RADIOIODINE TREATMENT OF GRAVES' DISEASE – DOSE/RESPONSE ANALYSIS

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Summary: The clinical outcome of 153 Graves' disease patients treated with a wide dose range of radioactive iodine-131 (RAI) was analyzed retrospectively. Six to nine months after the first dose of RAI 60 patients (39%) were hypothyroid (or rather thyroxine-substituted) and 26 (17%) were euthyroid, while 67 patients (44%) did not respond properly: in 32 (21%) their antithyroid drug (ATD) dose could be reduced but not withdrawn (partial response) and 35 (23%) remained hyperthyroid or the same dose of ATD was necessary (no response). The outcome did not correspond significantly to the administered activity of RAI (medians 259, 259, 222, and 259 MBq for hypothyroid, euthyroid, partial, and no response subgroups, respectively), or the activity retained in the gland at 24 h (medians 127, 105, 143, and 152 MBq). The effect was, however, clearly, and in a stepwise pattern, dependent on initial thyroid volume (17, 26, 33 and 35 ml, $P < 0.001$) or activity per gram tissue retained at 24 h (6.02, 4.95, 4.75, and 4.44 MBq/g, $P = 0.002$). Also, higher residual level of thyrotoxicosis at the time of RAI treatment was connected with worse outcome. The dose-dependency of outcome was further analyzed. When our sample was divided into tertiles, according to the adjusted dose, the same modest success rates (47%) were seen in the lower and middle tertiles. However, doses higher than 5.88 MBq/g (the upper tertile) resulted in success rate of 75%. Finer division into decils has shown a threshold-like increase in cure rate between the 7th and the 8th decil. In the first 7 decils (doses ≤ 6 MBq/g) the complete response rate was 45 to 50%, in the 8th decil (6.0 to 7.8~MBq/g) it rose to 80% and was not further increased with increasing dose. Direct comparison of higher (> 6 MBq/g, cure rate 80%) and lower (≤ 6 MBq/g, cure rate 46%) doses gave highly significant difference ($P < 0.001$). With our dosing range we found a dose-dependent clinical outcome that suggests an optimum delivered dose near 6.5 MBq/g, resulting in successful treatment of ca 80% patients.

Key words: *Radioiodine; ^{131}I; Graves' disease; Hyperthyroidism; Dose/response analysis*

Introduction

Despite more than 60 years' experience with radioactive iodine-131 (RAI) treatment of hyperthyroidism some controversial questions remain (1–3). In the United States RAI is often recommended as first-line treatment whereas in Europe it is a treatment of choice for relapsed hyperthyroidism (4, 5). Initially, the aim of the iodine-131 therapy was to achieve euthyroidism through low dose regimens. However, now we are aware of the fact that the development of hypothyroidism is progressive, with an annual incidence of 2–3% even many years after therapy (6). Moreover, low-dose RAI has a higher treatment failure rate, in which case further antithyroid drug (ATD) treatment and additional RAI doses are needed (7). Nowadays, the goal of the RAI therapy is to control hyperthyroidism by rendering the patient hypothyroid (8). That requires higher doses, resulting in higher cure rates (2). Still, there is little consensus regarding the most appropriate dosing regimen (2, 9). While some prefer fixed doses of 5, 10, or 15 mCi (185, 370, or 555 MBq) for Graves' disease (10–12) others try to individualize the dose using calculations based on Quimby-Marinelli formula and dependent on the thyroid gland size and the 24-hour RAI uptake (13), or even effective RAI half-life measurement (14).

