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The Customization of Hyperthyroidism Radioiodine Treatments: Clinical Outcomes

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Abstract

The administration of standard activities for the hyperthyroidism radioiodine treatment is still a common clinical practice. Otherwise, customized treatments, based on *in vivo* uptake preliminary studies, represent a promising alternative to the former approach, allowing the optimization of the administrated activity. The aim of this study is the evaluation of the effectiveness of this practice by the analysis of its clinical outcomes (i.e. disease remission and thyroid mass reduction).

As required by the customized procedure, during the pre-treatment phase (treatment planning) the following parameters were evaluated: the radioiodine uptake maximum value, the radiopharmaceutical effective half-life and the functional thyroid volume. A retrospective analysis was carried out by exploiting these data and the clinical information collected during the patient follow-up at the Sant'Anna Hospital in Como, Italy. At last, they were correlated to the customized radioiodine activities.

The statistical analysis of the connection between these activities and the clinical outcomes has supported the evidence of the capability of this approach to provide good therapeutic results and, at the same time, to assure a higher level of patient healthcare.

Keywords: Hyperthyroidism; Radioiodine therapy; Treatment customization; Thyroid response

Introduction

Radioiodine therapy (^{131}I sodium-iodide) is currently the treatment of choice in most hyperthyroidism cases [1-3]. The prescribed dose is generally referred to a standard man and involves the administration of standard activities (300 and 600 MBq according to the thyroid mass). In this case, the specific anatomical and pathological conditions of the patient are not taken into account. The critical issue is that the therapeutic activities may be adequate to obtain the disease remission, but do not provide a convenient protection level concerning the risks due to the patient exposure to ^{131}I ionizing radiations [4-8]. Otherwise, customized treatments, based on *in vivo* functional tests, represent a valid alternative, which enables the optimization of the patient dose and, at the same time, assures a good clinical outcome [9,10] For each patient, the activity optimization requires the identification of the critical parameters that characterize the radioiodine uptake (namely, the percentage maximum value and the radio-tracer effective half-life) and the evaluation of the target volume within the thyroid [11-17].

In this work, the results of such a customized therapeutic approach were studied by analyzing the clinical response, in terms of disease remission and thyroid mass decrease. This analysis concerns the patients affected by hyperthyroidism that were treated at the Sant'Anna Hospital in Como, Italy.

To this purpose, a retrospective analysis was carried out by exploiting the clinical information collected during the follow-up and correlating these data to the administered radioiodine activities.

Materials and Methods

A retrospective analysis was carried out collecting the pre-treatment and follow up data relating to outpatients suffering from hyperthyroidism that underwent radioiodine therapy at the Sant'Anna Hospital in Como, Italy. The data sample covered the entire period between 2006 and 2013, accounting for 151 patients, and its preliminary outcomes were presented in a previous work [18].

The thyroid specific pathologies under study were the following: Graves' disease (50.9%), multinodular (16.6%) and uninodular (32.5%) pre-toxic and toxic goiter.

According to the SIE-AIMN-AIFM (Società Italiana di Endocrinologia - Associazione Italiana di Medicina Nucleare - Associazione Italiana di Fisica in Medicina) guidelines [12-14], the customized activity was computed by applying the following equations, related to the pathologies under examination:

$$A = \frac{m_0 \cdot D}{U_{max} \cdot T_{1/2eff}} \cdot (5{,}656 - 5{,}08 \cdot \frac{m \cdot D}{U_{max}})$$

(Basedow-Graves' disease)

$$A = 5{,}829 \cdot \frac{D \cdot m}{U_{max} \cdot T_{1/2eff}}$$

(multinodular and uninodular pre-toxic and toxic goiter)

where U_{max} is the uptake percentage maximum value, and $T_{1/2\text{-}eff}$ is the radiopharmaceutical effective half-life, m is the nodular/gland mass and D the therapeutic dose.

