Effects of absorbed dose of ^{131}I isotope on the effectiveness of ablation of thyroid remnant tissue

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Abstract

Introduction: The aim of the study was the assesment of effective ablative dose of absorbed ^{131}I radiation, based on dosimetric measurements.
Material and methods: The study group comprised one hundred (100) patients in whom papillary thyroid carcinoma (PTC, 54 cases) and follicular thyroid carcinoma (FTC, 46 cases) had been diagnosed. The activities of ^{131}I, administered to those patients, ranged from 1643 MBq (44.4 mCi) to 4033 MBq (109 mCi). The following parameters were determined in the patients before radioiodine therapy: the mass of thyroid remnants [M (g)], iodine uptake [U %], and the effective half-life of radioiodine [EHL (days)]. After obtaining the results of measurements, the dose [D (Gy)] absorbed by thyroid remnants was retrospectively calculated by means of our own modification of the Marinelli formula. Additionally the effect of the analyzed parameters on ablation effectiveness was assessed.
Results: In 80 patients (80%) the performed ablation was evaluated as effective. The most effective (91%) was the ablation in the group of patients who received an absorbed dose of 2400 Gy or higher. A correlation was found between the absorbed dose and the effectiveness of ablation (rs=0.23; $p<0.05$). The effectiveness of ablation was also related to the mass of thyroid remnants, being higher in patients with the mass ≤1.5 g (91%) than in those with the mass >1.5 g (68%) ($p<0.03$).
Conclusions: A correlation has been demonstrated between ablation effectiveness and the ^{131}I dose absorbed by thyroid remnants. The highest effectiveness of ablation was obtained after the administration of D ≥2400 Gy.

Key words: differentiated thyroid carcinoma; radioiodine-131, dosimetry, ablation.

Introduction

Surgical treatment is the first procedure in the therapeutic algorithm of differentiated thyroid cancer [1-3]. The published reports of observations performed on large groups of patients reveal the highest efficacy of surgery consisting in total thyroidectomy [4, 5]. Radioactive iodine treatment is used as therapy, complementary to surgery, for the ablation of thyroid remnants [6].

In order to obtain the highest effectiveness of radioiodine in the ablation of thyroid remnants, the following main two ways of application of ^{131}I are used:

- The use of constant activity of ^{131}I in the range between 925 MBq (25 mCi) and 5550 MBq (150 mCi) ^{131}I in all patients [7-9].

- Individual calculations of radioiodine activities, based on factors influencing the absorbed dose of radiation, i.e. iodine uptake, the effective half-life of ^{131}I isotope in the organism and the mass of thyroid remnants [7, 8, 10, 11].

The present study aimed at indicating the usefulness of measurements employed for the assessment of the absorbed dose in calculation of the optimal activity of radioiodine ^{131}I in order to obtain the most effective ablation of thyroid remnants in patients with differentiated thyroid cancer after surgery.

Material and methods

The analysis included one hundred (100) patients [89 women and 11 men, their age ranging between 9 and 79 years, mean age 45 years (44.85±13.9 yrs)]. Papillary thyroid carcinoma (PTC) was found in 54 cases (54%) and follicular thyroid carcinoma (FTC) in 46 cases (46%). None of the analyzed patients, evaluated in clinical examination as well as in Xray of the chest and ultrasonographic examination (US) of the neck, revealed any symptoms of metastasizing neoplastic disease. Thus, the patients were qualified for treatment with an ablative activity of radioiodine and not with therapeutic activity.

Four weeks after thyroidectomy all patients were qualified for thyroid remnant ablation. During that period of time they remained off thyroxine in order to obtain stimulation by endogenous TSH. For those patients in whom complete TSH stimulation was not obtained, the period between thyroid surgery and radioiodine treatment was prolonged up to 6 weeks. In all the patients prepared for ablation, diagnostic activity of 5.55-7.4 MBq (150-200 µCi) of ^{131}I was administered orally after a 2h fast and patients were asked to refrain from eating for the next 2 hours. Twenty-four (24) hours after administration of ^{131}I, thyroid uptake of iodine [U (%)] was determined by means of uptake probe under typical conditions. Neck scintigraphy (rectilinear scanner) and neck sonography (7.5 MHz probe, EsaoteBiomedica AU3 Partner) were carried out on the same day. Thyroid iodine uptake measurements were repeated for 3 to 7 days and effective half-life of radioiodine [EHL (days)] was calculated. The thyroid volume [V (cm^3)] was calculated by the following formula: 0.5 × a × b × c, where a, b, c = maximal dimensions of thyroid remnant, as determined by US. The density of thyroid tissue is known to be approx. 1.0 g/cm^3 [12]; thus the thyroid mass [M (g)] was calculated from volumetric data.