The studies comparing these schedules gave conflicting results (15–18) Turner et al. (18) suggest that a calculated dose of radioiodine has no advantage over a fixed dose of 5 or 10 mCi (185 or 370 MBq). Also, Leslie et al. in their recent randomized study (17) found no difference between fixed doses (235 or 350 MBq) and calculated ones (2.96 or 4.44 MBq/g thyroid adjusted for 24 h RAI uptake). In contrast, Peters et al. (16) recommend individual dose calculation. In their prospective, randomized trial they also revealed a strong correlation between the success of therapy and the radiation dose actually absorbed by the thyroid. Another approach was suggested by Jarlov et al. (15). In their trial a semiquantitative fixed dose regimen, i.e. 5 mCi (185 MBq) for patients with small glands, 10 mCi (370 MBq) for medium glands, and 15 mCi (555 MBq) for large glands, was as effective as individual dose calculation. Calculated doses are more widely used in Europe than in

America where fixed doses are preferred (19). According to the recent recommendation of the American Thyroid Association and American Association of Clinical Endocrinologists a fixed dose of 10–15 mCi is recommended (8). A recent study by Sztal-Mazer et al. found that higher doses of RAI result in faster treatment success (20).

Our approach has been based on calculation, and aimed at delivering ca 80 to 150 Gy to the gland. However, in the course of time, and namely between the years 1999 and 2001, similarly to other centers (21), we tended to increase the doses in order to improve the cure rate. Therefore, our register from this period includes patients treated with various doses. They are also well defined in baseline data (including thyroid volume and 24 h-RAI uptake) and in their clinical outcome. We report here a retrospective survey of these data, with a tentative dose/response analysis suggesting an optimum dose of ca 6 to 7 MBq/g thyroid adjusted for 24 h-RAI uptake.

Material and Methods

Graves' disease patients (n = 153) treated with RAI in our thyroid unit between the years 1999 and 2001 were analyzed retrospectively. The diagnosis was confirmed by positive thyrotropin receptor antibodies and by the typical ultrasound finding of diffusely hypoechoic and hypervascularized thyroid. Most patients came with at least 1-year history of the disease, relapsing after their ATD had been withdrawn. Typically, they received another course of ATD and were sent to our center for more "definitive" treatment. They were asked to withdraw their ATD three days before the expected RAI administration. On the day preceding the RAI treatment their thyroid gland volume was measured by ultrasound (Hewlett-Packard Image Point), blood samples were taken for free thyroxine (fT4), free triiodothyronine (fT3), thyrotropin and TSH-receptor antibodies (TSH-R-Ab), and the testing dose for 24 h-RAI uptake measurement was given.

Next day the treatment dose of RAI (as NaI solution) was administered orally. The dose calculation was based on Quimby-Marinelli formula, using the thyroid volume, the 24 h-RAI uptake, and the expected (not measured) effective RAI half-life of 6 days. Generally, we aimed at delivering ca 80 to 150 Gy but the doses varied in the course of time. Also, some patients were given higher calculated doses because even for smaller glands with high uptake we rarely used less than 5 mCi (185 MBq). As we did not measure the RAI half-life and as it may vary considerably between patients (16, 22) we report here the dose not in Gy but in MBq per gram thyroid tissue retained at 24 hours (MBq/g).

The original ATD dose was restarted 3 to 6 days after the RAI treatment and the patients were discharged to their endocrinologists. In their follow-up the dose of ATD was adjusted (often withdrawn), and, if necessary, L-thyroxine replacement was started.

The patients were reassessed in our center 6 to 9 months later (clinical examination, ultrasound, fT4, fT3, TSH, and TSH-R-Ab) and the response was classified as (a) none = the same dose of ATD required or patient hyperthyroid, (b) partial = ATD dose could be reduced but not withdrawn, (c) euthyroid = ATD withdrawn and patient euthyroid or (d) hypothyroid = L-thyroxine substitution or patient hypothyroid (stratified response). For clinical purpose, response (a) and (b) were considered as treatment failures, and another RAI dose was offered. Here, only the effect of the first dose in each patient is presented. Response (c) and (d) were considered as successful treatment.

As the data rarely were normally distributed, non-parametric tests (Mann-Whitney and Kruskal-Wallis) were used for statistical analysis. For nominal data chi-square test was used.

Results

1. General outcome and gender

The clinical response is summarized in Table 1. The treatment was successful in 86 patients of 153 (56%), while 67 patients (44%) did not respond properly. Most patients were women (84%). While there was a slightly higher failure rate in men (13/25, i.e. 52%) than in women (54/128, i.e. 42%), this difference was not significant (chi-square test).

