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Hyperthyroidism Radioiodine Treatments with A Customized Dosimetric Approach

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ABSTRACT

The radioiodine therapy, which is considered the elective treatment of most hyperthyroidisms, requires the administration of high radioiodine activities. Although standardized activities are still widely adopted, a customized approach offers the significant advantage to characterize the functional behaviour of the volumes to be treated. In this way, both the clinical outcomes and the dose optimization are achieved.

In this work, the main features concerning the customization are discussed, with particular attention to the dosimetric and clinical parameters. A specific focus is devoted to the patient dose, trough the administered activity calculation method. The radiation protection critical issues are also commented, with regard to the patient, to the people in his direct contact (family members, nurses, doctors ...) and to the environment contamination.

The long experience in the field of radioiodine hyperthyroidism treatments of the S. Anna Hospital in Como (Italy) is presented. The dosimetric approach is full described, together with a

thorough review of the state of the art, and the clinical outcomes, expressed in term of remission of the disease, are presented. Upon completion, a recent method to estimate the patient residual contamination, based on external radiometric survey, is described.

Keywords: Customized radioiodine therapy, Benign thyroid disorders, Outpatient radiation exposure; Release of patient

INTRODUCTION

The development of the diagnostic nuclear medicine, together with the results of the new investigations of radioimmunoassay and radiochemistry, have expanded the interest for nuclear medicine therapy [1].

A metabolic radiotherapy is a highly specific and targeted therapy, which consists in the patient administration of a particular radiopharmaceutical, which causes the direct irradiation of the volume of interest, exploiting the selectivity property to reach the target in all its locations [1,2]. These treatments provide a significant dose saving of the healthy tissues, but an unavoidable whole body irradiation. This evidence, together with the administration of high activities, creates radiation protection critical issues with regard to the health of critical exposure group (e.g. family members, nurses, doctors, etc...), as well as the contamination of the environment [3-7]. However, the most critical aspect remains the clinical dosimetry [8]. For these reasons, a reliable analysis of all these items requires the choice of an optimized approach and a direct verification of its reliability by means of clinical and experimental evidences.

The radiometabolic therapy is a successful and widespread procedure for the benign thyroid disease care, such as hyperthyroidisms (i.e. uni-nodular or multi-nodular goiter and Basedow-Graves' diseases) [9-11].

The administration of a standard radioiodine activity, based mainly on the thyroid mass, has been used since years and still represents a common practice. However a more throughout method exploits patient-specific considerations, which allows to personalize the activity to be administered [8,12-18]. A pre-therapeutic study is therefore performed on the basis of the patient uptake curve and of the functional volume estimation.

The present work provides a wide description of the customized hyperthyroidism treatment by the administration of radioiodine ^{131}I. It explains the main features of this therapy, with particular attention to the clinical and physical contents, with a focus on the patient dose and the administered activity calculation. Together with a comprehensive review of the current literature, the long time experience in this field of the Sant'Anna Hospital of Como (Italy) is presented [19,20]. An extended follow-up analysis is provided, in which the dosimetric and clinical response data are showed. The results pointed out that a patient-tailored therapy should ensure a good clinical outcome, maintaining the exposure of healthy tissues as low as possible. At the same time, the administration of lower activities, if possible, concurs in reducing the radiation

protection impact and avoids unduly patient exposition and environmental contamination as well. An innovative method to estimate the residual internal activity in outpatient treated with a customized radioiodine activity is presented, together with experimental and clinical results [21,22].

MATERIALS AND METHODS

The Radioiodine Features

The choice of the proper radionuclides for an effective metabolic therapy, with the lowest toxicity, is mainly based on the following physical and biological features [1]:

- type of radiation emission;
- energy spectrum;
- physical half-life;
- chemical behavior (i.e. target binding).

Most therapy agents exploit β-particle emissions for their capability to penetrate tissues for a limited range, which allows them to dissipate about 95% of their energy into the target organ. Low energy beta particles have a path corresponding to a few cell diameters (sub-millimeter range). At intermediate energies, like ^{131}I emissions (E_{max} = 0.61 MeV [23]), the dose distribution within the tissue is less homogeneous, although the therapeutic effect is still good.

