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Estimation of the results of radioiodine therapy (^{131}I) in Graves' hyperthyroidism (GB) during 10 years' follow-up

Radioiodine therapy, along with drug therapy and surgery, is one of the three methods of Graves' hyperthyroidism treatment (7). The frequency of the use of these three methods is different depending on the country. Pharmacological therapy is the most frequently used in Europe, Japan and South America, whilst ^{131}I therapy is the treatment of choice in North America (14). Radioiodine therapy is recognized commonly as safe and effective therapeutic method, used over 50 years. However, a lot of controversy still exists regarding the indications to use, patients selection, treatment goals, dose selection as well as the prognostic factors for outcome (4).

The aim of the study was the estimation of the radioiodine therapy results in the patients with Graves' hyperthyroidism, during 10 years' long term of follow-up.

MATERIAL AND METHODS

During the period 1994–1995, the study group of 100 patients with Graves' hyperthyroidism has been classified for ^{131}I therapy. The observed group of the patients included 84 females and 16 males, aged from 27 to 76 years (mean 48 years) at the moment of radioiodine therapy.

After initial evaluation in the Department of Endocrinology, the diagnosis of GB was confirmed by the *in vitro* study – the estimation of free thyroxine level (FT4), free triiodothyronine (FT3), thyrotropin (TSH), thyrotropin receptor autoantibody (TSI) as well as the *in vivo* study – thyroid $^{99m}TcO_4$ scintigraphy, iodine uptake after 24 h and 48 h (RAIU-24 h, RAIU-48 h). All these studies have been performed in the Department of Nuclear Medicine. Then the patients have received therapeutic activity of ^{131}I calculated individually for each patient according to Marinelli formula. One year after ^{131}I therapy, all the patients have been estimated whilst thyroid function was evaluated every one month.

Ten years since the first therapy, an attempt at getting into touch with the study group of patients has been made. The TSH level and in some cases FT4 and FT3 levels were measured. Before ^{131}I therapy and during one-year period after ^{131}I therapy, serum FT4 and FT3 levels were estimated by the fluoroimmunological method (FIA) type "Delfia" of Pharmacia LKB, and serum TSH level by the immunofluorometric method (IFMA) type "Delfia" of Pharmacia LKB. Normal values ranged between FT4 8.5–19.0 pmol/l, FT3 3.4–8.9 pmol/l and TSH 0.4–5.5 mIU/l, respectively. Actually, after 10 years, the measurement methods of the thyroid hormones and TSH have been changed,

hence serum TSH levels were measured according to the immunoradiometric method (IRMA) using BRAHMS Diagnostica GmbH kits. Normal values TSH ranged between 0.4–4.9 mIU/l.

RESULTS

Before therapy, the serum thyroid hormones and TSH levels have ranged, respectively: FT4 10.3–90 pmol/l (mean 43.1 ± 40.05), FT3 5.7–74. 8 pmol/l (mean 26.38 ± 35.46), TSH 0.02–0.08 mIU/l (mean 0.022 ± 0.034). The administered therapeutic activity ranged from 148.0 to 1113.7 MBq (mean 488.3) or 4.0–30.1 mCi (mean 13.197). The applied intrathyroidal absorbed dose ranged between 70–250 Gy (mean 97.9). After one-year follow-up, euthyroidism (EU) was observed in 29 subjects (29%), hypothyroidism (HP) in 31subjects (31%), whereas hyperthyroidism (H) still remained in 40 persons (40%). From among 40 patients with persistent hyperthyroidism after the first dose, 39 patients were continued to be further observed and treated, while one patient did not consent to the continuation of therapy (no contact after 10 years). After expiration of a period of consecutive 8–12 months (mean 10 months), 23 subjects (23%) received the second therapeutic dose of ^{131}I, which resulted in euthyroidism in 4 patients and hypothyroidism in 18 cases. Hyperthyroidism still remained in 1 patient and moreover, this person did not agree to continue ^{131}I therapy (the lack of touch with this person after 10 years).