Tab. 1: Stratified response to RAI treatment.

Response	Whole group (n = 153)	Men (n = 25)	Women (n = 128)
a) None	35 (23%)	9 (36%)	26 (20%)
b) Partial	32 (21%)	4 (16%)	28 (22%)
c) Euthyroid	26 (17%)	1 (4%)	25 (20%)
d) Hypothyroid	60 (39%)	11 (44%)	49 (38%)

2. Prognostic factors for outcome

The outcome was clearly not dependent on the administered activity of RAI or the activity retained in the gland at 24 h. Actually, the administered activity was very similar in all the outcome groups and the retained activity was even higher in the "failure" group (Table 2 and 3).

Also, higher residual level of thyrotoxicosis and higher disease activity at the time of RAI treatment was connected with worse outcome, as suggested by higher fT3 level, 24 h-RAI uptake, and TSH-R-Ab in the "failure" group (Table 3).

Tab. 2: Baseline characteristics in stratified response groups.

	a) None (n = 35)	b) Partial (n = 32)	c) Euthyroid (n = 26)	d) Hypothyroid (n = 60)	
fT4 (pmol/l)	15.2 (13.8–20.7)	19.7[a] (15.6–33.9)	15.7 (13.7–17.0)	15.9 (14.0–19.5)	$P = 0.013$
fT3 (pmol/l)	4.8 (3.9–7.5)	6.1[b] (4.0–14.1)	3.9 (3.5–5.2)	4.2 (3.5–5.1)	$P = 0.009$
TSH (mIU/l)	0.4 (0.0–1.7)	0.1 (0.0–0.8)	0.2 (0.0–1.6)	0.7 (0.0–2.9)	$P = 0.088$
TSH-R Ab (U/l)	1.6 (0.0–9.2)	2.2 (0.9–8.3)	1.5 (0.8–2.4)	1.3 (0.0–3.0)	$P = 0.147$
Volume (ml)	35 (21–50)	33 (24–47)	26 (17–41)	17[c] (12–26)	$P < 0.001$
Uptake (% at 24 h)	58 (45–74)	62[d] (51–82)	51 (39–57)	51 (38–65)	$P = 0.011$
Activity given (MBq)	259 (185–370)	259 (185–346)	222 (179–370)	259 (185–370)	$P = 0.963$
Activity retained (MBq at 24 h)	152 (105–246)	143 (117–216)	105 (73–183)	127 (86–195)	$P = 0.067$
Dose per g at 24 h (MBq/g)	4.44 (3.96–5.35)	4.75 (4.07–5.15)	4.95 (3.92–5.69)	6.02[e] (4.41–10.54)	$P = 0.002$

Values are expressed as medians, with interquartile range in parentheses.
P values aply to Kruskal-Wallis test (non-parametric analysis of variance among the groups).
Dunn test was used to identify the different groups: [a] b > a,c; [b] b > c,d; [c] d < a,b; [d] b > c,d; [e] d > a.

Tab. 3: Baseline characteristics in clinically significant outcome groups.

	Success (n = 86)	Failure (n = 67)	
fT4 (pmol/l)	15.8 (13.7–18.7)	16.5 (14.4–25.3)	$P = 0.100$
fT3 (pmol/l)	4.1 (3.5–5.1)	5.2 (4.0–9.0)	$P = 0.001$
TSH (mIU/l)	0.6 (0.0–2.5)	0.2 (0.0–1.5)	$P = 0.058$
TSH-R Ab (U/l)	1.3 (0.0–2.7)	1.9 (0.8–9.1)	$P = 0.041$
Volume (ml)	19 (13–29)	35 (22–47)	$P < 0.001$
Uptake (% at 24 h)	51 (38–64)	60 (47–80)	$P = 0.002$
Activity given (MBq)	259 (185–370)	259 (185–370)	$P = 0.562$
Activity retained (MBq at 24 h)	122 (80–189)	148 (111–239)	$P = 0.012$
Dose per g at 24 h (MBq/g)	5.18 (4.13–8.34)	4.52 (4.05–5.16)	$P = 0.004$

Values are expressed as medians, with interquartile range in parentheses.
P values aply to Mann-Whitney test.