To obtain the kinetic parameters U_{max} and $T_{1/2\text{-}eff}$, a ^{131}I sodium-iodide track activity (about 2 MBq) was administered in the pre-treatment phase. The uptake curve was measured with a collimated probe at 2, 24, 96 hours from the administration time, with an adjunctive point at 6 hours for Graves' disease cases. The data were fitted by a bi-exponential mathematical function by means of a home-made automatic software (Profit) [13,19]. An example of an experimental uptake curve is shown in Figure1.

The functional thyroid volume *m* was evaluated by both tomographic SPECT (using ^{99m}Tc-pertecnetate) and CT images reconstructed by a SIEMENS SYMBIA T integrated diagnostic system. Both images were combined by means of a proprietary 3-D fusion software, working independently from the acquisition modalities. The volume estimation was also performed by means of a home-made software developed by the multi-paradigm numerical computing environment MATLAB, based on the Recovering Iterative Thresholding Method (RIThM) [20].

After an initial rough estimate of the volume of interest, this algorithm calculates the following parameters: the source-to-background ratio (SBR) and the threshold value corresponding to the amended SBR value. By the volume estimate using threshold-volume data, a new volume calculated by the image thresholding was obtained. The process goes on until convergence; an example of the final volume reconstruction can be seen in Figure 2.

The therapeutic dose *D* to be imparted to the functional mass is a decision pertaining to the nuclear medicine physician, on the basis of clinical protocols.

The subsequent procedure phase was based on the intravenous administration of the customized ^{131}I sodium-iodide activity, its quickly absorption into the bloodstream and its gradual uptake by the thyroid gland.

To asses the clinical outcome of this therapeutic approach, a follow-up study was performed by collecting all the clinical information in a dedicated data base. To analyze the clinical outcomes, the following parameters were taken into account:

- the different pathologies;
- the hyperthyroidism remission (into hypothyroidism or euthyroidism);
- the functional thyroid mass reduction.

The treatment effectiveness was verified by periodical hormone (TSH, FT3, FT4) 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.

The statistical analysis was performed by the SPSS.20 Statistics software (SPSS inc. Chicago, IL, USA) and their results were expressed in terms of mean, median, interquartile range (IQR), 25th and 75th percentiles and outlier values.

Results

The collected data regard almost all patients subjected to the hyperthyroidism treatment (only some cases have been omitted because incomplete information was available). The number, gender a mean age of this statistical sample (151 cases) is shown in Table 1.

In Table 2, U_{max} and effective half-life $T_{1/2\text{-}eff}$ mean values and standard deviations are summarized, according to the different thyroid pathologies under examination.

Table 3 provides the statistical distribution of the *thyroid functional masses* (TFM).

The mean prescribed dose was 224.7 ± 60.3 Gy for Basedow-Graves' disease pathology and 212.9 ± 60.1 Gy for uninodular and multinodular goiter one. The resulting administered activity is resumed in Table 4.

The detailed analysis of clinical cases was focused to evaluate the outcome of radioiodine therapy in the different thyroid gland diseases versus the administered activities. This analysis underlined two main important items: the wide range of administered activities (Table 4) and the small number of re-treatments.

In patients affected by Greaves' disease, an 85.1% remission percentage (75.4% in hypothyroidism and 24.6% in euthyroidism) was observed

