

Dosimetry and thyroid cancer: the individual dosage of radioiodine

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Abstract

Adjuvant therapy of differentiated thyroid cancer with radioactive iodine (¹³¹I) is a standard procedure for the ablation of remnant thyroid tissue following surgery and for the treatment of iodine-avid metastases. Presently, there are two dosimetric concepts for the treatment of thyroid cancer using radioiodine: a) the bone marrow dose limited approach and b) lesion-based dosimetry. Both concepts and their clinical applications are described. In addition, the use of ¹²⁴I as a diagnostic and dosimetric agent is discussed. Treatment of children and adolescents with radioiodine requires special precautions; individualized approaches in this setting are reviewed. The limitations of treatments aiming at high absorbed doses are addressed as well as the doses to normal organs. Finally, new concepts for further elaborating the potential of thyroid cancer treatment using ¹³¹I are introduced.

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Introduction

Treatment of differentiated thyroid cancer (DTC) with radioactive iodine (¹³¹I; often referred to as ‘radioiodine’) is a standard procedure for the ablation of remnant thyroid tissue following surgery and for the treatment of iodine-avid metastases. An excellent overview of the procedures, and risks related to DTC therapy with radioiodine can be found in the textbook by Schlumberger & Pacini (2003).

The activity to be used for radioiodine therapy still remains subject to discussion. Usually, patients are treated with standard activities reflecting the physician’s rating of the highest safe or ‘adequate’ dosage rather than with an optimized treatment activity based on prior measurement of the patient’s individual biokinetics. Such a standard activity poses a risk of either under-dosing the patient or of exceeding common safety limits (Van Nostrand *et al.* 2002, Tuttle *et al.* 2006).

There is a broad range of fixed activities of ¹³¹I recommended to be administered (see e.g. Meier *et al.* (2002) and Luster *et al.* (2008)). In many cases, an activity between 1.1 and 3.7 GBq is prescribed for the first radioiodine therapy after thyroidectomy in newly diagnosed DTC to ablate the remaining glandular tissue. Higher amounts of ¹³¹I are given in subsequent therapies or in case of metastatic disease. Normally, the

activity is limited for safety reasons to around 7.4 GBq. A summary on the use of fixed activities for the treatment of DTC until 2002 can be found in a review article by Menzel *et al.* (1996), Van Nostrand *et al.* (2002) and Haq *et al.* (2004) adopt a more aggressive approach for advanced stages of the disease employing empiric fixed activities of radioiodine of 9 GBq (Haq *et al.* 2004) and 11.1 GBq at 3-month intervals (Menzel *et al.* 1996).

The main disadvantage in using a fixed activity approach is the failure to consider the individuality of the patient. The ‘optimal’ activity of radioiodine to treat metastatic thyroid carcinoma is the lowest possible amount of radioiodine that delivers a lethal dose of radiation to the entire lesion/metastasis while minimizing side effects. Empiric fixed activities by their very nature make no attempt to determine either the minimal radioiodine activity that will deliver a lethal dose or the maximum allowable reasonably safe absorbed dose.

An additional shortcoming is that multiple empiric fixed activities may not be equivalent to the same total radioiodine absorbed dose calculated by dosimetry given at one time. Dose rate is crucial, and thus, multiple smaller doses may have lower therapeutic benefit than the same total dose given at one time

(see e.g. Samuel *et al.* (1998)). On top of that, previous nonlethal doses may reduce the effectiveness of subsequent doses (Medvedec 2005).

Therefore, the rationale for using a dosimetry-based approach is to replace the conventional fixed activity regimen by a modern setting, which allows the administered therapeutic activity to be increased while avoiding undesired side effects. Using this strategy, the absorbed dose to iodine-avid tissue (remnants/metastases) can be optimized without inducing potential toxicity.

One could also consider decreasing the administered activity based upon a dosimetric approach as proposed by Hänscheid *et al.* (2009). However, for establishing such an approach, clinical data are missing at present.

As has been pointed out in a recent article on radioiodine therapy dosimetry by Salvatori & Luster (2010), 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 external beam radiation therapy, will become commonplace, improving the efficacy of the treatment and, therefore, individual clinical outcomes.

Dosimetric concepts

Presently, there are two dosimetric concepts for the treatment of thyroid cancer using radioiodine:

- a) The bone marrow dose limited approach, originally described by Benua *et al.* (1962):

This concept is mainly aiming at the safety of the treatment. Blood, as a surrogate of the organ at risk, i.e. the red bone marrow, was considered as the critical organ in this approach. The generally accepted surrogate dose threshold to avoid serious myelotoxicity is a blood absorbed dose of 2 Gy.

- b) The lesion-based dosimetry, based mainly on the data of Maxon *et al.* (1983) and Maxon & Smith (1990):

This concept aims at improving the efficacy of the treatment by achieving an absorbed dose threshold of more than 300 Gy to remnants and of more than 80 Gy to iodine-avid tissue. The value of 80 Gy was originally defined for the treatment of cervical lymph node metastases, and is assumed to be accurate also for distant metastases.