On the other hand, there was a clear-cut and stepwise relationship between the outcome and the initial thyroid volume or the dose per gram tissue adjusted for 24 h-RAI uptake (Table 2, Fig. 1).

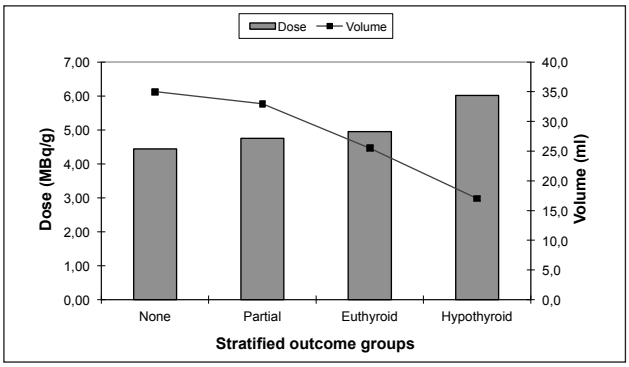

Fig. 1: Median estimated doses of ^{131}I (per g, 24 h after the therapy) and initial thyroid volume in different outcome groups.

3. Dose/response analysis

The stepwise relationship between the outcome and the dose per gram adjusted for 24 h uptake led us to looking for an inverse relationship, with the dose as the independent variable. Our sample was divided into tertiles, according to the adjusted dose (Table 4). The table shows the same success rates of 47% in the lower and middle tertiles. In the upper tertile, however, doses higher than 5.88 MBq/g adjusted for 24 h uptake resulted in clearly better outcome, with success rate of 75%. This suggested a threshold dose somewhere near the border between the 2nd and the 3rd tertile.

Tab. 4: Dose dependence of success rate.

Tertile	Dose range (MBq/g)	Success (n)	Failure (n)	Success rate (%)
1	0.95–4.31	24	27	47
2	4.32–5.87	24	27	47
3	5.88–37.26	38	13	75

By chi-square test, 10.409, $P = 0.005$.

In order to analyze further the dosing range where the success rate increased we divided our sample into deciles (Fig. 2). There was a sharp increase in cure rate between the 7th and the 8th decile. In the first 7 deciles (doses ≤ 6 MBq/g) the success rate was 45 to 50%, in the 8th decile (6.0 to 7.8 MBq/g) it rose to 80% and was no further increased with increasing dose. This suggested a clear-cut difference in efficacy between lower (≤ 6 MBq/g) and higher (> 6 MBq/g) doses. Direct comparison of these groups gave highly significant difference (Table 5).

In contrast, with the "absolute" administered activity (i.e. not adjusted for volume and uptake) as the independent variable, no dose-dependency could be demonstrated (Table 6).

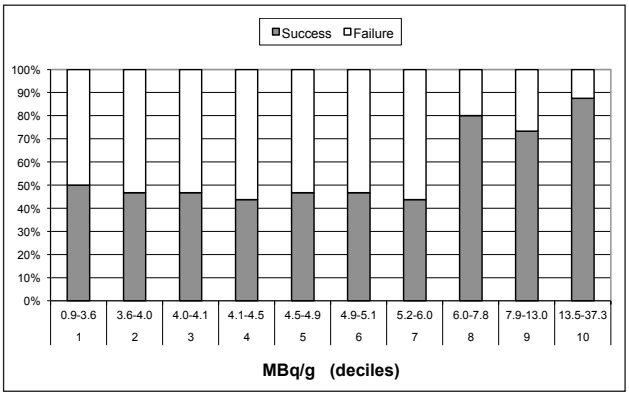

Fig. 2: Frequency of successful treatment as a function of estimated dose of ^{131}I in the thyroid gland (per g) 24 h after the therapy in 153 patients (by decile).

Tab. 5: Comparison of low and high calculated dose.