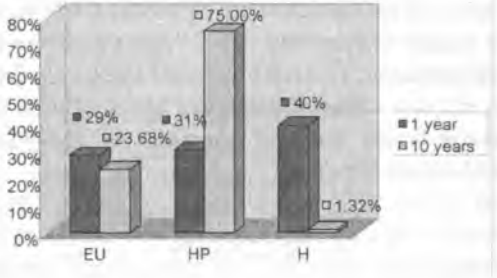

Fig. 1. The results of ^{131}I treatment in short-term (one year) and long-term (10 years) follow-up

After ineffective treatment with the second therapeutic dose of ^{131}I, the next 7 patients (7%) required to take the third dose. Among this group, 2 persons acquired euthyroidism, the next 5 persons hypothyroidism. After 2 months since the administration of the second dose of ^{131}I, transient hypothyroidism was observed (TSH = 28 mIU/l) in one of these 5 persons, and then after 6 months the relapse of hyperthyroidism exacting the third dose of ^{131}I has been noticed. One person (1%) received the fourth dose of ^{131}I , since then permanent hypothyreosis has appeared. Eight patients with hyperthyroidism after the first therapeutic dose of ^{131}I had not received the next dose of ^{131}I . Among this group, subclinical hyperthyroidism (FT3 and FT4 normal, TSH decreased) appeared in 6 patients. After 4 years, hypothyroidism developed in one of these subjects, however after 10 years, in another three consecutive persons hypothyroidism was noted. The next two patients remained euthyroid. Two subjects with persistent hyperthyroidism (FT4 and FT3 raised, TSH decreased) received non-systematic antithyroid drug therapy – Thiamazole. In the 7th year of observation, one of these persons still remained hyperthyroid (after this time follow-up has been stopped – the lack of touch with the patient), whereas hyperthyroidism remained in the second person until the10th year of observation.

Table 1. The treatment results of patients with hyperthyroidism depending on the number of the applied therapeutic ^{131}I doses

Number of doses	Number of patients	Results of the treatment		
		Euthyreosis (EU)	Hypothyreosis (HP)	Hyperthyreosis (H)
1 dose	100	29	31	40
2 doses	31	4	18	9
3 doses	8	2	5	1
4 doses	1	0	1	0

Totally, permanent elimination of hyperthyroidism was obtained in 90% patients whereof in 60% of the subjects just after one dose of ^{131}I administration, in 22% after two, in 7% after three, and in 1% after four doses. Ten years after ^{131}I therapy, from among the initial group of 100 patients, the contact was established with 78 patients or their families. No information was obtained about the remaining 22 subjects. Among 78 patients, 76 subjects have been submitted to the control, one person died, and still another person changed the address. The serum TSH levels of 76 studied subjects ranged between 0.04–41.82 mIU/l (mean 5.13 ± 7.3). Euthyroidism was observed in 18 persons (23.7%). Hypothyroidism was diagnosed in 57 persons (74.56%), and hyperthyroidism (TSH < 0.04 mIU/l, FT4 = 22.6 pmol/l, FT3 = 10.2 pmol/l) in 1 patient (1.3%). Among 57 patients with hypothyroidism, 47 patients (61.4%) were treated with levothyroxine. The other 10 persons (13.16%) remained without treatment. In 6 patients of this group, TSH level was higher than 10 mIU/l, while in the other 4 patients it ranged between 5–10 mIU/l. Among the above mentioned 10 persons, 6 patients had normal thyroid function after one year of ^{131}I therapy. In 2 patients hyperthyroidism was diagnosed, whereas in 2 consecutive subjects early hypothyroidism (up to one year since ^{131}I therapy) required substitutive therapy. In none of the patients with hypothyroidism diagnosed earlier withdrawal of hypothyroidism was observed.

DISCUSSION

Radioiodine therapy eliminates hyperthyroidism effectively, however the final result, that is to say increasing hypothyreoidism awakens a lot of controversy. Several questions still exist related to the goal of therapy – if it is obtainment of normal thyroid function or the elimination of hyperthyroidism. Hypothyroidism occurring after ^{131}I therapy is considered to be the complication and negative final result of the treatment as well as favourable goal of therapy (13). According to Willemsen et al.'s (15) opinion the absorbed dose of 150 Gy is usually sufficient. However, some investigators (15) have suggested that in particular cases (concomitant, severe heart diseases, unfavourable reactions to antithyroid drugs) it is desirable to use higher, ablative ^{131}I therapy with absorbed dose of 300 Gy in order to rapidly eliminate hyperthyroidism after one therapeutic dose administration. A number of studies (5, 9) pointed out a concomitant relationship between the applied intrathyroid absorbed dose and the rapidity of achieved favourable therapy outcomes.