Bone marrow dose limited approach

The method originally reported by Benua *et al.* (1962) and, applied to a larger patient series, by Leeper (1985) allows an estimate to be calculated for the radiation

dose that will be delivered to the hematopoietic system from each GBq administered to any patient. This is possible because it involves the collection of data over the course of four or more days after the administration of a tracer activity of ^{131}I to the patient. The measurement procedures involve serial blood sampling and serial measurements of the patient's whole body activity using a calibrated probe.

Given the time period in which this methodology was developed, it follows that the dosimetry calculations were based on the classic formulations rather than on the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine (MIRD) absorbed fraction method (Schlumberger & Pacini 2003, Lassmann *et al.* 2008). Generally, both approaches are in good agreement; however, the patient specificity is improved using the MIRD formalism as described by the Lassmann *et al.* (2008). Furthermore, it should be emphasized that these calculations yield the radiation dose to the whole-blood compartment and not to the bone marrow directly. In the original setting of Benua, a subgroup of patients, namely those that received 2 Gy or less to the blood, showed no serious side effects.

In the classic Benua approach, the blood is considered as the critical organ that is irradiated either from the particles emitted from activity in the blood itself or from the emissions originating from activity dispersed throughout the remainder of the body.

The maximum treatment activity $A_{\text{administered}}$ is calculated as the activity of ^{131}I that would deliver a combined beta particle absorbed dose D_{β} and gamma ray absorbed dose D_{γ} of 2 Gy to the blood compartment, and is given by:

$$A_{\text{administered}} \text{ (MBq)} = \frac{2 \text{ Gy}}{D_{\beta} \text{ (Gy/MBq)} + D_{\gamma} \text{ (Gy/MBq)}}$$

D_{β} which is calculated by integrating the blood activity biokinetics (measuring blood samples in a gamma-counter), whereas the D_{γ} -dose is taken from serial measurements of the patient with a gamma-probe.

Individual patient-specific geometry parameters such as weight and height are not considered when assessing the activity to be administered. In addition, the measurements are often not repeated during therapy in order to compare the estimated pretherapeutic absorbed dose to the absorbed dose achieved after therapy.

Recently, in the framework of several international multicenter trials for the study of the biokinetics after the use of recombinant human TSH (rhTSH; Luster *et al.* 2003, Hänscheid *et al.* 2006), the absorbed dose

to the blood was calculated with a modified method deduced from a procedure originally described by Thomas *et al.* (1993). Refinements to this model have been introduced to account for:

- 1) the contribution from penetrating radiation from activity in distant blood to the blood dose,
- 2) the mass dependency of the S value representing the radiation from the total body to the blood, and
- 3) a mean value $S_{\text{blood} \leftarrow \text{blood}}$ representing an average for blood circulating in vessels of different diameters with different S values (Lassmann *et al.* 2004).

The equation for the mean absorbed dose \bar{D}_{blood} to the blood per unit administered activity becomes:

$$\frac{\bar{D}_{\text{blood}}}{A_0} \left(\frac{\text{Gy}}{\text{GBq}} \right) = 108 \times \tau_{\text{ml of blood}} (\text{h}) + \frac{0.0188}{(\text{wt}(\text{kg}))^{2/3}} \times \tau_{\text{total body}} (\text{h})$$

τ_{source} stands for the residence time in a source organ representing the integral of the activity–time curve in the source organ (cumulated activity) divided by the administered activity; wt represents the patient's weight in kg. The modified expression accounts for the activity in distant blood vessels and the influence of the individual patient mass.

Therefore, only two compartments need to be monitored for radioactivity: blood and the whole body. The activity in the blood is determined from periodic heparinised blood samples. The activity in the whole body, i.e. remaining in the patient, could be monitored redundantly using independent techniques: 24 h urine collections, whole-body counting with a probe using a fixed geometry and, if applicable, conjugate views of whole body scan obtained by a dual-headed gamma camera.

Details of the recommended data sampling frequency and of the calculation process can be found in the recently published standard operational procedures (SOP) of the EANM (Lassmann *et al.* 2008). In Fig. 1, an example of a post-therapeutic dose assessment after administration of 3.6 GBq ^{131}I is given. Panel A shows the measured data and the corresponding fits (whole-body dose rate and blood activity normalized to the administered activity), and panel B shows the temporal change of the absorbed dose and the dose rate.

