Quantitative evidence of thyroid stunning in ^{131}I cancer treatment

Hadjieva D. Tatiana

Centre of Nuclear Medicine and Radiation Oncology, Faculty of Medicine, Sofia, Bulgaria

Abstract

BACKGROUND: An obvious paradox remains in the diagnosis, treatment and follow-up of differentiated thyroid cancer by ^{131}I. The higher the activity for raising diagnostic precision, the greater is the potential reduction in therapeutic effects. This is due to a phenomenon called thyroid stunning.
MATERIAL AND METHODS: ^{131}I tracer and therapeutic parameters: uptake, effective half-life and thyroid remnants mass were compared in two different groups of patients. Pre-treatment planning of radioiodine (RI) ablation was performed in 30 patients after administration of 0,185–74 μBq. The same parameters comparison was performed in the second group of four cases. They received two or three single fractions of 600–2400 MBq 3–15 days apart (a long-term abandoned regime).
RESULTS: 1. Comparative data collected by pre-treatment planning and subsequent RI administration supported the thesis that low range tracer activity (0,7–74 μBq) does not cause thyroid stunning. We have registered higher or similar uptake in thyroid bed after 1100–3700 μbq in 90% of cases. Only in 10% of cases was therapeutic uptake lower than the tracer one. In 18% of patients the higher rate of uptake was associated with additional thyroid tissue visualized on the post-treatment scan. Half-life reduction only could be interpreted in the direction of stunning, but such changes characterizes every RI treatment, if it takes more than one administration. Data elucidate why our pre-treatment planning failed in one-third of the patients.
2. We have clearly observed thyroid stunning after 600–2400 MBq ^{131}I. In one case only, even after 1200 MBq, stunning did not take place. Individual RI kinetics appear highly unpredictable. The author advocates avoiding high activity first pre-treatment scan in advanced cases with elevated thyroglobuline. It remains an unanswered question what time is necessary for stunning to recover.
Key words: radioiodine tracer and treatment kinetics, thyroid stunning, pre-treatment planning

Correspondence to:
Dept of Radiation Oncology,
8, Bjalo More St, 1527 Sofia, Bulgaria
Tel: (+35 92) 4344497, fax (+35 92) 467181
e-mail: rad@cserv.mgu.bg

Introduction

It is well known that if ^{131}I diagnostic activity is higher, the visualization of occult cancer foci after thyroidectomy will be better (1–4). Tracer diagnostic activity ranges from 74 to 370 MBq, depending on the stage of differentiated thyroid cancer (3–6). High absorbed dose from β particles of tracer radioiodine (RI) can impair subsequent therapeutic kinetics in thyroid or tumour tissue, thus reducing its efficacy — these effects have been called thyroid stunning. The paradox is evident — the higher the activity for raising the diagnostic precision the greater is the potential reduction in therapeutic effects.

The phenomenon of thyroid stunning has been reported since 1986 (7). Evidence came mainly from visual assessment of whole body scans (8). Recently, Coakley (8) stressed the need for quantitative data.

We detected the phenomenon of high dose stunning in the 1980s after doing some measurements of an atypical RI fractionation regime. Our data proved the low efficacy of such a regime and it has been abandoned. The information remained in my research files.

A few years later in our practice we introduced pre-treatment planning as a quantitative approach to RI treatment (9). The data we have collected from pre-treatment and treatment measurements of RI kinetics could now be employed to elucidate the problem of „the stunning of the thyroid".

The purpose of this paper is to analyze whether low RI activity (on 74 MBq level or less) and high RI activity (over 1000 MBq) are efficacious to modify subsequent RI kinetics in thyroid (tumour) remnant tissue.

Material and methods

Group 1

Thirty patients with pT1-3pNo-1 papillary and follicular thyroid cancer were prepared for radioiodine ablation of thyroid råst after subtotal or nearly total thyroidectomy. A procedure called pre-treatment planning (Monday to Friday tests) was worked out to calculate exact ^{131}I activity needed for successful ablation (9,10). Activity of 0,185 Mbq ^{131}I was used to measure the uptake in thyroid bed ($U_{max.d.}$). We applied the standard uptake method and modified it with measurements up to the 72nd hour. Data were used to calculate the effective half-life ($T_{eff.d}$) of RI. Thyroid bed scan was performed after administration of 74 MBq ^{131}I. Mass of thyroid rest (m_d) was calculated by a scintigraphic method using face and profile scan images (9). All measured tracer activity parameters were applied in pre-treatment planning.

