapies, thereby finally improving the management of these patients; however, its use is restricted by its limited availability.

rhTSH was recently approved as an alternative to thyroid hormone withholding (THW) as a means of elevating TSH for thyroid remnant ablation in DTC patients. ^{124}I PET/CT was used by Freudenberg et al. to study remnant radioiodine kinetics, comparing the residual radiation dose (measured in Gy/GBq) of the administered ^{131}I activity (RDpA) obtained under the two stimulation methods [22]. The authors retrospectively divided 55 consecutive totally thyroidectomised, radioiodine-naïve patients into two groups. The rhTSH group (n=16) received ^{124}I on continuous thyroid hormone replacement therapy, 24 h after two consecutive daily intramuscular injections of 0.9 mg rhTSH. The THW group (n=39) received ^{124}I after weeks-long THW, when serum TSH first measured ≥25 mIU/l. PET investigations were performed 4, 24, 48,

72 and 96 h after ^{124}I administration and PET/CT 25 h after ^{124}I administration. Median stimulated serum thyroglobulin was found to be 15 times higher and M1 disease almost twice as prevalent in rhTSH versus THW patients. Mean± standard deviation RDpA was statistically equivalent between the groups. The data presented in this paper suggest that rhTSH or THW deliver statistically comparable radiation doses to residual thyroid tissue and may be chosen on the basis of safety, quality of life, convenience and pharmacoeconomic factors. The authors also note that institutional fixed radioiodine activities formulated for use with THW need not be adjusted for rhTSH-aided ablation.

In another attempt to develop an optimised dosimetry protocol for radioiodine therapy of DTC, ^{124}I PET was used to analyse iodine kinetics of DTC metastases and lesion dose per administered ^{131}I activity (LDpA) [23]. The authors evaluated the time-activity concentration curves of 37 lesions in 17 patients who had undergone near-total thyroidectomy. LDpA determination involved ^{124}I PET images acquired at 4, 24, 48, 72 and 96 h after intake of a capsule containing 20–40 MBq of ^{124}I. The LDpAs, calculated using data from all five PET time points, served as reference. The lesions were classified into three groups, according to potential for cure with ^{131}I therapy: low, medium or high LDpA. Using the reference approach, the differences in the empirical kinetic parameters within the LDpA groups were evaluated. The results showed that the effective ^{124}I half-life, linear activity-concentration rate (alpha) and 24-h activity concentration (CpA) (the latter two per administered ^{124}I activity) differed significantly among the LDpA groups ($p<0.05$). LDpAs were highly correlated with 24-h CpAs. Using the 4-, 24- and 96-h measurements, a rho c value of greater than or equal to 0.90 was found, and the mean absolute percentage deviation was less than or equal to 16%. Similar statistical values were obtained for an adapted approach, which was based on the 24- and 96-h PET data points only. The authors concluded that the lesion classification into LDpA groups was feasible using a single PET scan at approximately 24 h. Because of the highly variable kinetics, one additional measurement at approximately 96 h was needed to obtain a sufficiently reliable LDpA estimate. According to the authors the adapted 24- to 96-h approach appears to be the optimal ^{124}I protocol and constitutes a reliable simplification of the five-point protocol.

The potential value of ^{124}I PET in the field was recently highlighted by Hobbs et al., who used patient-specific three-dimensional radiobiological dosimetry (3-D RD) to plan ^{131}I treatment for an 11-year-old girl affected by differentiated papillary thyroid cancer with advanced lung involvement and cerebral metastases [24]. Radioiodine pharmacokinetic assessments and calculation of the recommended administered activity, based on lung toxicity constraints, were performed in real time (i.e. during the data acquisition interval) using ^{124}I PET. The results were made available to the treating physician in time to influence treatment planning and these estimates were compared with conventional dosimetry methodologies. In subsequent, retrospective analyses, the 3-D RD calculations were expanded to include additional tumour dose estimates, and the conventional methodologies were re-examined to reveal the causes of the differences observed. The higher recommended administered activity given by this approach, compared with an S value-based method, resulted in a favourable clinical outcome. In short, this approach allowed more aggressive treatment while adhering to patient-specific lung toxicity constraints.