The presented model might not to be applied in the presence of extensive metastatic bone involvement, as

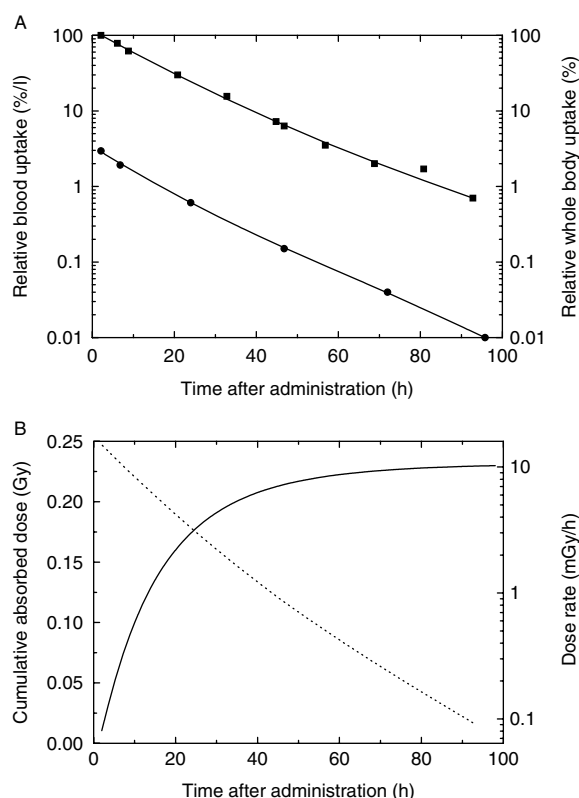


Figure 1 Time curves of a post-therapeutic blood dose assessment according to the EANM SOP (Lassmann *et al.* 2008) after administration of 3.6 GBq ^{131}I (absorbed dose to the blood: 0.23 Gy). (A) Measured relative uptake and corresponding bi-exponential fits per liter of blood (filled circles, left axis) and of the whole body (filled squares, right axis). (B) Cumulative absorbed dose to the blood (solid line, left axis) and absorbed dose rate (dotted line, right axis).

the blood-based absorbed dose calculation could underestimate the absorbed dose to the red marrow.

It should be carefully applied in patients affected by diffuse pulmonary micro-metastases, since the critical organ could be the lung itself instead of the hematopoietic red marrow. In the Benua approach, fatal complications were avoided after restricting the incorporated activity at 48 h to 4.5 GBq and, in the case of diffuse lung metastases, to <3 GBq.

Sgouros *et al.* (2006) used the 3-GBq activity retention limit originally introduced by Benua *et al.* (1962) in order to derive patient-specific lung absorbed doses and dose rates in order to account for differences in lung geometry. The authors obtain a dose–rate constraint value, which yields when applied to an adult male phantom and to the phantom of a 15-year-old yields 48-h activity limits of 3.72 and 2.45 GBq respectively. Using this approach, severe

radiation-induced lung toxicity, expected at normal lung absorbed doses of 25–27 Gy, is avoided.

The strengths of the blood-based dosimetry approach are (Lassmann et al. 2008) as follows:

- 1) determination of the maximal safe activity of radioiodine for each patient individually;
- 2) identification of patients for whom empiric fixed activities are not safe;
- 3) the potential to administer higher activities at once instead of multiple administrations of lower activities in a ‘fractionated’ therapy in order to avoid changes in tumor/lesion biokinetics after multiple therapies that have been observed, e.g. by Samuel et al. (1998);
- 4) no necessity to determine lesion volumes;
- 5) a long history of use in several institutions;
- 6) an expected increase in the probability of curing patients in and advanced stages of the disease with fewer courses of therapy.

Limitations that need to be mentioned are as follows:

- 1) a benefit of the strategy is plausible but no valid clinical data exist on improved response and/or outcome rates;
- 2) the absorbed dose to the tumor is not known. Higher activities might be administered without achieving a higher therapeutic effect when using this methodology;
- 3) the current debate regarding the issue of ‘stunning’ argues that diagnostic administrations of ^{131}I could alter tumor/lesion biokinetics and, consequently, the absorbed dose in a subsequent treatment.

Lesion-based dosimetry

The objective of remnant or lesion dosimetry is to determine the radioiodine activity that delivers the recommended absorbed dose of radiation to ablate thyroid remnant or to treat metastatic disease while minimizing the risk to the patient. The absorbed doses are traditionally considered to be 300 and 80 Gy respectively (Maxon et al. 1983, Maxon & Smith 1990). In contrast to these pretherapeutic dosimetric procedures, the radiation absorbed dose delivered by the ^{131}I therapeutic activity itself to the thyroid remnant or to lesions also may be measured post-therapy, attempting to correlate this dose with clinical results.

In order to perform these calculations, it is necessary to measure the uptake and clearance of ^{131}I from

identifiable thyroid remnants and/or metastatic lesions. This calculation of lesion dose is generally based on the same model as described above. For example, if the lesions become smaller, the nodule module of OLINDA/EXM could be used for a spherical model of the tumor and/or the lesion (Stabin et al. 2005). Furthermore, if the dimensions of the lesions are smaller than ~ 5 mm (assuming that this could be accurately determined), then the range of the beta-particles can no longer be neglected in the dose calculation (Li et al. 2001).