Ablative activity of radioiodine ^{131}I was administered under similar conditions as for test dose (2 h fast, refraining from eating for next 2 hours). The activities of administered ^{131}I ranged from 1643 MBq (44.4 mCi) to 4033 MBq (109.0 mCi).

The outcome of ablation was evaluated 6 months after radioiodine administration. In patients who were 4 weeks off L-T$_4$ treatment, neck and whole body scan (WBS) examinations were done 72 h after oral administration of 74-111 MBq of ^{131}I (2-3 mCi) by means of rectilinear scanner and gamma-camera (X-Ring, Mediso), respectively. The lack of iodine-uptaking foci in the neck was considered as effective ablation. In turn, the finding of iodine-uptaking areas within the neck was evaluated as unsuccessful ablation.

The following parameters were compared: the mass of thyroid remnants, ^{131}I uptake above the neck and the EHL in the group of patients in whom ablation had been regarded as successful, with the results in the patients in whom ablation had turned out to be ineffective.

Having applied dosimetric measurements, performed in the course of preparation of the patients for ablation, the dose absorbed by thyroid remnants [D (Gy)] was retrospectively calculated. A subsequent evaluation of the results was done by means of the modified formula by Marinelli et al. [13]:

$$D = \frac{U \times A \times EHL}{M \times 25},$$

where: U = iodine uptake (%) – determination of the activity above the neck 24 h after ^{131}I administration; A = the activity of administered radioiodine ^{131}I (MBq); EHL = effective halflife of radio-iodine; M = thyroid mass (g).

Statistical analysis

The studied parameters revealed a distribution which significantly differs from normal (Kolomogorov-Smirnov test, Lilliefors test, Shapiro-Wilk test). That was the reason for using only non-parametric tests in the statistical evaluation: Mann-Whitney's test for a comparison of statistical distributions in the two studied groups and the Kruskall-Wallis test for a comparison of several groups. The analysis of correlation was performed by means of the non-parametric Spearman's test. The χ^2 test (Fisher's test) was used for an evaluation of qualitative (categorised) variables. The level of significance $p<0.05$ was regarded as statistically significant.

Results

TSH concentrations in serum, determined before ablation, were within the range from 0.48 µUl/ml to 86.8 µUl/ml; the mean concentration was 39.18±16.63 µUL/ml (x±SD). It is noteworthy that TSH levels below 25 µUl/ml were found in fourteen (14) patients. In eight (8) of them, we succeeded to obtain only an incomplete stimulation with endogenous TSH, within the range from 5 to 25 µUl/ml, and six (6) patients had TSH concentration within the normal values, despite 6 weeks' withdrawal of L-T$_4$

thyroxine administration. Those patients were, however, qualified for ablation because of contraindications to radical surgery or due to the lack of their consent to further surgical treatment. The above-mentioned patients were not excluded from the studied group, since the study itself did not aim at the evaluation of TSH influence on the effects of the therapy but at the precise role of assessment of the parameters determining the value of the absorbed dose, in the process of ablative treatment of thyroid remnants.

The thyroid volume, calculated on the basis of US examination, juxtaposed with neck scintigraphy, ranged from 0.2 to 11.0 g, with the mean value of 2.22±2.12 g (x±SD).

The iodine uptake of thyroid remnants above the neck (confirmation of ^{131}I uptake ability of tissue in question) was from 1.1% to 41.0%, with the mean value of 11.45±8.36% (x±SD).

The effective half-life of ^{131}I ranged from 1.2 to 8.0 days (4.0±1.74 days (x±SD). In none of the patients did post-ablative scintigraphy reveal any foci of radioiodine uptake in extrathyroid locations.

The outcome of ablation treatment

The lack of foci of iodine uptake above the neck was confirmed in 80 patients (80%) by means of scintigraphy and of the WBS examination performed in a 6-month period, within post-therapeutic follow-up; the ablation was considered ineffective in 20 patients (20%).

Analysing the effects of such parameters as thyroid mass, iodine uptake and EHL, it was found that in the group in which the ablation was ineffective, the mass of thyroid remnants was significantly higher vs. the group of patients in whom the ablation was effective (p<0.05). A significant difference was found in the values of the absorbed dose in those groups. In Group II (effective therapy), the absorbed dose of radiation was markedly higher in comparison with Group I (ineffective therapy) (p<0.05). No such correlation was observed when comparing the radioiodine activities applied to the patients (Table I).

A correlation was found between the mean value of the dose absorbed by thyroid remnants, and the effectiveness of ablation (rs=0.23, p<0.05) (Table II).