Therapeutic activity of 2200–3700 MBq was administered to each patient three days after tracer administration. The same parameters $U_{max.t}$; $T_{eff.t}$; m_t were measured during RI treatment by equipment that was specially designed for that purpose (9). Absorbed dose in thyroid remnant was calculated according to MIRD concept (11).

By comparing parameters of tracer and therapeutic RI kinetics we are evaluating the influence of 37 MBq tracer activities on therapeutic RI kinetics.

Group 2

In the early 1980s a senior expert coming back from a scientific visit in the USSR tried to announce in practice a „new" fractionated regime with 600–2400 MBq per fraction, given at 3–15 days interval. She empirically believed that such treatment would be better tolerated. The opinion was based on the work of Kisseleva (12). In 4 patients that had indication for radioiodine ablation total RI activity of 2400–4100 Mbq for the whole treatment was divided into two or three unequal fractions.

We measured RI kinetics parameters before and during the whole treatment procedure in those four patients. Tracer and each fraction therapeutic RI kinetics data were compared to examine the benefit of the new regime. Now such a comparison reveals the stunning effect of high first fraction activity.

Results

Group 1

Mean values of tracer (pre-treatment planning) and therapeutic RI kinetics parameters of 30 patients are demonstrated in Table 1.

RI uptake observed in pre-treatment planning procedure of 30 patients varied according to the size of operation and the size of remnant mass. Mean values were 4.0 $\pm$ 2.6% with individual variations ranging from 0.5 to 10.0% (Table 1). Treatment uptake was very dissimilar to the tracer one. In 74% of cases uptake increased up to 3 times, in 16% the value corresponded to the tracer test and only in 10% was it lower than predicted.

Smaller comparative changes were registered in the second parameter of RI kinetics — Effective half-life (T_{eff}). Variations of tracer $T_{eff.d}$ were found between 1.0–6.0 d, with a mean value of 3.1 $\pm$ 1.4 d. The same factor for therapeutic kinetics $T_{eff.t}$ was 2.3 times shorter.

Thyroid remnant mass after nearly total and total thyroidectomy appeared on tracer scan with a mean value of 1.4 $\pm$ 0.6 gr. and variation from 5.7 to 0.4 gr. In 18% of cases we recorded additional tissue on post-treatment scan. We consider this as a strong argument against thyroid stunning after low RI activity, a quantity that has been used in pre-treatment planning. Such extra-tissue also explained the ground tracer uptake value increases during therapeutic application.

Comparative differences of tracer and treatment RI kinetics are not in the direction of thyroid tissue stunning. They elucidate why our pretreatment planning failed in one-third of the patients (9).

Group 2. Fractionated RI treatment regime

Case 1

Female patient with pT3pN0Mo papillary thyroid cancer underwent subtotal thyroidectomy. Thyroid remnant was left on the contra lateral to tumour lobe, considered to be a normal thyroid tissue. Kinetics parameters are shown in table 2. We evaluated three main parameters in pre-treatment procedure: Thyroid remnant mass — 5.7 g, Maximal up-take ($U_{max.d}$) — 11.5% and Effective half-life ($T_{eff\ d}$) was calculated to be 6.5 d. In the whole treatment procedure three RI fractions were subsequently administered: first fraction of 1600 MBq was given at 0 time; second fraction of 600 MBq was administered at 169 hours (on 7th day); third fraction of 1200 MBq was applied at 293 hours — on 12th day. Treatment kinetics parameters for each fraction are given in Table 1. First treatment fraction uptake ($U_{max\ t1}$) was 20.5%. It was much higher than tracer uptake. We calculated the first treatment fraction half-life ($T_{eff\ t1}$) to be 4.6 d by following RI activity in the neck up to 186 hours. Second fraction $U_{max\ t2}$ was 7.5%. It had a lower rate than the previous one. $T_{eff\ t2}$ of the second fraction was 4.6 d — shorter than $T_{eff\ t1.}$ Measurement of the third fraction $U_{max\ t3}$ showed the lowest figure for the whole treatment — 4.0%. Corresponding $T_{eff\ t3}$ had the shortest rate — 1.3 d (Table 1).

The surface under the kinetics curve referred to a gram mass and represents the absorbed dose in Gy (Figure 1). The realized absorbed dose from the first fraction was 584 Gy. Only 22 Gy was delivered to thyroid tissue from second activity of 600 MBq and additionally same 22 Gy was received after third 1200 MBq fraction.