In order to determine the concentration of ^{131}I , one needs to know how much activity is contained in the lesion. One way in which this can be examined is based on an analysis of selected regions of interest on conjugate view gamma-camera images (Siegel et al. 1999). These images are obtained at several time points measured from the time of administration of a tracer activity. Typically, subsequent image acquisition would happen up to 96 h, but later samples might be necessary if the uptake and clearance are delayed. In addition, transmission images to correct for attenuation in the region of the lesion, as well as images of a standard for calibration purposes, might be necessary (Siegel et al. 1999). A curve-fitting procedure is then used to evaluate the assumed single-exponential half-life value and to extrapolate the curve to zero time in order to determine the initial activity in the lesion.

Particularly when using probe data or planar scintigrams, another important parameter needed for calculating the specific activity is the mass of the lesion. For ablation therapies, the various procedures for determining the remnant size such as ultrasound or computed tomography (CT) are unreliable as no validated method exists to exactly determine the mass of thyroid remnants shortly after surgery (Hänscheid et al. 2006); consequently, one has to be careful when reporting absorbed doses to the target tissue. For lesion dosimetry, higher spatial resolution images like CT can be used for attenuation correction and to determine the mass.

The main disadvantages of a lesion-based approach to thyroid cancer treatment dosimetry are (Lassmann et al. 2008) as follows:

- 1) a wide range of absorbed doses to lesions/metastases even within one patient;
- 2) inhomogeneous absorbed dose distributions within one lesion may result in incomplete tumor destruction;
- 3) a mono-exponential model may not accurately reflect the kinetics of the radioiodine in the lesion;

- 4) ill-defined corrections have to be applied for the initial phase of increasing uptake (up to ~ 24 h) caused, e.g. by the delayed resorption of orally administered ^{131}I ;
- 5) an accurate measurement of the lesion mass is not always possible;
- 6) statistical errors in the measurements due to bad counting statistics particularly at late time points;
- 7) unknown biologic effectiveness of the treatment due to the potentially heterogeneous iodine uptake on a microscopic scale which cannot be accounted for in conventional scintigraphic images.

Clinical findings

Bone marrow dose limited approach

The blood or red marrow dosimetry offers not only the possibility of increasing the administered activity. The same method allows reducing the activity in order to guarantee safety of the treatment. It is a fact that the fixed activity approach, being completely blind, can give blood absorbed doses higher than 2 Gy.

Kulkarni *et al.* (2006) performed pretreatment blood dosimetric studies on 127 patients with 74 MBq of ^{131}I . Then, once measured the blood-specific absorbed dose (Gy/GBq) of their patient group, they calculated the percentage of patients who would have received more than 2 Gy to the blood according to different hypothetical fixed activity administrations. For example, for an assumed empiric dosage of ^{131}I of 7.4 GBq, the percentage of treatments for which patients would have exceeded the 2 Gy limit were $<11\%$. A more detailed analysis of these percentages as a function of the administered activity is shown in Fig. 2.

Tuttle *et al.* (2006) analyzed retrospectively 535 hypothyroid blood dosimetries in 328 patients with apparently normal renal function. They found that the maximum tolerated activity (corresponding to 2 Gy to blood) was <7.4 GBq in 8% and <9.25 GBq in 19% of their patients. Factors associated with a lowering of the maximum tolerated activity to <9.25 GBq were age at dosimetry >45 years, the female sex, subtotal thyroidectomy, and radioiodine-avid diffuse bilateral pulmonary metastases. Administered activities of 7.4–9.25 GBq frequently exceeded the calculated maximum tolerated activity in patients 70 years old or above. Therefore, the authors conclude that dosimetry-guided radioiodine therapy may be preferable to fixed-dose treatment strategies in older patients with thyroid cancer and in patients with

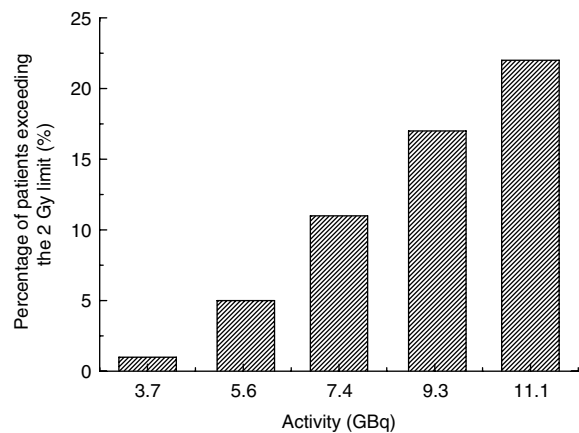


Figure 2 Percentage of patients who would have received a blood absorbed dose >2 Gy in case of empiric fixed activity administration (adapted from Kulkarni *et al.* (2006)).

radioiodine-avid diffuse bilateral pulmonary metastases, even when renal function is normal.

Recently, rhTSH was approved as an alternative to thyroid hormone withdrawal (THW) to elevate TSH for thyroid remnant ablation in DTC patients (Pacini *et al.* 2006). However, improved renal function causes $\sim 30\%$ faster radioiodine clearance under euthyroidism versus hypothyroidism, and high ablation success rates are reported with diverse rhTSH-aided ^{131}I activities (Hänscheid *et al.* 2006, Remy *et al.* 2008).