Besides, gamma emission is useful in imaging and biodistribution studies, not only for the radiopharmaceutical behavior monitoring, but also to identify the body locations and provide an estimation of their geometric dimensions.

The radionuclide physical half-life should be comparable with its permanence in the organism, to obtain the maximum therapeutic effect with the minimal cytotoxicity.

The chemical behavior of the radionuclide determines its physiological uptake and its capability to bind the target tissue or organ, improving the treatment selectivity and the resulting effectiveness.

The hyperthyroidism treatment is carried out by the ^{131}I intravenous or oral administration (systemic therapy). The radioiodine belongs to the class of beta-emitting radioisotopes, that have been widely used in clinical and still represents the most used therapy class. The advantage of such a radioisotope, in addition to its physiological uptake, lies in the energy of the emitted particles.

The ^{131}I has a 8.1 d [23] half-life and the beta emission energy in the therapeutic range is of 191.4 keV [23], corresponding to a 0.8 mm path in the soft tissue. These particles are accompanied by 364.5 keV [23] gamma radiations, useful for the biodistribution study and for the absorbed dose evaluation.

The Treatment of The Hyperthyroid Diseases

The thyroid is an endocrine gland located in the anterior region of the neck and is composed by two lobes connected by an isthmus. A normal thyroid gland presents a characteristic butterfly shape and its weight is 17 g and 20 g in a female and male adult respectively [I4]. Each lobe has an ellipsoidal shape with a pointed upper pole, the apex, and a lower pole that just overflows from the isthmus. The best known hyperthyroidism diseases, both clinic and subclinic (i.e. total inhibition of TSH value), are the toxic or pre-toxic nodular goiter (adenoma) and the diffuse toxic goiter [9,10]. The diffuse toxic goiter appears as a uniform increase and spread of the gland, with possible mediastinic extensions. The main treatment modalities are: drug, radionuclide therapy with radioiodine and surgery [9].

^{131}I radiation therapy has been widely used for the treatment of all the thyroid diseases listed above. The basic features of this treatment lie in the choice of the proper radionuclide: its short way through the body up to the target minimizes its uptake at any different location.

The radioiodine treatment is based on the selective introduction of a specific amount of radioiodine (^{131}I sodium-iodine) within the target organ. Like the stable iodine, the radioactive isotope is taken up primarily in the thyroid, allowing a selective concentration of the radionuclide in the gland. Once absorbed from the gastrointestinal tract, the iodine is carried by the blood flow and trapped by the thyroid, where it is organically bound. As a result of the radioactive decay, a large energy is released in the organ itself. A radioiodine fraction recirculated as a marked thyroid hormone and is metabolized by liver and muscles, while its excretion is mainly in the urine. The minor paths are represented by: saliva, sweat, feces and expiration.

The radioiodine therapy exploits the damage due to the energy deposition in the pathologic tissue by the radioiodine beta particles. The effect of such a deposition is an inflammation of the tissues, resulting in fibrosis and reduction of the capacity of synthesis of the gland. To receive an effective therapy, the thyroid tissue has to be exposed to an adequate amount of radiation. The quantitative determination of the specific therapeutic activity is the great challenge of this treatment modality. Generally, in thyrotoxicosis the administered activities can range from 150 MBq to about 400 MBq [10] and are highly dependent on the specific pathology to be treated. In the case of toxic nodular goiter, the goal is the ablation of the autonomous areas, to reach and maintain euthyroidism. For Basedow-Graves, the hyperthyroidism is permanently maintained and the lowest possible dose is given to healthy tissue.

A noteworthy remark pertain to the oral and the intravenous administration of radioiodine aspect, which requires special safety measures as this radiopharmaceutical, in liquid form, is extremely volatile.

The Clinical Dosimetry

The clinical dosimetry provides an estimate of the dose imparted to the patient by a radiopharmaceutical until the moment of its complete excretion from the body (the so called committed dose) [24].