Table 1. Comparison of mean value and range of tracer and therapeutic RI parameters in 30 cases

^{131}I Activity	Uptake(%)	Effective half-life(d)	Thyroid tissue mass (gr.)
Tracer activity (0.185–74MBq)	4.0 $\pm$2.6 (0.5–10.0)	3.1$\pm$ 1.4 (1.0–6.0)	1.4 $\pm$0.6 (5.7–0.4)
Treatment activity (2200–3700 MBQ)	6.0 $\pm$2.6	1.3$\pm$ 0.8	1.8$\pm$ 0.7 (5.7–0.4)
Changes	In 30% – ↑	2.3 times shorter	In 18% — extra tissue

Table 2. Individual ^{131}I kinetics parameters in 5,7 gr. tissue remnant of Case 1. Pre and On-treatment measurements

Activity administered (MBq)	Maximal uptake (%)	Effective half- life (d)	Thyroid rest mass (g)	Dose (Gy)
Pretreatment test after 0.037	11.5	6.5	5.7	—
First treatment — 0 time — 1600	20.5	4.6	—	540
Second treatment — 169 h at 7 th day — 600	7.5	1.3	—	22
Third treatment — 293 h at 12 th day — 1200	4.0	0.6	—	22

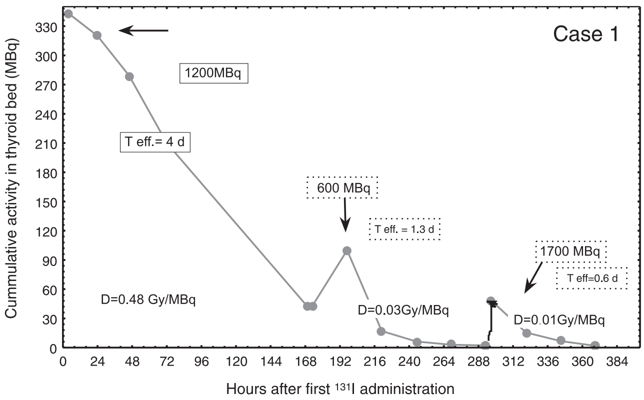

Figure 1. Radioiodine treatment kinetics in thyroid bed during three consecutive RI fractions. Decrease of absorbed dose delivered during the treatment.Thyroid stunning.

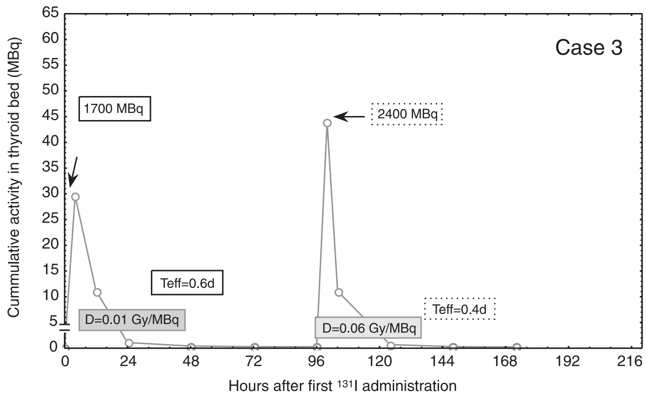

Figure 3. Radioiodine treatment kinetics in thyroid bed during two consecutive RI fractions and decrease of absorbed dose delivered during the treatment. Thyroid stunning.

Learning about the low efficacy of such a regime and observing the process of stunning, in the treatment of the next patient we tried to increase the time — interval between fractions. The second fraction was administered when RI was largely eliminated.

Case 2

RI kinetics of patient P.J. was presented in Figure 2. She was a 67-year-old female with pT3pN1aM0 papillary carcinoma treated by nearly total thyroidectomy.

After 1100 MBq first fraction uptake was 2.6% and T_{efft1} was 1.4 d. The dose delivered was 65 Gy — 0.05 Gy/MBq. After 96 hours when the uptake became low, 1500 Mbq was additionally administered. The second fraction (1550 MBq) uptake was higher than the first one — 3.8%, but T_{efft2} was less than a day — 0.5 d. This resulted in a smaller dose of 0.03 Gy/MBq — 57 Gy, despite the higher RI fraction applied.

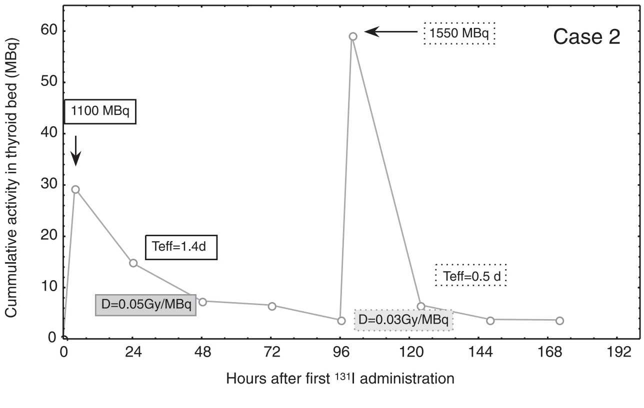

Figure 2. Radioiodine treatment kinetics in thyroid bed during two consecutive RI fractions. Decrease of absorbed dose delivered during the treatment. Thyroid stunning.