An analysis of the distribution of the relative absorbed dose coefficients (the absorbed dose coefficient is defined as the absorbed dose divided by the administered activity) in 66 patients after radioiodine therapy of DTC is shown in Fig. 3 (Lassmann *et al.* 2007). The data are normalized to the lowest specific absorbed dose. Patients were either hypothyroid ($n=32$) or euthyroid ($n=34$). The mean absorbed dose coefficients for euthyroid patients are $\sim 30\%$ lower as compared with patients after thyroid hormone withdrawal (hypothyroid). The highest absorbed dose coefficient is almost sixfold higher as compared with the data of the patient with the lowest absorbed dose coefficient. This figure illustrates a) the wide distribution of absorbed doses to the blood when using standard activities and b) the faster radioiodine clearance for euthyroid patients as compared with hypothyroid patients.

In a recent publication by Hänscheid *et al.* (2009), the authors discuss if a lower targeted blood absorbed dose seems reasonable for remnant ablation therapy in low risk patients. Based on formulas and assumptions presented in this work, and data derived

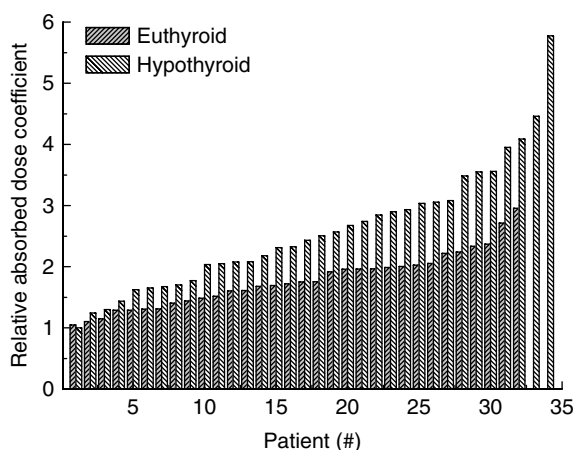


Figure 3 Relative distribution of the absorbed dose coefficients (absorbed dose to blood) after radioiodine therapy in 66 patients after thyroid hormone withdrawal (hypothyroid) or after the use of recombinant human TSH (euthyroid) (Lassmann et al. 2007). The data are normalized to the minimal absorbed dose coefficient.

from a series of patients treated with 3.7 GBq ^{131}I (Hänscheid et al. 2006), the mean absorbed doses to the blood were 0.45 and 0.29 Gy when prepared for therapy with hypothyroidism or euthyroidism using rhTSH respectively. As the rate of remnant ablation between the two groups was similar, it may be adequate to routinely select a remnant ablative activity that delivers 0.3 Gy to the blood for patients of similar disease stage. However, as blood dose-based remnant ablation therapy is not yet validated, the paper stimulates the discussion if dosimetry-based ablation rate studies should be performed.

In the case of a pediatric patient presenting with diffuse lung metastases, Song et al. (2006) demonstrated the usefulness of dose planning using a) the conventional Benua approach, b) the dose–rate constraint approach introduced by Sgouros et al. (2006) described above, and c) a Monte Carlo calculation-based approach. Directly applying the Benua method, an administered activity of 3.9 GBq was obtained, the dose–rate constraint approach resulted in 2.4 GBq, whereas in the Monte Carlo approach the authors demonstrated that an administered activity of 1.7 GBq resulted in a lung dose of 27 Gy. Such discrepancy highlights the necessity of more studies to correlate between the Benua dosing method and absorbed doses to normal organs and tumors.

Lesion-based dosimetry

The objective of remnant or lesion dosimetry is to determine the radioiodine activity that delivers the

recommended absorbed dose of radiation to ablate thyroid remnant or to treat metastatic disease while minimizing the risk to the patient. The doses are traditionally considered to be 300 and 80 Gy respectively (Maxon et al. 1983, Maxon & Smith 1990). In contrast to these pretherapeutic dosimetric procedures, the radiation absorbed dose delivered by the ^{131}I therapeutic activity itself to the thyroid remnant or to lesions also may be measured post-therapy to correlate this dose with clinical results.

de Keizer et al. (2003) evaluated the tumor dosimetry following ^{131}I treatment after rhTSH stimulation. They performed dosimetric calculations after ^{131}I tumor uptake measurements from post-treatment ^{131}I scintigrams and tumor volume estimations from radiological images. Their reported median tumor radiation absorbed doses were between 1.3 and 368 Gy, thus showing a high variability in the lesion absorbed doses. Only 5 out of 25 lesions investigated received a dose of more than 80 Gy.

Similar findings were reported by Sgouros et al. (2004) who used ^{124}I for a voxel-based pretherapeutic lesion dose assessment.

A successive change in the biokinetics of pulmonary metastases after several therapies has been observed by Samuel et al. (1998). In their study, they demonstrated that dosimetric parameters such as radioiodine uptake as a percentage of therapeutic activity, effective half-life and radiation dose delivered to the lungs which were evaluated with each therapy, showed a progressive decline in each of these parameters with successive therapies.