The absorbed dose in a specific target depends on the time-space distribution of the radiopharmaceutical in the human body and on the physical characteristics of the radioisotope. If the radioisotope activity at the t time, in the distribution volume of mass m are known, the energy release to the mass m in the time dt and the corresponding absorbed dose D can be calculated as:

$$D[Gy] = \int_0^{\infty} \frac{k\tilde{A}\sum_i n_i E_i \varphi_i}{m} dt \qquad (1)$$

where k is a proportional constant, m the target mass, n_i the number of radiation with energy E_i and φ_i the energy fraction absorbed in the target. The cumulated activity is expressed by the following formulation:

$$\tilde{A} = \int A(t)dt \qquad (2)$$

From an operational point of view, however, a reliable evaluation of this quantity is rather difficult to perform. So the committed dose can be calculated using mathematical models, as the MIRD method (developed by the Medical Internal Radiation Dose of the American Society of Nuclear Medicine), which consider separately the target, the source organs and the different radiation interactions. The MIRD method gives standard factors to compute the committed dose. All these factors are estimated by applying the Monte Carlo method to a mathematical phantom whose internal organs represent the human standard ones.

The Hyperthyroidism Customized Treatments

The actual guidelines for the customized radioiodine therapy are set by the SIE-AIMN-AIFM (Società Italiana di Endocrinologia - Associazione Italiana di Medicina Nucleare - Associazione Italiana di Fisica in Medicina) [14,24,26]. According to these guidelines the administered activity can be estimated by applying the following equations:

$$A = 5{,}829 \cdot \frac{D \cdot m}{U_{max} \cdot T_{1/2eff}}$$ Multinodular and uninodular pre-toxic and toxic goiter (3)

$$A = \frac{m \cdot D}{U_{max} \cdot T_{1/2eff}} \cdot (5{,}656 - 5{,}08 \cdot \frac{m \cdot D}{U_{max}})$$ Basedow-Graves' disease (4)

These formulas take into account the functional mass m, the therapeutic dose D and the two kinetic parameters, the effective half-life $T_{½eff}$ and the maximum uptake U_{max}. Both equations are derived from the MIRD formula-based dosimetric method.

The SIE-AIMN-AIFM guidelines suggest a first level of customization suggesting the following kinetic values: $T_{½eff}$ = 132 hours, $U_{max} = U_{24}$ (24^{th} hour uptake).

A full customization requires the pre-treatment study of the thyroid uptake through the administration of a radioiodine track activity (about 2 MBq).

Exploiting the iodine gamma emission, the uptake can be measured by means of a collimated scintillation detector at 2, 24, 96 hours from the administration time, with an adjunctive point at 6 hours for Graves' disease cases.

According to the two compartments model, the ^{131}I kinetic in benign thyroid disease is well described by a bi-exponential function. Mathematical tools have been developed for this specific purpose (commercially produced or home made). They are based on common spreadsheets or computing environments and integrate the entire complex algorithms for calculating the activity to be administered. In general, these programs allow to choose between one and multinodular goiter and diffuse toxic goiter, to draw the fitting curve and to calculate its related parameters. At the Sant'Anna Hospital, the experimental data were analyzed by a home made software (PROFit) [27], which estimates the effective half-life and the maximum uptake. As regard to the thyroid mass, a careful distinction must be drawn between [28]:

- the anatomical volume, which refers to the organ morphology;
- the functional volume, which represents the metabolically active volume in which the radioiodine concentrates.

Since the two volumes not necessarily coincide, the radiotherapy interest regards only the functional one. There are different techniques for determining the thyroid mass and the most frequently used are the ultrasonography and the scintigraphy.

Ultrasonography is a method of significant importance in the morphological study of the thyroid, due to its large diffusion, economy and simplicity of use. The morphological and echostructural study of the gland allows to detect the sizes of the lobes, of the isthmus and of the nodules. The volume of interest is determined by assigning an ellipsoidal geometry to the organ and is calculated by the following formula:

$$V = \frac{\pi}{6} abc \qquad (5)$$

where a, b and c are the axes of the ellipse. These measures are necessarily operator-dependent and inter-observer 10% changes on thyroid volumes are reported in the literature.

CT images allows to document the morphological extension of a possible mediastinal goiter and to detect the presence of lymphonodal metastases.