Conclusion

The wealth of recent publications on radioiodine treatment of benign thyroid diseases and thyroid carcinoma clearly bears witness to the importance that individual patient dosimetry is acquiring in contemporary nuclear medicine therapy. Investigators are addressing, in depth, different aspects of radioiodine kinetics, and their efforts reflect a growing awareness and understanding of the clinical applications of radioiodine radiobiology.

Recent technological advances (PET/CT and SPECT/CT) and the availability of new radiopharmaceuticals (^{124}I) are offering us new and better opportunities to go beyond the administration of fixed activities. Using dose-point kernel convolution methods together with sophisticated calculations, or direct Monte Carlo calculations, accurate 3-D absorbed dose estimates can now be derived from SPECT or PET imaging.

Although only prospective, randomised trials can really reinforce the need for dosimetry in everyday clinical practice, there is nevertheless increasing evidence that the evaluation of radioiodine biokinetics and absorbed doses to lesions and normal organs could substantially improve the quality and outcome of radionuclide therapy.

It is to be expected, and hoped, that in the near future radionuclide treatments with administered activities based on prescribed absorbed doses, as used in EBRT, will become commonplace, improving the efficacy of the treatment and, therefore, individual clinical outcomes.

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References

1. Sisson JC, Avram AM, Rubello D, Gross MD. Radioiodine treatment of hyperthyroidism: fixed or calculated doses; intelligent design or science? Eur J Nucl Med Mol Imaging 2007;34 (7):1129–30.