Chiesa et al. (2009) described a total of 17/20 lesions with doses below 80 Gy in their patient group. Their data also suggest that the repetition of treatment of a lesion drastically reduces its uptake, with a loss of therapeutic efficacy along the sequence of fixed activity administrations.

Some groups (Freudenberg et al. 2007, Flux et al. 2010) combine the lesion- and blood-based dosimetric approaches; however, larger patient series are warranted to further support this strategy (De Klerk & Oyen 2009).

The use of ^{124}I for dosimetry

Traditional radiopharmaceuticals that accurately quantify radioiodine uptake in thyroid remnants and metastases such as ^{123}I or ^{131}I have different limitations: the former presents problems regarding supply and short half-life, the latter a relatively low sensitivity and the risk of induction of the ‘stunning’

phenomenon. The recent availability of a positron emission tomography (PET) tracer such as ^{124}I has created new perspectives for PET/CT, both as an effective staging tool to detect recurrent/residual disease and for dosimetry of (metastatic) lesions.

The use of ^{124}I was proposed for quantifying volume, *in vivo* tumor concentration, and biodistribution for DTC (Pentlow *et al.* 1996, Eschmann *et al.* 2002, Sgouros *et al.* 2004). Owing to the complex decay process of ^{124}I , tumor-associated quantification cannot be performed in the same way as for F-18. Pentlow *et al.* (1996) measured resolution, linearity, and the ability to quantify the activity contents of imaged spheres of different sizes and activities for different background activities. It was shown that the quantification process for ^{124}I could reliably reproduce the activities administered. PET with ^{124}I was also successfully applied to the measurement of thyroid volume (Crawford *et al.* 1997, Eschmann *et al.* 2002).

The first rigorous approach to PET ^{124}I -based thyroid cancer dosimetry has been described in a publication by Sgouros *et al.* (2004), in which the authors showed by using the PET results as input to a fully 3D dose planning program spatial distributions of absorbed doses, isodose contours, dose-volume histograms, and mean absorbed dose estimates for a total of 56 tumors. The mean absorbed dose values for individual tumors ranged from 1.2 to 540 Gy. The absorbed dose distribution within individual lesions was widely distributed ranging from a minimum of 0.3 Gy to a maximum of 4000 Gy showing the high variability of dose ranges even within one patient.

The aims of the study by Capocchetti *et al.* (2009) were to evaluate the usefulness of ^{124}I PET/CT as a tool for DTC staging immediately before ^{131}I therapy, optimizing the activity for remnant ablation, and individualizing dosimetry in patients with multiple distant metastases. In two cases, individualized pretherapeutic ^{124}I -based dosimetry led to a maximum safe activity of 13 and 9 GBq respectively. In 16/21 lesions studied, the absorbed was <80 Gy. On the basis of their findings, the authors conclude that ^{124}I PET/CT could be routinely employed in order to obtain a reliable dosimetry in patients with multiple metastases or to stimulate consideration of alternative therapies, and thereby finally improving the management of those patients; however, its use is restricted by the limited availability.

Freudenberg *et al.* (2007, 2009) performed through ^{124}I PET/CT a study of remnant radioiodine kinetics

comparing the remnant radiation dose in Gy/GBq of the administered ^{131}I activity obtained under two stimulation methods: hypothyroidism (THW) versus euthyroidism after the use of rhTSH. 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 i.m. 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 and PET/CT 25 h after ^{124}I administration. The mean \pm s.d. specific absorbed dose was statistically equivalent between the groups (rhTSH, 461 ± 600 Gy/GBq; THW, 302 ± 329 Gy/GBq; two-sided $P=0.258$). The data presented in these papers suggest that rhTSH or THW delivers statistically comparable radiation doses to thyroid remnant. The authors also note that institutional fixed radioiodine activities formulated for use with THW need not be adjusted for rhTSH-aided ablation.

The small sample size in the rhTSH group might, however, limit the results of the statistical comparison in this work. Further, preferably multicentric clinical trials with higher statistical power are needed for elucidating this finding.

Jentzen *et al.* (2008), using ^{124}I PET, analyzed iodine kinetics and lesion dose per administered ^{131}I activity of DTC metastases to derive an optimized dosimetry protocol for radioiodine therapy of DTC. The authors evaluated the time–activity–concentration curves of 37 lesions in 17 patients who had undergone near-total thyroidectomy. The lesion dose 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 absorbed doses to the lesions, 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 (≤ 5 Gy/GBq; $n=14$), medium (between 5 and 10 Gy/GBq; $n=9$), or high specific lesion dose (> 10 Gy/GBq; $n=14$). The reference-specific lesion doses were compared with those derived from only 2, 3, or 4 PET data points and from one adapted 2-point approach. The results showed that the effective ^{124}I half-life, the specific activity–concentration rate, and the specific 24 h activity–concentration differed significantly among the groups. The authors conclude that the classification into specific lesion dose groups was feasible using a single PET scan at ~ 24 h. Because of the highly variable kinetics, one additional

measurement at ~ 96 h was needed to obtain a sufficiently reliable lesion dose estimate. They also state that the adapted 24–96 h approach appears to be the optimal ^{124}I protocol, and is a reliable simplification of the 5-point protocol.