Case 3

RI ablation was performed in pT1pN1aM0 female after thyroidectomy (Figure 3; Table 2). Treatment consists of fraction of 1700 MBq and fraction of 2400 MBq delivered in 96 hours time-interval. Mass of the thyroid remnant was 1.7 gr.; $U_{max\,t2}$ was 1.7% and $T_{eff\,t1}$ was very short: 0.6 d. Absorbed dose delivered by first fraction was only 17.8 Gy — 0.01 Gy/MBq. Kinetics parameters of the second fraction was similar to those of the first fraction — $U_{max\,t2}$ — 1,8% and $T_{eff\,t2}$ — 0.4 d. As a result of stunning, the absorbed dose was six-fold lower — 0.06 Gy/MBq and the overall second fraction dose was 20 Gy (Figure 3).

Case 4

Female patient, 47 years old with pT1pN1aMo papillary cancer, was planned for RI ablation after nearly total thyroidectomy. Parameters of tracer kinetics were: thyroid remnant mass was 2.8 g; Tracer uptake $U_{.d}$ was 5.1%; Effective half-life $T_{eff\,d}$ was 5.8 d (Figure 4, Table 2). Total treatment activity of 3100 MBq was divided into two fractions — first fraction of 1700 MBq was administered at 0 time. Second activity of 1400 MBq was administered 72 hours later. Kinetics parameters of the first treatment fraction were: $U_{t1\,-}$ 1.8% and $T_{eff\,t1}$ — 5.4 d. Second fraction parameters of radioiodine kinetics were: U_{t2} — 3.5% and $T_{eff\,t2}$ — 0.5 d. The surface under the kinetics curve represents cumulative activity changes with time. The surface under the second curve was superimposed on the first curve tale. As a result, the doses realized after both fractions were equal — 0.01 Gy/MBq (Figure 4).

Table 3. Individual ^{131}I kinetics parameters in thyroid tissue remnant of Case 2, 3 and 4

Cases	Activity administered (MBq)		Maximal uptake (%)	Effective half- life (d)	Thyroid rest mass (g)	Dose (Gy)
2.	First treatment at 0 time	1100	2.6	1.4	0.7	65
	Second treatment at 96 h	1550	3.8	0.5		77
3.	First treatment at 0 time	1700	1.7	0.6	1.7	17.8
	Second treatment at 96 h	2400	1.8	0.4		20
4.	First treatment at 0 time	1700	1.8	5.5	1.8	18
	Second treatment at 72 h	1400	3.5	0.5		16

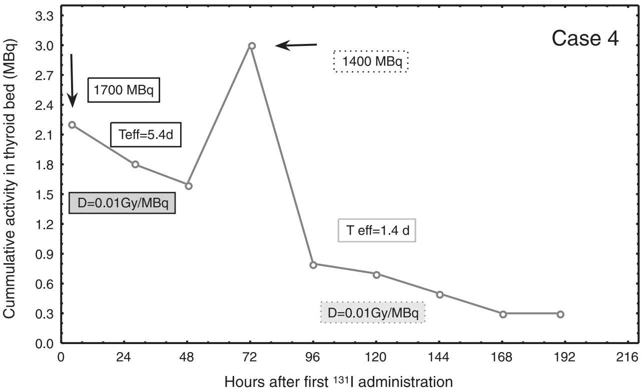

Figure 4. Radioiodine treatment kinetics in thyroid bed during two consecutive RI fractions. Similarity of both absorbed doses delivered during the treatment. No thyroid stunning.

Discussion

1. Effect of low (0,185–74 MBq) tracer activities to subsequent ^{131}I kinetics.

Comparative data collected by pre-treatment planning and subsequent RI administration supported the thesis that low range tracer activity (0.7–74 MBq) does not cause thyroid stunning (3, 5). We registered higher or similar uptake in thyroid bed after application of 1100–3700 Mbq in 90% of cases. Only in 10% was therapeutic uptake lower than the tracer one. In 18% of patients the higher rate of uptake was associated with additional thyroid tissue. Appearance of extra-tissue on post-treatment scan is an often-cited observation (1–6, 9).