Magnetic resonance imaging is considered the reference technique for the measurement of the whole thyroid volume. Due to its high contrast resolution and multiplanar capabilities, an accurate assessment of the neck and mediastinum regions is achieved. Despite the required short time, motion artefacts may be present, due to both respiration and swallowing, and therefore a careful preparation and a good cooperation of the patient are required.

TC and RM unfavourable cost/benefit ratio is the main limiting factor for these imaging methods. Furthermore, they do not provide functional information.

A more suitable imaging approach is provided by SPECT scanner, which allows the estimation of the functional volume with several radiotracer, such as ^{99m}Tc, ^{123}I and ^{131}I. The most employed radionuclide is the ^{99m}Tc-pertechnetate, because of its favorable dosimetry (6 hours physical half-life), high quality images and a low absorbed dose. It gives only information about trapping (excluding the organically bound iodine) but correctly describes the uptake in hyperthyroidism. To a best assessment of the functional thyroid areas the ^{123}I is employed, because it better follows the biological behavior of iodine food. The scintigraphy image quality is good and the dosimetry is favorable, but a low commercial availability and a high cost limit its use. The ^{131}I presents a non-negligible dosimetric impact.

All planar scintigraphy images are normally analyzed using the technique of the iso-count lines. The structure of interest is highlighted with respect to the surrounding background, so that the resulting surface comprises all pixels whose intensity is higher than the selected percentage value (threshold value). This threshold must be optimized for each gamma camera and experimental set up. Once the ellipse that best approximates the structure to be measured (lobe or nodule) is chosen, the volume is then calculated by:

$$V = \frac{\pi}{6} ab^2 \qquad (6)$$

where a and b are the major and the minor axes of the ellipse. Since the picture does not display the anterior-posterior dimension of the ellipsoid, this one is assumed to be equal to the other minor axis.

3D SPECT imaging for thyroid representation ensures the greatest accuracy in the volume analysis and separates adjacent structures. Indeed, transaxial, coronal and sagittal slices can be easily reconstructed. As for the planar scintigraphy, the optimal iso-count surface enables the measure of the real target sizes.

For completeness, PET imaging offers an excellent spatial resolution, however, because of the high cost of the tracer (^{124}I-sodium iodide), this technique is not used for the thyroid imaging of benign diseases.

In this study the functional volume estimation was performed by processing tomographic ^{99m}Tc-pertecnetate SPECT or SPECT/CT images acquired by the SIEMENS SYMBIA T integrated diagnostic system and by applying Equation (5).

An additional functional volume evaluation was carried out by means of digital processing tools. The one used at the Sant'Anna Hospital is a home-made software coded using the multi-paradigm numerical computing environment MATLAB and is based on the Recovering Iterative Thresholding Method (RIThM) [29] which requires experimental threshold-volume calibration. An example of the final volume reconstruction can be seen in Figure 1.

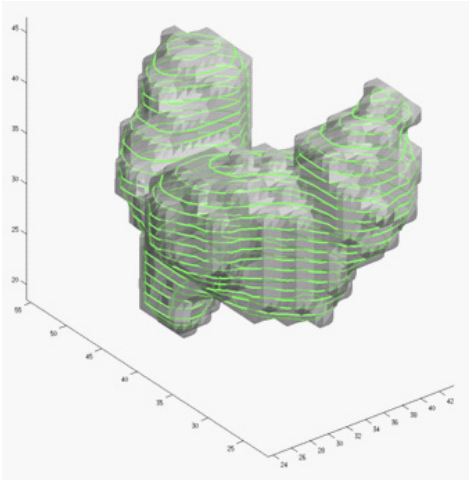

Figure 1: An example of a thyroid volume reconstruction by RIThM.

Afterwards, the statistical analysis of the data collected during the patient follow-up at the Sant'Anna Hospital in Como (Italy) is proposed [19,20]. These data regard almost all patients subjected to the hyperthyroidism treatment (only some cases have been omitted because incomplete information was available).

The treatment effectiveness was verified by periodical hormone checks and clinical response evaluations after ATD (Antithyroid Drug Therapy) administration, for all patient affected by pre-toxic or toxic single nodule and multinodular goiter. These clinical data are suitable to prove the total or partial hyperthyroidism remission.