	Success (n)	Failure (n)	Success rate (%)
Dose ≤ 6 MBq/g	50	58	46
Dose > 6 MBq/g	36	9	80

By chi-square test, 13.322, $P < 0.001$.

Tab. 6: Comparison of low, intermediate and high "absolute dose" (administered activity).

Dose range	Success (n)	Failure (n)	Success rate (%)
111–185 MBq (3–5 mCi)	32	20	62
222–333 MBq (6–9 mCi)	23	28	45
370–1036 MBq (10–28 mCi)	31	19	62

By chi-square test, 3.839, $P = 0.147$, N.S.

4. Possible effect of pretreatment

Most patients were pretreated with methimazole (n = 129) or propylthiouracil (n = 22), only 2 patients came with no pretreatment. The cure rate was not significantly different between methimazole-pretreatment (73/129) and propylthiouracil-pretreatment (11/22, chi-square, N.S.) but due to the small sample in propylthiouracil group the power of the test was very low. Both non-pretreated patients were cured (1 was euthyroid and 1 hypothyroid).

Discussion

With our RAI dosing range the overall cure rate of 56% was similar to some series (14–16, 23, 24), while other authors report a better success rate (10, 11, 20, 25) This may be mainly due to the variation in doses used in these studies, in

ATD pretreatment, and/or in ethnic and geographical factors. Also, our sample might be generally less sensitive, because in our country RAI treatment is rarely used as first line therapy for Graves' disease. Therefore, our patients were mostly those with persistent or relapsed disease after a full course of ATD treatment.

From the baseline parameters, the thyroid volume, the pre-treatment thyroid status (fT3, RAI uptake, TSH-R-Ab), and the dose adjusted for volume and uptake were important prognostic factors of outcome, with a stepwise relationship for volume and adjusted dose. The prognostic importance of volume (2, 21, 25–28), thyroid status (21, 25, 27, 28) and adjusted dose (29) has already been observed. In some series (21, 25, 28) but not in others (27, 30), males gave a less reliable response. In our study, this tendency was not significant but perhaps the male subgroup was too small to detect a minor gender difference.

The possible "radioprotective" effect of ATD resulting in worse outcome in ATD-pretreated patients has been discussed (3, 31). There seems to be a consensus that pretreatment with propylthiouracil would decrease the success rate (31–33), whereas carbimazole and methimazole may not influence the outcome if withdrawn a few days before RAI treatment (27, 29, 31, 34). We have also seen a somewhat worse outcome in propythiouracil-pretreated patients but, as in our country methimazole is the predominant ATD, our propylthiouracil group was too small to confirm it.

In the context of ongoing discussion on fixed vs. adjusted doses (3, 22, 35), our study seems to favor the dose adjustment. Namely, the "absolute" (non-adjusted) dose did not correlate with outcome at all. In contrast, the dose adjusted for volume and uptake was a strong predictor of cure rate, with doses > 6 MBq/g resulting in successful treatment in 80% patients. This success rate was similar to those found by others with comparably high adjusted doses: 86% for ca 6.4 MBq/g [36], 85% for 7.4 MBq/g [27], 90% for 7.4 MBq/g [37], 72% for 7 MBq/g [38], 85% for 7.1 MBq/g [39]. Lower adjusted doses gave similarly lower cure rate: 39% for ca 2.1 MBq/g and 41% for ca 3.2 MBq/g [14], 50% for 3.7 MBq/g [24], 55% for 4.4 MBq/g [23]. Dose/response relationship with several adjusted doses in the same group came from post hoc analysis of the "fixed dose" subgroup in the prospective study by Peters et al. [16]. Recalculation from Gy using their measured mean effective half-life of RAI (4.7 d) would give the following pairs of values for cure rate and estimated adjusted dose: 11% for 2.4 MBq/g, 50% for 4.7 MBq/g, 67% for 7.1 MBq/g, 80% for 9.5 MBq/g, 93% for 19.0 MBq/g. Together with 58% cure rate in their adjusted dose (ca 5.6 MBq/g) group it gives a dose response curve similar to our one, or that obtained by integrating the above values from individual studies. All these results, including ours, suggest that a reasonably high success rate over 70% requires adjusted doses around 7 MBq/g. A similar conclusion was reached by Grosso et al. (39). They found that it is not useful for the thyroid to absorb a dose over 150 Gy (7 MB/g), except in the case of high disease activity.