Another controversial aspect is the best approach to radioiodine dose selection. Some centers use fixed ^{131}I dose, but some have calculated ^{131}I dose based on type of thyroid gland (diffuse goitre, toxic multinodular goitre, toxic adenoma), thyroid size and radioiodine uptake (10). All patients included in our study received therapeutic activity of radioiodine determined using the method of the calculated individual target dose absorbed. In our study, after one year of observation, the obtained elimination of hyperthyroidism in 60% of patients is comparable with the result (67%) of Catargi et al. (5). Moreover, the percentages of patients with EU (26%), HP (41%) and H (33%) were also similar

to the results of the presented study. These authors used the same method of ^{131}I dose estimation. Less efficient therapy (i.e. the obtainment of EU and HP) has been presented by Howarth et al. (9) and Jarlov et al. (10), 40% and 48%, respectively. With respect to our study outcomes (HP 31%, EU 29%), in both papers the groups of the patients with HP (12% and 17%) were smaller than the groups with EU (28% and 31%). However, Jarlov et al. (10) obtained elimination of hyperthyroidism in 61% persons with the use of the fixed dose method. Slightly more (69.5%) efficiency of therapy, expressed by receiving of EU and HP, were described by Allahabadia et al.(4), otherwise with lesser15% group with EU. Much higher efficiency of ^{131}I therapy showed Alexander et al. (3) and Chiovato et al. (6), 86% and 90.3%, respectively. In the group of 800 subjects, euthyroidism has been obtained by Abdlrazek et al. (1) in 71% of patients, what significantly differs from our results (29%) as well as those of other authors (3–6, 9, 10).

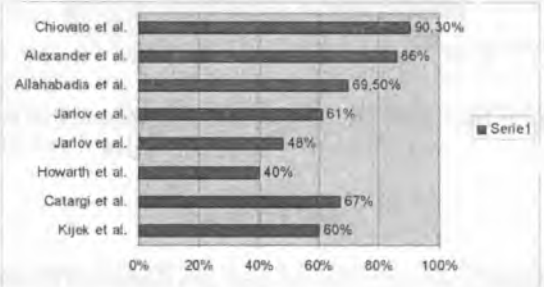

Fig. 2. The comparison of the treatment efficacy one year after the first ^{131}I dose acc. to different authors

The administration of the second consecutive therapeutic dose of radioiodine increased the number of patients with hypothyreoidism in relation to the patients with euthyroidism and persistent hyperthyroidism in our group. The six-person group with subclinical hyperthyroidism, after the first ^{131}I dose, remaining without further treatment (without antithyroid drugs or radioiodine – 131) is especially worthy of notice. All patients of this group acquired normalization of TSH levels in long--term (4 to 10 years) observation. These changes did not occur in 2 patients with elevated FT4 and FT3 levels. Further observation of these patients has showed that the subjects without symptoms of hyperthyroidism, but only with decreased TSH level, and with normal FT4 and FT3 levels, do not require the treatment with the next ^{131}I dose or with antithyroid drugs. In such patients we can expect normalization of thyroid function in a longer period. In our study group we did not observe transient hypothyroidism described by the others (8). Only in one case after the second ^{131}I dose, TSH level increased during the second month after therapy, reaching the value of 28 mIU/l. It much outnumbered 8 mU/l level described by Gomez et al. (8) as a characteristic feature of transient hypothyroidism.

Also, in none of the persons with early hypothyroidism (acquired in the first year after therapy) withdrawal of hypothyroidism was observed. In our study group, the percentage of patients (31%) with hypothyroidism revealed in the first year of therapy has increased to 74.56%, after 10 years of observation. The increased number of patients with hypothyroidism in long-term (7–10 years) observation was noted by the other authors (2, 11, 12) as well. Marcocci et al. (11) observed the rise of hypothyroidism from 36.9% in the first year since ^{131}I therapy to 79.3% in the later period. These results are similar to the outcomes of our study group. Metso et al. (12) received a smaller group

(24%) of patients with hypothyroidism in the earlier period of observation as well as a smaller group (59%) in the later period of observation. Much higher percentage of patients with hypothyroidism after the first year and after 10 years (55.8% and 86.1%, respectively)) has been described by Ahmed et al. (2).

