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ORIGINAL ARTICLE

Thyroid stunning in radioiodine-131 therapy of benign thyroid diseases

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Abstract

Purpose Existence and cause of thyroid stunning was controversially discussed for decades but the underlying mechanism remains unclear. Numerous studies describe thyroid stunning in radioiodine-131 therapy (RIT) of differentiated thyroid carcinoma. However, there are no studies evaluating thyroid stunning in benign thyroid diseases caused by the radioiodine uptake test (RIUT). Therefore, the influence of pre-therapeutic tracer radiation dose on therapeutic iodine-131 uptake was evaluated retrospectively.

Methods A total of 914 RIT patients were included. Exclusion criteria were anti-thyroid drugs, pre- and/or intra-therapeutic effective half-lives (EHL) beyond 8.04 days and externally performed RIUT or 24 h RIUT. All patients received RIUT 1 week before RIT. Thyroid volume was estimated via ultrasound. Tracer radiation dose to the thyroid was calculated retrospectively. The dependence of changes in the pre-therapeutic to the therapeutic extrapolated-maximum-^{131}I-uptake (EMU) from the dose in RIUT was evaluated statistically.

Results EMU in RIUT ranged from 0.10 to 0.82 (median: 0.35) and EMU in RIT ranged from 0.10 to 0.74 (median: 0.33). Averaged over the whole cohort the therapeutic EMU decreased significantly (2.3% per Gray intra-thyroidal tracer radiation dose). A disease-specific evaluation showed dose-dependent thyroid stunning from 1.2% per Gray in solitary toxic nodules ($n = 327$) to 21% per Gray in goiters ($n = 135$) which was significant for the subgroups of disseminated autonomies ($n = 114$), multifocal autonomies ($n = 178$) and goiters ($p < 0.05$) but not for Graves' diseases ($n = 160$) and solitary toxic nodules ($p > 0.05$).

Conclusions The presented data indicate for the first time a significant dependence of pre-therapeutic radiation dose on thyroid stunning in goiter and disseminated and multifocal autonomy. To achieve the desired intra-thyroidal radiation dose, RIT activity should be adapted depending on the dose in RIUT.

Keywords Radioiodine therapy · Radioiodine uptake test · Thyroid stunning · Benign thyroid disease · Thyroid

Introduction

For decades, radioiodine-131 therapy (RIT) has been a worldwide well-established and accepted treatment for patients with benign and malignant thyroid diseases [1, 2]. The aim of RIT is to ablate thyroid tissue by oral or intravenous administration of iodine-131. Iodine-131 is a radioisotope known to accumulate in thyroid cells due to expression of the sodium/iodine symporter (Na^+/I^--Symporter) [3], and to destroy thyroid tissue by emitting β-radiation with a maximum energy of up to 600 keV (mean energy: 190 keV) and a physical half-life of 8.04 days. The mean range of iodine-131 electrons in thyroid tissue is 0.44 mm (maximum range: 2.2 mm) [4].

Thyroid stunning was first reported in 1951 by Rawson et al. [5] and is defined as a reduced therapeutic iodine-131 uptake in the thyroid after pre-therapeutic administration of iodine-131 for diagnostic purposes. The existence and cause of thyroid stunning have been controversially discussed for

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decades but the fundamental physiology of this phenomenon is still not elucidated to date [6–14]. There are numerous studies describing thyroid stunning for therapeutic activities in differentiated thyroid carcinoma (DTC) in vivo [15–17] and in vitro [18–22]. However, there are also several studies evaluating thyroid stunning for low diagnostic activities of iodine-131 (40 or 74 MBq) in patients with DTC [23–25]. As possible explanation, the β-radiation of iodine-131 may lead to a decreased number of functioning thyroid cells as well as a reduced capability of viable thyroid cells to store iodine-131 [6, 14]. However, there are few publications concerning thyroid stunning in benign thyroid diseases due to considerably lower administered activities of iodine-131. These studies address thyroid stunning in fractionated administrations of therapeutic iodine-131 activities [26–28]. Currently, there is no published study referring to thyroid stunning in benign thyroid diseases caused by the iodine-131 radiation associated with the pre-therapeutic radioiodine uptake test (RIUT).

In this study the influence of the target dose (Gy) caused by the pre-therapeutically administered RIUT activity on therapeutic thyroidal iodine-131 uptake is evaluated statistically. The results may be used to develop indication-specific, dose-dependent correction factors leading to methodical changes of the RIUT, to account for stunning-related changes in uptake and improve the effectiveness of RIT in benign thyroid diseases.