It was found that in the group of patients who received a dose of 2400 Gy or higher dose absorbed by thyroid remnants, the effectiveness of ablation was 90.7% (n=43, effective ablation in 39 patients) (Table III). A gradual rise of absorbed dose did not cause any distinctive increase in the frequency of effective therapies. The highest effectiveness was obtained in the group of patients who received absorbed dose higher than 4000 Gy (n=26, effective ablation in 24 patients). It was not, however, a statistically significant difference.

A comparison of the number of ineffective ablations in the groups of patients who received an absorbed dose above 2400 Gy (n=43, ineffective ablation, 4 patients) with those who received doses below that value (n=57, ineffective ablation, 16 patients) indicated a statistically significant difference (Fisher's test, p<0.05).

No correlation was found between ablation effectiveness and the applied activity of radioiodine (χ^2 test, p=0.9). It refers to the activities within the range between 1643 MBq (44.4 mCi) and 4033 MBq (109 mCi).

A correlation was demonstrated between the mass of remaining thyroid tissue and the effectiveness of ablation (p<0.01) (Table IV).

It was found that in the patients with thyroid mass – remaining after thyroidectomy – equal to or lower than 1.5 g, the effectiveness of ablation was 91%, while in the group of patients with remnants of mass bigger than >1.5 g, the effectiveness did not exceed 68% only (p<0.03) (Table V).

A negative correlation was found between TSH concentration and the mass of thyroid remnants (rs= –0.34; p<0.001) (Table VI).

Discussion

Radioactive iodine has for many years been used for ablation of thyroid remnants. However, till now, there has been no unequivocal definition of such ^{131}I dose which would provide the best therapeutic effects. A way to determine the activity of radioactive iodine is to define the parameter which would actually be informative about the amount of radiation energy deposited within iodine uptaking tissue in the course of therapy; this amount is determined as an absorbed dose [14]. Application of standard radioactive iodine activities in the therapy of the analysed patients resulted in obtaining a broad range of doses absorbed by thyroid remnants (from 64.5 Gy to 21659.6 Gy), allowing the relation between absorbed dose and the efficacy of therapy with radioactive iodine to be demonstrated. On the other hand, contrary to literature data, no effect of the applied radioiodine activity was found on the effectiveness of performed ablation, which may be explained by the narrower range of radioiodine activities used in our study [1643 MBq (44.4 mCi) – 4033 MBq (109.0 mCi) vs. 555 MBq (15.0 mCi) – 9102 MBq (246 mCi)] [8, 10]. The mass of the remaining thyroid remnants turned out to be, in fact, the only parameter influencing the effects of ablation. This may, in turn, have resulted from a lower dose absorbed by the thyroid remnants and/or a weaker stimulation of thyrocytes by endogenous TSH, as a negative correlation was found between the mass of thyroid remnants and TSH concentration in serum of the patients included in the study. Thus, even more important is the

Table I. Statistical analysis of the obtained values of thyroid mass, iodine uptake, EHL, absorbed dose and the activity of 131I in patients with effective or ineffective ablation

Group number	Mass (g)	Iodine uptake (%)	EHL (days)	Absorbed dose (Gy)	Applied activity of ^{131}I (MBq)
I (n=20)	Mean value:	Mean value:	Mean value:	Mean value:	Mean value:
Ineffective therapy	3.2	14.5	3.6	2419	2721
SD=2.45	SD=10.56	SD=1.77	SD=2936.2	SD=536.5	
II (n=80)	Mean value:	Mean value:	Mean value:	Mean value:	
Effective therapy	2.0	10.6	4.1	4101	2755
	SD=1.89	SD=7.7	SD=1.7	SD=4361	SD=564.9
p	p=0.01	p=0.2	p=0.1	p=0.05	p=0.8
Mann-Whitney test	Statistically	Statistically	Statistically	Statistically	Statistically
	significant	insignificant	insignificant	significant	insignificant
	difference	difference	difference	difference	difference

Table II. Influence of absorbed dose on the effect of ablation

	Groups with regard to absorbed dose			
	D <1000 Gy	D >1000 Gy	D >2400 Gy	D >4000 Gy
Number of patients in group	19	81	43	26
Number of patients with ineffective ablation	6	14	4	2
Number of patients with effective ablation	13	67	39	24
Fisher's test level of significance	p<0.05			
Spearman's correlation coefficient value	rs=0.23			

Table III. Influence of absorbed dose on the effectiveness of ablation

Absorbed dose (Gy)	Percent of effective ablations (%)	Effective ablation	Number of patients in group	Fisher's test
D>2000	83	44	53	0.29
D>2200	86	43	50	0.1
D>2400	91	39	43	0.017
D>3000	90	34	38	0.05
D>4000	92	24	26	0.04