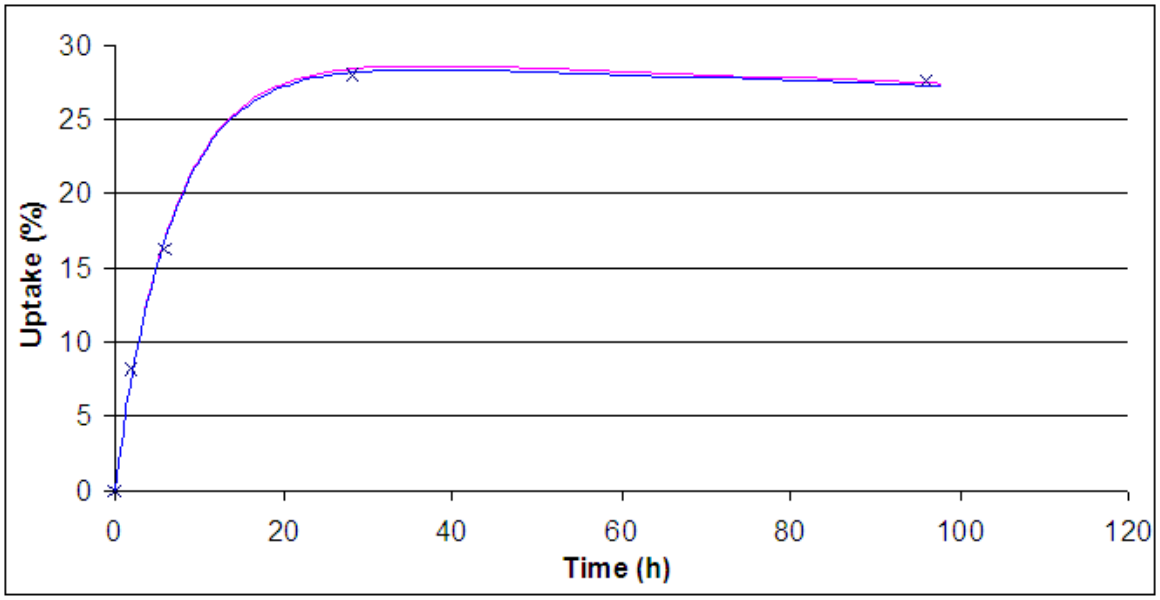

Figure 1: Example of a radioiodine uptake curve, consisting of the uptake experimental points, detected at 2, 6, 24 and 96 hours after iodine administration through a collimated probe, and the interpolating bi-exponential mathematical function.