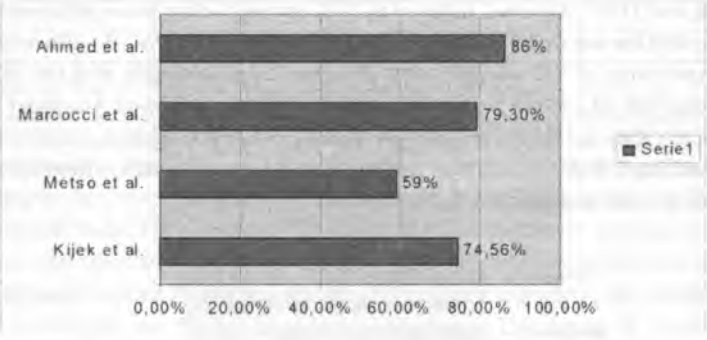

Fig. 3. The comparison of hypothyroidism frequency 10 years after the used ^{131}I therapeutic activity

CONCLUSIONS

Radioiodine therapy is an easy, effective and safe method of Grave's hyperthyroidism treatment. In a long-term observation ^{131}I therapy induces hypothyroidism requiring permanent control and systematic substitutive therapy. Each next therapeutic ^{131}I dose increased the number of patients with hypothyroidism and simultaneously decreased number of the patients with permanent hyperthyroidism as well as with euthyroidism. The patients with prolonged subclinical hyperthyroidism after ^{131}I therapy without symptoms of hyperthyroidism can be observed without therapy. With time the entire equalization of the thyroid function or transition to hypothyroidism can be expected.

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SUMMARY

Radioiodine therapy used from over 50 years in the treatment of thyroid diseases, awakens still a lot of controversy. The aim of our study was the estimation of the radioiodine therapy results of the patients with Graves' disease during 10 years' follow-up. One hundred subjects, 84 females and 16 males, aged 27–76, with Graves' hyperthyroidism have been included into the study. The therapeutic activity of ^{131}I was calculated for each patient individually, according to Marinelli formula. In the treatment of hyperthyroidism, the first dose of ^{131}I was given to 100 subjects, the second dose to 31 patients, while 8 patients received the third, and only 1 patient the fourth dose, respectively. During the first year of observation, 29 patients obtained euthyroidism, 31 patients hypothyroidism, and in the other 40 patients, hyperthyroidism has remained. After 10 years of follow-up, 76 patients out of the initial group of 100 subjects with the sick thyroid function have been estimated. The study showed euthyroidism in 18 persons, hypothyroidism in 57 persons, while hyperthyroidism has remained in one person. The radioiodine therapy is an effective method of Graves' hyperthyroidism treatment, however inducing an increased long-term hypothyroidism requires to be managed.

Ocena wyników leczenia jodem radioaktywnym (^{131}I) nadczynności tarczycy w przebiegu choroby Gravesa–Basedowa (GB) w 10-letnim okresie obserwacji

Terapia ^{131}I stosowana od ponad 50 lat w leczeniu chorób tarczycy wciąż budzi wiele kontrowersji. Celem pracy była ocena wyników leczenia radiojodem pacjentów z chorobą Gravesa–Basedowa w 10-letnim okresie obserwacji. Analizą objęto 100 pacjentów, w tym 84 kobiety i 16 mężczyzn, w wieku 27–76 lat z hypertyreozą w przebiegu choroby Gravesa–Basedowa. Aktywność terapeutyczną ^{131}I oszacowano indywidualnie dla każdego pacjenta stosując formułę Marinellego. W leczeniu nadczynności tarczycy 100 osobom podano 1 dawkę ^{131}I, 31 osobom drugą dawkę ^{131}I, 8 pacjentów otrzymało trzecią dawkę, zaś jeden pacjent czwartą dawkę. W pierwszym roku obserwacji eutyreozę uzyskało 29 osób, hypotyreozę 31 osób, a u 40 osób utrzymywała się hypertyreoza. Po upływie 10 lat

z początkowej 100-osobowej grupy chorych funkcję tarczycy oceniono u 76 osób. Badania wykazały obecność eutyreozy u 18 osób, hypotyreozy u 57 osób, zaś u jednej osoby utrzymywała się hypertyreoza. Terapia radiojodem jest skuteczną metodą leczenia hypertyreozy w przebiegu choroby GB, powodującą w odległym czasie narastanie hypotyreozy wymagającej leczenia substytucyjnego.