The Radiation Protection

The ^{131}I activities for the hyperthyroidism treatments are very high, with significant residual amounts in the days immediately following their administration. As suggested by the actual guidelines [30] a single external measurement can offer both a reliable evaluation of the risk level and an approximate information about the residual activity.

A mathematical algorithm was recently proposed [21,22] to correlate patient activities and external measurements which is based on the relationship between activity, ambient dose equivalent H*(10) rate [31], iodine gamma constant Γ and source-detector distance d. To account both the 3D body distribution of iodine and the photon attenuation by the tissues, an effective distance (d_{eff}) was introduced as an additional contribution d_x to the source-detector distance.

In this way, both the mean depth of the ^{131}I 3D distribution and the photon-tissue interactions can be properly evaluated . For this reason, two measurements are required, at d_1 and d_2 known distances. Applying the inverse square law to H*(10) rates and :

$$C = \sqrt{\frac{\dot{H}^*_2(10)}{\dot{H}^*_1(10)}} \qquad (7)$$

the mathematical relation between these variables becomes:

$$d_1 + d_x = C\,(d_2 + d_x) \qquad (8)$$

Therefore, the patient activity can be calculated as:

$$A = F^2 \frac{\dot{H}^*(10) d^2}{\Gamma} \qquad (9)$$

where the factor F is defined as:

$$F = (d + d_x) / d \qquad (10)$$

As regards to radioactive contamination, solid and liquid wastes need a detailed management system. For the solid wastes produced during the treatment procedure (vials, syringes, cotton, …), a storage period commensurate with the iodine half-life and with its concentration is prescribed to assure a proper decay. Usually, a 1-2 months decay is required to lower the contamination to an adequate amount. Besides, a fist level direct control is recommended on each waste container coming from the Nuclear Medicine, together with a second monitoring level extended to any solid hospital waste, to prevent any radioactive escape. Liquid wastes consist in the patient excreta. Their high concentration needs a special processing based on multiple storage tanks, whose total volume has to assure almost 1 month delay before the outside disposal. Each disposal must be submitted to an approval which, in turn, is subordinated to a preliminary activity measurement. Some attention must also be devoted to the radioactivity fraction excreted after patient discharge, even if it is generally out of control. For this reason, a preliminary study must be carried out through specific environmental models.

RESULTS

The Main Treatment Outcomes

The number, gender and mean age of the statistical population are: 41 women (61.7 years old) and 14 men (58.1 years old) concerning the uninodular goiter, 21 women (68.0 years old) and 1 men (69.0 years old) are related to the multinodular goiter and 55 women (54.0 years old) and 19 men (67.1 years old) refer to the Basedow-Graves' disease.

The uptake experimental points and the corresponding mathematical fitting curves made it possible to calculate the functional parameters characterizing the active thyroid volumes. A high variability was found for these parameters: thyroid masses (5÷108g), U_{max} values (9.2÷82.2%) and $T_{1/2\text{-}eff}$ (37.9÷191.2h).

For Greaves' patients with no disease remission, the initial average active mass was 50.2÷25.4 g after a single treatment. In these cases, the target mass decreased to 33.2÷13.4 g, whereas U_{max} and the $T_{1/2\text{-eff}}$ values just showed small changes between the first and the second treatment. As a consequence of this mass reduction, regularly occurring in the second treatment, similar or higher dose prescriptions required iodine activities lower than the first ones.

In Table 1 the mean values and the standard deviations of U_{max}, $T_{1/2\text{-eff}}$, together with the ones regarding the thyroid functional mass TFM, are presented, as a function of the three different pathologies.

Table 1: U_{max}, $T_{1/2\text{-eff}}$ and TFM values (mean and standard deviation) for the different thyroid pathologies.

	U_{max} (%)		$T_{1/2\text{-eff}}$ (h)		TFM (g)	
	mean	σ	mean	σ	mean	σ
uninodular goiter	32.0	9.8	144.8	74.9	17.2	12.0
multinodular goiter	34.0	11.5	145.3	32.6	18.4	9.0
Basedow-Graves' disease	49.1	16.0	143.8	27.4	34.5	16.4

The statistical analysis evidences a significant difference between the uninodular and multinodular goiter assembled data and the Basedow-Graves' disease ones ($P < 0.001$) for both U_{max} and TFM, while no significant difference occurs as regard to the $T_{1/2\text{-eff}}$ values ($P < 0.345$).