Data delivered from our pre-treatment planning of 30 patients support the concept that low activity up to 74 MBq does not produce thyroid (tumour) stunning (9). If the cases are in early tumour stage and have corresponding low thyroglobulin value we believe the tissue visualized is a rest of normal thyroid.

In 80 patients we recorded half-life cut down during the whole long-term treatment process that could take years. Such changes characterize every RI treatment if it takes more than one administration (10). Therefore half-life reduction should not be essentially interpreted as thyroid stunning. It is not a reversible event, but a consequence of gradual thyroid cell damage after regular irradiation.

Comparative data of RI tracer to therapeutic kinetics revealed some of the reasons why pre-treatment planning of exact ^{131}I activity did not fulfill its aim in one-third of cases. They elucidate some discrepancies recorded in dose planning (9).

2. Effect of high 1000–2000 MBq activities to subsequent ^{131}I kinetics

Administration of high activity RI over 1000 MBq does provoke thyroid tissue stunning. Dynamics of RI kinetics parameters of case 1 clearly illustrates some mechanisms of stunning phenomenon. Out of the whole 584 Gy ablative dose 91% was realized from the first 1200 MBq (0.48 Gy/MBq). That absorbed dose considerably blocked second fraction kinetics administered 7 days apart. Afterwards twofold reduction of RI uptake and effective half-life cut down by a factor of 1.4 provided a considerably lower absorbed dose — 0.03 Gy/MBq. It represents only 3.7% of the overall dose. A further three-fold decrease of absorbed dose was calculated for the third RI fraction (0.01 Gy/MBq). This was a consequence of five-fold lower third fraction uptake and seven-fold shorter third fraction half-life.

Data measurements of Case 2 and 3 confirmed our conclusions: subsequent treatment given several days apart resulted in lower absorbed dose by a factor of 1.25 to 1.6. This could be called thyroid stunning.

Although stunning is a common phenomenon we registered great individual differences. RI uptake of next fraction did not always appear with a lower rate. The size of target tissue mass may have some influence on RI kinetics. Case 4 data illustrate that even after 1700 MBq stunning may not take place. We did not registered considerable variations in kinetics of both fractions in. thyroid tissue and therefore the both fraction absorbed dose was similar — 0.01 Gy/MBq.

Our finding could enlighten some of the controversies in the literature on thyroid stunning, called by Park HM an ongoing dilemma' (5).

Some speculations could provide an explanation of that issue. In 1974 Pfannenstiel hypothesized that in the first hours after RI „stroke" absorbed dose delivering occurs by very high dose rate. It destroys thyroid cells and quickly releases large amount of RI (13). We observed a consistent trend of half-life reduction for every subsequent treatment. Half-life value became shorter and shorter after several treatments and fell below one day (8, 9) Therefore every subsequent treatment became less effective. Several authors stressed the fact that initial treatments are the most efficient ones due to half-life cut down (1, 3, 9). Changes in iodine turnover also may give some explanation of these phenomena (1, 14).

Leger et al. tried to described the quintessence of thyroid stunning event as (15):

1. A possible decrease in iodine potential of thyroid cells as well as iodine turnover.

To our understanding this could be summarized and presented quantitatively by decrease in absorbed dose.

1. A reduction of functional thyroid cells that probably is not homogeneous in the thyroid rest.

The evidence of that is lack of thyroid tissue on the subsequent scan. We were not able to prove or disprove that, because we failed to scan thyroid rest in the fractionated regime.

Conclusions for practice

1. Tracer low RI activity below or equal to 74 MBq did not produce stunning of administered therapeutic ^{131}I given 3 days apart.
2. We clearly observed thyroid stunning after 600 and over MBq ^{131}I. In some cases even after high doses delivering a stunning could not take place. Individual RI kinetics appears highly unpredictable.
3. What are the practical implications of such a study? Administration of 1000 MBq or more several days apart was an archaic practice abandoned a long time ago in my country. It only gave us a sad chance to explore quantitatively the changes in RI kinetics.

We consider as rational the Leger proposition to avoid high tracer whole body scan (WBS) before treatment, performing it afterwards (15).

We are proposing in advanced cases with elevated thyroglobulin, treatment should start without pre-treatment WBS. Final staging should be worked out on therapeutic WBS.

For early stage RI ablation is optional. It is indicated in case when a low- tracer test does not provoke stunning. Several solutions are feasible. Such patients do not need urgent RI treatment, so ablation could be postponed until 2–3 months after surgery. Post-treatment WBS is also a rational alternative to avoid high activity pre-treatment tracer test.

What time is necessary for stunning to recover remains an unanswered question. It became of great importance if distant metastases that needed vital treatment were detected in follow up.

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