Materials and methods

A retrospective single-center study of 3425 patients with benign thyroid diseases (goiter, Graves' disease, solitary toxic nodule, disseminated and multifocal autonomy) who were treated with RIT between 1999 and 2014 was performed. The study was approved by the local ethics committee. As anti-thyroid drugs are known to influence bio-kinetics and bio-distribution of iodine-131 [29, 30], patients who received anti-thyroid drugs up to 7 days prior to and during RIUT and/or RIT were excluded from the study ($n = 1983$). Other exclusion criteria were pre- and/or therapeutic calculated effective half-life (EHL) beyond the physical half-life of 8.04 days or below 2 days, which are apparently related to errors in measurement, all cases where EHL had to be estimated due to 24-h uptake test ($n = 518$) and externally performed RIUT ($n = 10$). Finally, 914 patients (648 female; median age: 65 years, range: 21–95 years) were included. In all, 160 had Graves' disease, 327 solitary toxic nodules, 114 disseminated autonomies, 135 goiters and 178 multifocal autonomies. All patients received RIUT 1 week prior to inpatient RIT to determine individual extrapolated-maximum-^{131}I-uptake (EMU) and EHL which are necessary to calculate the required RIT activity to deliver the prescribed therapeutic dose to the target volume [29]. For each patient two measurements of the intra-thyroidal iodine-131 uptake (24 or 48 and 72, 96 or 120 h after administration) were performed with a calibrated gamma scintillation probe (Thyreomat, SIEMENS). Measurements were performed with the patient sitting in front of the probe for 60 s at a reproducible distance of 30 cm. The probe was collimated to avoid irradiation from extra-thyroidal organs. EHL was calculated using a mono-exponential curve fit to the measured non-decay-corrected time-activity data. Individual thyroidal EMU was calculated by extrapolation of the fitted curve to the time of administration. From these data the pre-therapeutic applied radiation dose (Gy) in the target volume was calculated retrospectively for all patients using the Marinelli equation [31]. RIUT and RIT were performed according to the guidelines of the German Society of Nuclear Medicine (DGN) in their current versions [29, 30].

Target doses were 250 Gy for Graves' disease, 400 Gy for the volume of solitary toxic nodules and 150 Gy for goiter and multifocal and disseminated autonomy [29, 30]. Thyroid and nodule volume was determined via ultrasound using the simplified ellipsoid formula (length × width × height/2). Ultrasonography was performed by different resident physicians under supervision of experienced senior nuclear medicine physicians. However, ultrasonography is a user-dependent technique with known interobserver variability leading to a corresponding variability of the dose. For RIUT, patients received iodine-131 in capsules containing a median activity of 2.8 MBq (range: 1.4–6.8 MBq). The calculated radiation doses are presented in Table 1. Subsequently, 7 days after administration of RIUT the patients underwent RIT with a median oral administration of 716 MBq (range: 152–1542 MBq). All patients were hospitalized on the nuclear medicine therapy ward for at least 48 h and were discharged after falling below the regulatory limit of 250 MBq for residual activity in the body [30]. During RIT the remaining activity in the thyroid was determined twice a day using a calibrated gamma scintillation probe (Thyreomat, SIEMENS). Patients were measured for 60 s at a distance of 6 m to the probe to avoid dead time effects. To avoid irradiation from extra-thyroidal organs the body of the standing patient was shielded by a mobile lead shield. From these values the bio-kinetic of iodine-131 (EHL and EMU) and the absorbed dose to the target volume were calculated individually without considering the contribution of the emitted gamma-rays [30, 31]. As the tracer-to-therapy change in EMU presumably reflects radiation-induced thyroid stunning, the dependence of the RIUT dose to these values was evaluated statistically.