Treatment of childhood cancer

Thyroid cancer, although very rare in childhood, represents the most common pediatric endocrine neoplasia. The low incidence and the resulting limited availability of prospective, randomized trials lead to a lack of evidence-based recommendations for treatment strategies. Total thyroidectomy and lymphadenectomy, when indicated, followed by ablative radioiodine treatment, are considered the cornerstones of initial patient management which decrease the risk of relapse. On the other hand, less aggressive treatment modalities should also be aimed at due to the high life expectancy of this special patient group and the potential impairment of the quality of life. These considerations have led to individualized ‘tailored’ therapeutic approaches based on prior risk stratification (Luster *et al.* 2007).

Hobbs *et al.* (2009) used a patient-specific 3D radiobiologic dosimetry for ^{131}I treatment planning for an 11-year-old girl with differentiated papillary thyroid cancer with advanced lung involvement, and cerebral metastases. 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 3D-absorbed dose calculations were expanded to include additional tumor dose estimates, and the conventional methodologies were reexamined to reveal the causes of the differences observed. A higher recommended administered activity than by the traditionally employed absorbed fraction method (Bolch *et al.* 2009) with a favorable clinical outcome was obtained. The authors concluded that this approach permitted more aggressive treatment while adhering to patient-specific lung toxicity constraints. Another observation was that a retrospective analysis of the conventional methodologies with appropriate corrections yielded absorbed dose estimates consistent with the 3D-absorbed dose calculation.

Optimized treatment using high activities

In patients with ‘high-risk’ DTC, therapy with the highest safe activity appears to be desirable to maximize the tumor radiation dose yet avoid myelotoxicity.

Verburg *et al.* (2010) sought to evaluate the safety and effectiveness of treating advanced DTC with high ^{131}I activities chosen primarily based on the results of dosimetry following the EANM SOP (Lassmann *et al.* 2008). The authors retrospectively assessed toxicity as well as biochemical and scintigraphic response in their first ten patients receiving such an ‘individualized’ therapy for advanced DTC. Ten patients received a total of 13 dosimetrically guided treatments with a median administered activity of 14.0 GBq (range: 7.0–21.4 GBq) ^{131}I . After 6 of 13 treatment courses in six of ten patients, short-term side effects of ^{131}I therapy, namely nausea, vomiting, or transient sialadenitis, were observed. Leukocyte and platelet counts dropped significantly in the first few weeks after ^{131}I treatment, but returned to pretreatment levels by 3 months post-therapy. Serum thyroglobulin levels decreased after 12 of 13 treatments (median reduction: 58%) in nine of ten patients. On the basis of their findings, the authors conclude that in their initial patient cohort, high-activity ^{131}I therapy for advanced DTC based on pretherapeutic blood dosimetry following the EANM SOP was safe and well tolerated. The authors also note that such treatment almost always produced a partial biochemical tumor response.

Lee *et al.* (2008) likewise determined the maximal safe activity calculated according to the original Benua approach for 47 patients. Their mean calculated safe activity was 12.5 GBq. Twenty-nine patients experienced transient cytopenia after therapy, but three patients did not recover to the baseline level. The authors state that the maximal safe dose provides an effective means of treatment in patients who failed to respond adequately to conventional fixed activity therapy.

Another study on thyroid cancer treatment based on dosimetry is using a slightly different approach. Dorn *et al.* (2003) reported on the clinical use of dosimetry-guided radioiodine treatment showing the safe and effective application of a 3-Gy bone marrow absorbed dose in 124 patients with DTC who underwent 187 dosimetric evaluations. One of the major shortcomings of this single-center approach, however, is that the dosimetric model used for bone marrow absorbed dose calculations is nonstandard and needs further evaluation.

The dose to normal organs

There are three recent studies which assess the absorbed doses to normal organs after radioiodine therapy (Jentzen *et al.* 2006, 2010, Kolbert *et al.* 2007), a missing piece in the assessment of DTC patient management.