Obviously, our retrospective survey did not give a direct answer to the preference of fixed vs. adjusted dose of RAI. This must come from prospective randomized studies directly comparing these treatment options. The first such study by Peters et al. (16) has brought rather conflicting results. While they found somewhat better cure rate with fixed dose 555 MBq (71%) than with adjusted dose 100 Gy (58%), from the dose response analysis in the fixed dose group (see above) they strongly recommend individual calculation aimed towards a higher dose 200 Gy. The stimulating semiquantitative approach published by Jarlov et al. (15) suggests that their regime of three fixed doses (185, 370 or 555 MBq) used for small, medium, and large glands assessed by palpation only is as effective as the dose calculation (3.7 MBq/g for diffuse glands) based on ultrasound volume measurement and 24 h-RAI uptake. In their subgroup with diffuse glands (presumably corresponding to Graves' disease) they reported 48% (14/29) and 61% (14/23) success rate with the calculated and fixed doses, respectively. Their study, however, addressed a more general question of all causes of hyperthyroidism, and therefore the sample with diffuse glands (52 patients) was relatively small. In the randomized comparison by Leslie et al. (17) of two fixed doses (235 and 350 MBq) and two adjusted doses (2.96 and 4.44 MBq/g) the authors found no difference in clinical outcome. However, their conclusion that dose adjustment does not confer any advantage over a fixed dose might be questionable, as the relatively small sample size gives their negative results a low power (40). Furthermore, the doses were smaller than those used in most recent studies. According to the recent recommendation of the American Thyroid Association and American Association of Clinical Endocrinologists a fixed single dose of 10–15 mCi is recommended (8). Collier et al. compared two fixed doses of RAI (370 vs. 555 MBq) with success rate 90% for both treatment arms. There was no significant difference between the lower and higher activity (30). However, Boelaert et al. in their recent study (25) confirmed that the higher the fixed dose of RAI, the higher the success rate. Patients who were administered a fixed dose of 600 MBq had a cure rate of 84.1% compared to those who were given either 370 MBq (74.9%) or 185 MBq (63%). Abraham et al. recommend using a fixed dose of 500 MBq; a higher dose (up to 800 MBq) may be required for patients with very large goiters and severe hyperthyroidism (2). Similar results were brought by Sztal-Mazer el al. (20). In their recent retrospective study they divided the patients into three groups according to the dose received ($\leq$ 15 mCi, 16–20 mCi, $\geq$ 21 mCi) with success rates 74%, 85%, 89% while average time to successful treatment was 8.1, 4.6, 2.9 months, respectively. It is the first study which not only provides evidence that success post-treatment correlates with administered dose, but also shows that successful treatment is achieved earlier with higher doses (20).

Conclusion

Our retrospective survey did not directly compare a fixed dose of RAI to and an adjusted one. Rather, it has shown an increased risk of treatment failure in smaller adjusted doses (i.e. ≤ 6 MBq per gram thyroid tissue retained at 24 hours). Intuitively, there is a greater risk of getting such "inadequate" doses with lower fixed activities (< 500 MBq) given to patients with larger goiters and higher disease activity (reflected by 24 h RAI uptake). A randomized study comparing a fixed dose of 500 to 600 MBq with an adjusted dose of approximately 6.5 MBq/g and sample sizes of up to 300 patients in each treatment arm may be desirable to assess the optimum approach. However, it seems well-established that in either regimen lower doses than those specified above confer a greater risk of treatment failure.

Acknowledgements

We are indebted to Prof. Jayne A. Franklyn, MD PhD (University of Birmingham, UK) for helpful discussions.

The study was supported by the research project of Ministry of Health, Czech Republic, NT 13535-3/2012.

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Received: 27/05/2014
Accepted: 11/06/2014

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