Statistical analysis was performed using Pearson's linear regression calculated with the designated statistics software

Table 1 Dosimetric data of the study collective

	Study cohort	Age [years]	Administered activity RIUT (MBq)			EMU in RIUT			Target dose caused by RIUT (Gy)			EMU in RIT			*P*	Radiation-induced stunning (%/Gy)
	n	Median	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max		
All patients	914	65	2.84	1.40	6.84	0.35	0.10	0.82	0.64	0.03	10.5	0.33	0.10	0.74	<0.05	−2.3
Graves' disease	160	52	2.89	1.60	4.85	0.44	0.20	0.76	1.51	0.31	10.5	0.41	0.10	0.74	>0.05	−1.6
Solitary toxic nodules	327	64	2.82	1.42	4.95	0.32	0.15	0.62	1.49	0.14	10.0	0.31	0.14	0.66	>0.05	−1.2
Multifocal autonomy	178	73	2.37	1.40	4.30	0.36	0.17	0.82	0.54	0.11	2.46	0.34	0.17	0.69	<0.05	−8.2
Goiter	135	70	2.95	1.46	6.84	0.32	0.10	0.70	0.35	0.03	1.96	0.31	0.16	0.61	<0.05	−21.3
Disseminated autonomy	114	65	2.83	1.50	6.79	0.34	0.11	0.69	0.59	0.08	3.88	0.34	0.19	0.60	<0.05	−4.4

BiAS for Windows (version 10.12, 05/2014). For statistical analysis the data were transformed logarithmically to approximate a normal distribution. For a better visualization the non-transformed data are displayed (Fig. 1a–f). For comparison of EMU in RIUT to RIT, the Wilcoxon matched pairs test for dependent samples was used. Statistical significance was given with p values < 0.05.

Results

Pre-therapeutically absorbed doses to the thyroid ranged from 0.03 Gy to 10.5 Gy (median 0.64 Gy; median target volume 20.2 ml (range: 1–477 ml)). Pre-therapeutically calculated EMU ranged from 0.10 to 0.82 (median: 0.35) and therapeutic EMU ranged from 0.10 to 0.74 (median: 0.33) (Table 1 and Fig. 1a). This decrease was significant for the whole cohort ($p < 0.05$). The indication-specific evaluation showed a significant EMU decrease from RIUT to RIT ($p < 0.05$) in solitary toxic nodules (median: 0.32 to 0.31), multifocal autonomies (0.36 to 0.34) and Graves' diseases (0.44 to 0.41) but not in goiter (0.32 to 0.31) and disseminated autonomies (0.34 to 0.34) ($p > 0.05$). To evaluate a potential thyroid stunning caused by the pre-therapeutically absorbed dose, the therapeutic EMU was related to the pre-therapeutic EMU. Without the influence of thyroid stunning this ratio should be one. If a radiation-induced thyroid stunning occurs, this ratio is expected to decrease below one. The calculated ratio of intra- to pre-therapeutic EMU ranged from 0.45 to 2.55 (median: 0.96) for the whole cohort.

Related to the tracer dose in RIUT and averaged over the whole cohort the therapeutic EMU decreased 2.3% per Gray pre-therapeutic absorbed dose. In the graphical analysis a declining trend is visible (Fig. 1a). For the logarithmic transformed values, Pearson's linear regression showed a significant reduction of therapeutic EMU depending on pre-therapeutically absorbed dose ($p < 0.05$). An additionally performed analysis of the data with an exclusion of outliers beyond 5 Gy and below 0.2 Gy did not change the determined significance. In all subgroups a dose-dependent thyroid stunning could be visualized graphically (Fig. 1b–f). Thyroid stunning ranged from 1.2% per Gray pre-therapeutic absorbed dose in the subgroup of patients with solitary toxic nodules ($n = 327$) (Fig. 1b) to 21% per Gray in the subgroup of patients with goiter ($n = 135$) (Fig. 1c). The subgroup of patients with Graves' disease ($n = 160$) showed a dose-related thyroid stunning of 1.6% per Gray (Fig. 1d) and the radiation-induced thyroid stunning in the subgroup of patients with disseminated autonomy ($n = 114$) was 4.4% per Gray (Fig. 1e). Although the whole study cohort ($n = 914$) showed a significant correlation ($p < 0.05$) between thyroid stunning