A further analysis was focused to evaluate the outcome of the radioiodine therapy in the different thyroid gland diseases versus the administered activities. The main findings concern the administered activity wide range: 411±147 MBq for the uninodular goiter, 419±145 MBq for the multinodular goiter and 461±156 MBq for the Basedow-Graves' disease. No statistically significant difference was evidenced.

In patients affected by Greaves' disease, a 85.1% remission percentage (75.4% in hypothyroidism and 24.6% in euthyroidism) was observed for single treatments. The remission time was 4.0 months, with a 3.3 interquartile range (IQR). All patient undergoing a second treatment achieved the complete disease remission (3.0 months remission time and IQR = 0.5), due to its evolution into hypothyroidism and to an average 65.2% active mass reduction.

The most clinical evidence of the therapeutic efficacy was found in patients affected by uninodular and multinodular goiter: a 100% remission was achieved by a single treatment (85.4% to hypothyroidism and 14.6% to euthyroidism). The remission time was 3.0 months (IQR = 1.8) for the uninodular goiter and 5.5 months (IQR = 2.3) for the multinodular one. A 4 months median recovery time for both pathologies (IQR = 3÷6) was adopted.

Some Radiation Protection Remarks

The algorithm to calculate the patient residual activity was validated by a clinical trial including 50 patients. By relating the actually administered activities to the computed ones, a good accordance between these values was demonstrated (0.5% mean error and 5.4 standard deviation).

Moreover, comparing these results with the estimates provided by a single external measurement, the average deviation from the expected values increases to 11%. Additional external double measurements were also performed both at the discharge time and four days after: the 11.3% and 43.0% excreted mean activities were respectively obtained.

With regard to the radioactive wastes, the planned storage time for solid ones, together with an appropriate monitoring program, proved a considerable reduction of the risk of releasing significant radioiodine activities in the environment. An analogous opinion can be applied to the liquid wastes, whose specific activity results plentifully under the 1 Bq/g threshold value, as expected from the environmental impact analysis.

CONCLUSION AND DISCUSSION

The hyperthyroidism treatment by radioiodine administration has become a widely used therapy. The administration of standard activities for the hyperthyroidism radioiodine treatment is still a common practice. Otherwise, customized treatments, based on in vivo preliminary studies, represent a valid alternative to the former approach and allow the optimization of the administrated activity. The effectiveness of this customized practice can be evidenced by the analysis of its clinical outcomes (high disease remission percentage and thyroid mass reduction).

To achieve this aim, during the pre-treatment phase (treatment planning) the following parameters was evaluated: the radioiodine uptake maximum value, the radiopharmaceutical effective half-life and the functional thyroid volume. As a consequence of the progressive availability of tomographic techniques (CT, SPECT, PET and RMI) the accuracy in determining the target volumes is much better than the one offered by planar images. The percentage change between the volumes calculated by the two different methods is of the order of 58%. Furthermore, the possibility of administering personalized treatments has increased the effectiveness of the therapy and avoided patient unwanted exposures.

The excellent outcome of the treatment customization becomes more and more significant if the concomitant reduction of the administered activity is considered, when compared to the one provided by standardized procedures.

These activities can be estimated at about 435 ± 150MBq / patient, while the standardized values are normally between 300 and 600MBq, depending only on the thyroid volume. Given the consolidated tendency to use activities close to 500-600 MBq, approximately 20 - 25% higher than the formers, the dose saving due to the customized approach becomes evident. This outcome is more than enough to justify the efforts required to implement the customization of the radioiodine treatments. In fact, if the related effective doses are aanalyzed, the saving of one radioiodine MBq corresponds to about a 11 - 24mSv reduction in the patient exposure, as a function of the maximum iodine uptake (25 - 55%). These outcomes are derived from a model that describes the behavior of administered iodide only and does not include both the effects of organically bound iodine and of the ones produced by its catabolism. For this reason, the above values should be slightly increased.

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