2. Brans B, Bodei L, Giammarile F, Linden O, Luster M, Oyen WJG, et al. Clinical radionuclide therapy dosimetry: the quest for the "Holy Gray". Eur J Nucl Med Mol Imaging 2007;34(5):772–86.
3. Flux G, Bardies M, Chiesa C, Monsieurs M, Savolainen S, Strand SE. Clinical radionuclide therapy dosimetry: the quest for the "Holy Gray" [letter to the editor]. Eur J Nucl Med Mol Imaging 2007;34(10):1699–700.
4. Shapiro B. Optimization of radioiodine therapy of thyrotoxicosis: what have we learned after 50 years? J Nucl Med 1993;34 (10):1638–41.
5. de Rooij A, Vandenbroucke JP, Smit JW, Stokkel MP, Dekkers OM. Clinical outcomes after estimated versus calculated activity of radioiodine for the treatment of hyperthyroidism: systematic review and meta-analysis. Eur J Endocrinol 2009;161(5):771–7.
6. Zakavi SR, Mousavi Z, Davachi B. Comparison of four different protocols of I-131 therapy for treating single toxic thyroid nodule. Nucl Med Commun 2009;30(2):169–75.
7. Walter MA, Schindler C, Christ-Crain M, Müller-Brand J, Müller B. Different strategies to overcome the effect of carbimazole on high- and low-dose radioiodine therapy: results from continuous dose-effect models. Eur J Clin Invest 2009;39(1):51–7.
8. Traino A, Xhafa B. Accuracy of two simple methods for estimation of thyroidal 131I kinetics for dosimetry-based treatment of Graves' disease. Med Phys 2009;36(4):1212–8.
9. Kobe C, Eschner W, Wild M, Rahlff I, Sudbrock F, Schmidt M, et al. Radioiodine therapy of benign thyroid disorders: what are the effective thyroidal half-life and uptake of 131I? Nucl Med Commun 2010;31:201–5.
10. Bachmann J, Kobe C, Bor S, Rahlff I, Dietlein M, Schicha H, et al. Radioiodine therapy for thyroid volume reduction of large goitres. Nucl Med Commun 2009;30(6):466–71.
11. Fast S, Nielsen VE, Bonnema SJ, Hegedüs L. Time to reconsider nonsurgical therapy of benign non-toxic multinodular goitre: focus on recombinant human TSH augmented radioiodine therapy. Eur J Endocrinol 2009;160(4):517–28.
12. Braverman L, Kloos RT, Law Jr B, Kipnes M, Dionne M, Magner J. Evaluation of various doses of recombinant human thyrotropin in patients with multinodular goiters. Endocr Pract 2008;14(7):832–9.
13. Cubas ER, Paz-Filho GJ, Olandoski M, Goedert CA, Woellner LC, Carvalho GA, et al. Recombinant human TSH increases the efficacy of a fixed activity of radioiodine for treatment of multinodular goitre. Int J Clin Pract 2009;63(4):583–90.
14. Sisson JC, Dewaraja YK, Wizauer EJ, Giordano TJ, Avram AM. Thyroid carcinoma metastasis to skull with infringement of brain: treatment with radioiodine. Thyroid 2009;19(3):297–303.
15. De Klerk JM, Oyen WJ. The continuous debate in literature about the usage of iodine-131 dosing for the ablation of thyroid remnants and metastases. Minerva Endocrinol 2009;34(1):57–69.
16. Lassmann M, Hänscheid H, Chiesa C, Hindorf C, Flux G, Luster M, et al. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. Eur J Nucl Med Mol Imaging 2008;35(7):1405–12.
17. Verburg FA, Hänscheid H, Biko J, Hategan MC, Lassmann M, Kreissl MC et al. Dosimetry-guided high-activity (131)I therapy in patients with advanced differentiated thyroid carcinoma: initial experience. Eur J Nucl Med Mol Imaging; 2009 Dec 24. [Epub ahead of print] doi:10.1007/s00259-009-1303-x.
18. Stahl AR, Freudenberg L, Bockisch A, Jentzen W. A novel view on dosimetry-related radionuclide therapy: presentation of a calculatory model and its implementation for radioiodine therapy of metastasized differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging 2009;36(7):1147–55.
19. Flux GD, Haq M, Chittenden SJ, Buckley S, Hindorf C, Newbold K et al. A dose-effect correlation for radioiodine ablation in differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2010;37:270–5. 2009 Sep 4. [Epub ahead of print] doi:10.1007/s00259-009-1261-3.
20. Hänscheid H, Lassmann M, Luster M, Kloos RT, Reiners C. Blood dosimetry from a single measurement of the whole body radioiodine retention in patients with differentiated thyroid carcinoma. Endocr Relat Cancer 2009;16(4):1283–9.
21. Capoccetti F, Criscuoli B, Rossi G, Ferretti F, Manni C, Brianzoni E. The effectiveness of 124I PET/CT in patients with differentiated thyroid cancer. Q J Nucl Med Mol Imaging 2009;53(5):536–45.
22. Freudenberg LS, Frömke C, Petrich T, Marlowe RJ, Koska WW, Brandau W, et al. Thyroid remnant dose: 124I-PET/CT dosimetric comparison of rhTSH versus thyroid hormone withholding before radioiodine remnant ablation in differentiated thyroid cancer. Exp Clin Endocrinol Diabetes; 2009. [Epub ahead of print] doi:10.1055/s-0029-1225350.
23. Jentzen W, Freudenberg L, Eising EG, Sonnenschein W, Knust J, Bockisch A. Optimized 124I PET dosimetry protocol for radioiodine therapy of differentiated thyroid cancer. J Nucl Med 2008;49(6):1017–23.
24. Hobbs RF, Wahl RL, Lodge MA, Javadi MS, Cho SY, Chien DT, et al. 124I PET-based 3D-RD dosimetry for a pediatric thyroid cancer patient: real-time treatment planning and methodologic comparison. J Nucl Med 2009;50(11):1844–7.