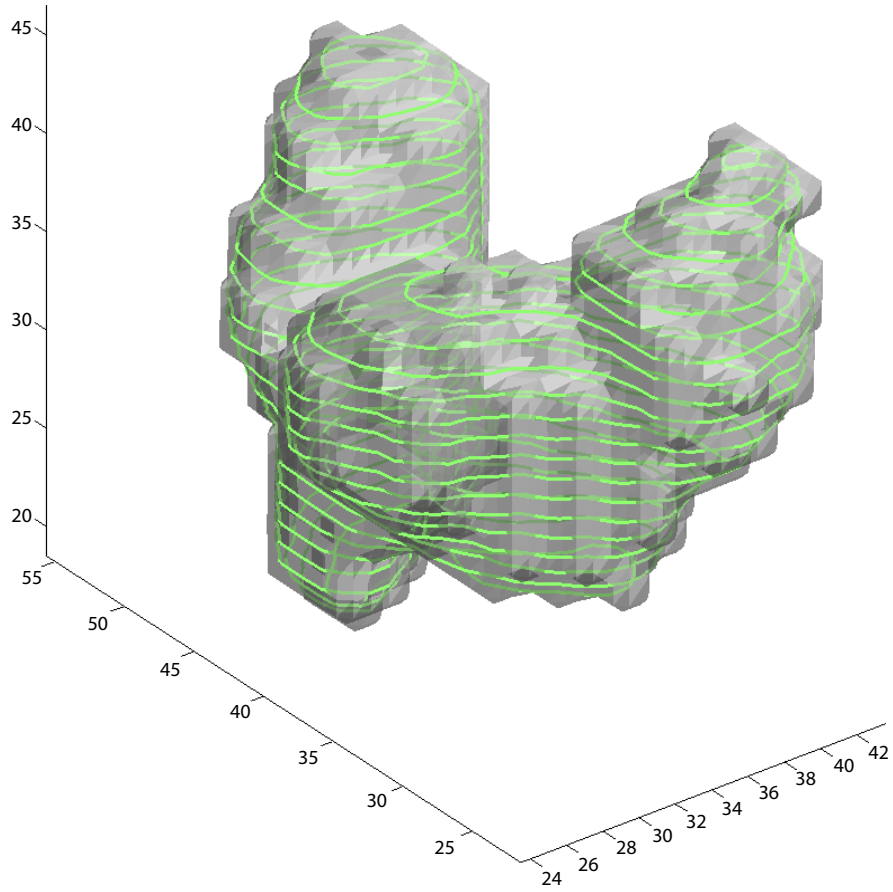

Figure 2: Example of a thyroid volume reconstruction performed by the home-made software.

	Gender (mean age)		
	women	men	Total
uninodular goiter	41 *(61.7)*	14 *(58.1)*	55 *(63.1)*
multinodular goiter	21 *(68.0)*	1 *(69.0)*	22 *(68.0)*
Basedow-Graves' disease	55 *(54.0)*	19 *(67.1)*	74 *(55.1)*

Table 1: Statistical distribution of the data base of this study

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

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

	TFM_{mean} (g)	σ (g)
uninodular goiter	17.2	12.0
multinodular goiter	18.4	9.0
Basedow-Graves' disease	34.5	16.4

Table 3: Thyroid functional masses for the different pathologies, estimated before the treatment.

	A_{mean} (MBq)	σ (MBq)
uninodular goiter	411	147
multinodular goiter	419	145
Basedow-Graves' disease	461	156

Table 4: Administered activities for the different thyroid pathologies.

for single treatments. The remission time was 4.0 months (IQR 3.3). No remission was obtained for the remaining patients. All patients undergoing a second treatment achieved the total remission (3.0 months remission time and IQR=0.5), due to an evolution into hypothyroidism and to an average 65.2% mass reduction.

In patients affected by uninodular and multinodular goiter, a 100% remission was achieved by single treatments (85.4% to hypothyroidism and 14.6% to euthyroidism). The remission time was 3.0 months (IQR = 1.8) for uninodular goiter and 5.5 months (IQR=2.3) for multinodular one.

A 4 months median recovery time (IQR=3 ÷ 6) for both nodular and Graves' pathologies was found.

High variability was found for: thyroid masses (5 ÷ 108 g), U_{max} values (9.2 ÷ 82.2 %) and $T_{1/2\text{-}eff}$ (37.9 ÷ 191.2 h).

For Greaves' patients with no disease remission, the initial average thyroid 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 $T_{1/2\text{-}eff}$ values

were still comparable both in the first and in the second treatment. As a consequence of this mass reduction in the second treatment, similar or higher dose prescriptions required lower activities than the first ones [9].

Discussion and Conclusions

In the present study on hyperthyroidism radioiodine treatments, a comparative analysis between the customized activities and the therapeutic outcomes (hypothyroidism and euthyroidism) was performed. Starting from these results, some clinical considerations can be drawn.

Firstly, the customized radioiodine therapy seems to be a very effective tool for the hyperthyroidism treatment, owing to the low re-treatment frequency in Graves' disease and the total remission in nodular goiter cases.

Secondly, the thyroid mass evaluation seems to be the most critical variable of the whole optimization process, since great thyroid volumes are suitable to increase the probability of a second treatment. This evidence proves that an important effort must to be done in this specific direction.

On the whole, the activity customization by AIMN-AIFM dosimetric protocol allows a real dose optimization with respect to the standardized activity approach. This consideration becomes even more obvious, if the large inter-subject variability is regarded. The statistical analysis of the connection between the administered activities and the resulting clinical outcomes has supported the evidence of the customized approach capability to provide excellent therapeutic results and, at the same time, to optimize the patient dose.

This work has demonstrated that is strongly preferable to adopt a customized radioiodine approach than the standard one for a more effective patient care, ensuring, at the same time, a higher degree of radiation protection.

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