Table IV. Correlation between the mass of thyroid remnants and the effectiveness of ablation

Group number	Mass (g)	Number of patients	Number of patients with ineffective ablation	Percentage (%)
1	M<1.0	35	3	8.6
2	1.0≤M<2.0	31	5	16.1
3	2.0≤M<3.0	14	3	21.4
4	M≥3.0	20	9	45.0
χ^2				p<0.01

Table V. Influence of the mass of thyroid remnants on ablation effects

Mass of thyroid remnants	Number of patients in the group	Number of patients with ineffective ablation
<1.5 g	52	5
≥1.5 g	48	15
Wilcoxon p test		p<0.03

Table VI. Correlation between the mass of thyroid remnants and the values of TSH concentrations

Groups with respect to TSH concentration			
Division into clinical groups	TSH concentration Normal values (0.3-5.0 µUl/ml)	TSH concentration Incomplete stimulation (5.0-24.9 µUl/ml)	TSH concentration Full stimulation (≥25.0 µUl/ml)
Number of patients in the group	6	8	86
Mass of thyroid remnants	Mean: 3.32 g	Mean: 3.87 g	Mean: 2.01 g
	SD 1.94 g	SD 3.62 g	SD 1.89 g
Spearman's coefficient of correlation value		rs=–0.34	
		p<0.001	

assessment of thyroid remnants, since the process of damaging large thyroid stumps is often ineffective, demanding application of subsequent doses of radioactive iodine [10, 11, 15].

The relatively not very high coefficient of Spearman's correlation (rs=0.23; p<0.05) between the absorbed dose and the efficacy of ablation suggests the existence of other elements (beside dosimetric) affecting the outcome of therapy. One of them may be the effectiveness of TSH stimulation. The existence of a correlation between TSH concentration and the efficacy of ablation may result from the stimulation of sodium-iodine symporter by the TSH, the stimulation being proportional to TSH concentration in serum. Reports about a direct effect of TSH on the efficacy of radioactive iodine therapy were previously presented by Hurley and Becker in 1988 [16]. In a recent study, the important role of hNIS expression in thyroid carcinomas in appropriate responsiveness to therapeutic radioiodine was clearly demonstrated [17]. All this indicates a need to use recombinant human TSH (rhTSH) in the preparation for ablation of those patients in whom the state of full stimulation by endogenous TSH is difficult to obtain or even impossible [18]. Also the radiosensitivity of thyroid remnants has been assessed with a vast approximation [19]. Patients with postoperatively diagnosed differentiated thyroid carcinoma are often operated on following a preoperative diagnosis of benign lesions in the gland. Sometimes it happens that a diagnosed cancerous focus is only one out of numerous pathological lesions in the thyroid. Thus, morphological features of the thyroid remnants highly depend on the character of the coexisting thyroid pathology. The experience emerging from the many years of application of radioactive iodine in the therapy of hyperthyroidism clearly indicates the varying degree of thyrocyte radiosensitivity, depending on the aetiopathogenesis of the disease [20]. One may then conclude that analogous phenomena occur in cases of thyroid remnant ablation, which finds its confirmation in the high frequency of effective ablations in the group of patients who received low absorbed doses of ionising radiation. Incomplete efficacy of ablation, despite very high absorbed dose, may result from thyrocyte dispersion in the site of the operated thyroid, as well as from small size of the thyroid remnants themselves. Taking into account the geometry and distance of beta radiation in the discussed situations, the majority of radiation energy may be deposited beyond the iodine uptaking tissue [21].

The published reports, while providing evidence for varying effectiveness of ablation of thyroid remnants, which depends on the applied activity of ^{131}I [especially it concerns activities either ≤1110 MBq (30 mCi) or ≥2200 (60 mCi)], indisputably indicate that in some patients ablation is possible with low activities of radioiodine [8, 22]. Thus, dosimetric evaluation in ablation planning should be used to identify groups of patients in whom low activities of ^{131}I will be satisfactory to destroy thyroid remnants, especially when it concerns patients with low risk of neoplastic process progression. The application of such balanced activities may provide a compromise between the therapeutic advantages resulting from the applied treatment and the risk of possible complications, while maintaining the high general efficacy of the therapy.

Conclusions

In summary, a correlation has been demonstrated between ablation effectiveness and the ^{131}I dose absorbed by thyroid remnants. On the other hand, no relationship has been observed between the applied ^{131}I activities and the effectiveness of ablation. Our results confirm that the mass of remaining thyroid remnants is an important parameter, affecting ablation effectiveness. The negative influence of the mass of thyroid remnants on ablation effectiveness reflects weaker stimulation of thyrocytes by endogenous TSH.

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