Kolbert *et al.* (2007) provide dose volume histograms and mean absorbed doses for 14 normal organs, including organs for which comprehensive doses have not been published (for example, the salivary glands). Calculations were done using a 3D voxel-based method. The highest mean dose, 0.26 Gy/GBq, was seen in the right submandibular gland, whereas the lowest mean dose, 0.029 Gy/GBq, was measured in the brain. This study is the first comprehensive approach to normal organ dosimetry in patients by use of a quantitative tomographic imaging modality. An interesting observation is that this work shows good agreement between the absorbed dose to the heart chamber and the blood absorbed dose as measured according to the method of Benua *et al.* (1962), thus indirectly confirming the validity of the method of Benua *et al.*

Salivary gland impairment following high activity radioiodine therapy of DTC is a severe side effect with a high impact on patients' quality of life. Dosimetric calculations using planar gamma-camera scintigraphy with ^{131}I and ultrasonography provided evidence that the average organ dose per administered activity is too low to account for observed radiation damages to the salivary glands (Jentzen *et al.* 2006). In 2010, the authors repeated the study using ^{124}I with ten DTC patients who underwent a series of six (or seven) PET scans and one PET/CT scan after administration of $\sim 23 \text{ MBq } ^{124}\text{I}$ iodide (Jentzen *et al.* 2010). The specific absorbed doses for the submandibular and parotid glands were $0.32 \pm 0.13 \text{ Gy/GBq}$ (0.18–0.55) and $0.31 \pm 0.10 \text{ Gy/GBq}$ (0.13–0.46) respectively. No significant differences between ^{124}I PET/CT and ^{131}I dosimetry were found. The authors conclude that a voxel-based calculation taking into account the nonuniform activity distributions in the glands is necessary to possibly explain the radiation-induced salivary gland damage.

Future dosimetry concepts

The concept of the biological effective dose (BED) is useful to explain the biological effects of radiation, since it is based not only on the absorbed dose, but also on the biological effects such as the competition between the dose rate and the repair rate of sub-lethal

single-strand DNA damage. The theoretical basis of this evaluation goes back to the linear-quadratic model, which was introduced in external beam radiation therapy in 1982 (Barendsen 1982) to explain different cellular survival fractions obtained with a fixed absorbed dose but with different dose rates or dose fractionations. One decade ago, Dale developed the theoretical formulas for calculating BED in targeted radionuclide therapy (Dale 1996). The calculation of the BED, which is independent from the irradiation modality, starting from the absorbed dose, allows the comparison of expected biological effects following different irradiation conditions.

Targeted radionuclide therapies are also characterized by strong nonuniformity of dose deposition. Some cells are 'over-killed', while others receive a nonlethal dose. The role of nonuniformity can be accounted for by the equivalent uniform dose (EUD) parameter (O'Donoghue 1999). An EUD of 100 Gy should give the same effect as a mean dose of 100 Gy when uniformly distributed.

Prideaux *et al.* (2007) re-analyzed the pediatric case of diffuse lung micro-metastases, including BED and EUD approach, after the administration of 1.32 GBq. The mean absorbed dose, mean biologically effective dose, and EUD for the tumor were 57.7, 58.5, and 25.0 Gy respectively. Corresponding values for normal lung tissue were 9.5, 9.8, and 8.3 Gy respectively. Their analysis demonstrates the impact of radiobiologic modeling on response prediction. The 57% reduction in the equivalent dose value for the tumor reflects a high level of dose nonuniformity in the tumor and a corresponding reduced likelihood of achieving a tumor response. Such analyses are expected to be useful in treatment planning for radionuclide therapy.

Another novel approach by Lassmann *et al.* (2010) is to assess the additional number of DNA double-strand breaks (DSBs) after radioiodine therapy caused by radiation exposure by a dosimetric biomarker. A marker for this DSB formation is the histone H2 variant H2AX (γ -H2AX). DSBs also attract the damage sensor 53BP1 to the surrounding chromatin, as is the DNA damage sensor 53BP1 that associates with the DSB-surrounding chromatin. The authors studied, in 26 patients after the first ^{131}I therapy, the induction, persistence, and the disappearance of radiation-induced γ -H2AX and 53BP1 foci after the first ^{131}I therapy of patients with differentiated thyroid carcinoma, a model for protracted, continuous, internal whole-body irradiation. Significantly elevated numbers of excess foci/nucleus were still present 120–144 h after therapy. The number of excess

radiation-induced foci/nucleus per absorbed dose rate increased with time, potentially indicating a slower rate of DNA repair, or alternatively, a higher *de novo* rate of focus formation. The authors concluded that radiation-induced γ -H2AX and 53BP1 nuclear foci are useful markers for quantifying DSBs after radioiodine therapy.

Conclusions

In a majority of patients, the fixed activity-based approach for the treatment of thyroid cancer may have its benefits due to its simplicity. In most cases, this therapy regime stays well below any toxicity limits. The main disadvantage in using this approach is the failure to consider the individuality of the patient. There is evidence for over- or more probably under-treatment of individual patients without realizing it. In addition, the efficacy of several treatments in one patient might be degraded.

In the case of lesion-based dosimetry, the pretherapeutic use of ^{124}I seems to be state of the art, although the matter of stunning has not been settled. In addition, careful calibration of the PET/CT scanners is mandatory. In the lesion-based approach, the pretherapeutic or therapeutic administration of ^{131}I does not take into account regional differences in the local iodine uptake.

Patient-specific blood-based dosimetry is comparatively easy to perform before and during therapy. In selected patient cases, this procedure will allow extending the activity beyond the limit of therapies using fixed activities and will reduce the risk of severe side effects.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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