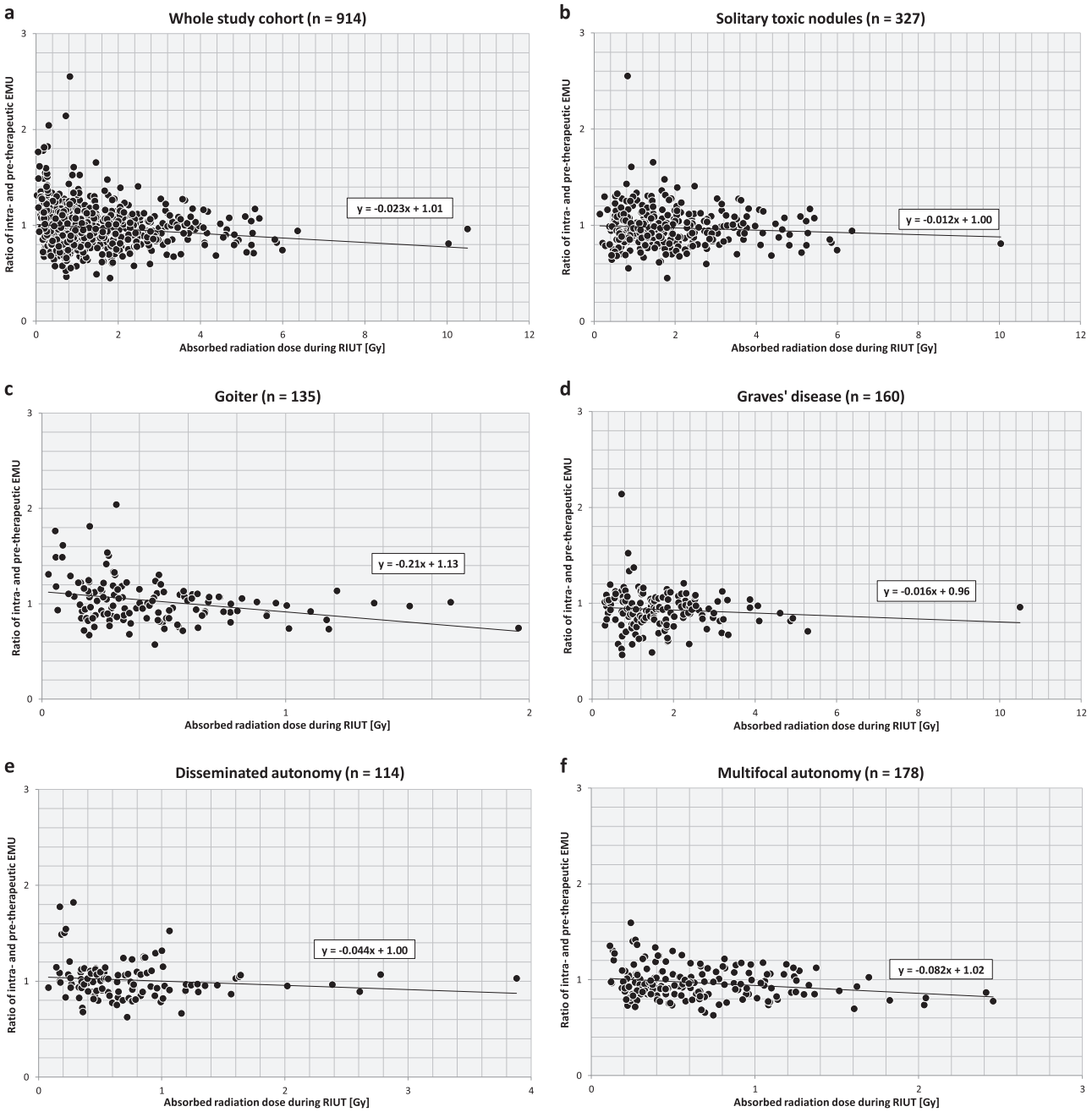

Fig. 1 Thyroid stunning in relation to absorbed radiation dose in RIUT of the whole study cohort **a** and the different subgroups **b–f**

and the radiation dose administered in RIUT, the evaluation of the disease-specific subgroups did not show this significant correlation for the subgroups of Graves' disease and solitary toxic nodules ($p > 0.05$) (Table 1). However, the patients with multifocal autonomy (8.2% per Gray) (Fig. 1f), disseminated autonomy (4.4% per Gray) (Fig. 1e) and goiter (21.3% per Gray) (Fig. 1c) showed a significant correlation between thyroid stunning and the radiation dose administered in RIUT ($p < 0.05$). An additional analysis of the data with exclusion of outliers did not change the statistical significance. An analysis of the effect of other possible factors of influence such as age, thyroid volume, RIUT activity, RIT activity or RIT dose did not show significant thyroid stunning.

Discussion

Thyroid stunning is explained by a decrease of functional thyroid cells due to cellular damage caused by radiation of

iodine-131 which results in a reduction of the number of cells with intact sodium/iodine symporter (NIS) and iodine uptake [14, 15, 29, 32]. Brenner [6] concluded that thyroid stunning may result either from a decrease of the number of functional cells caused by cell death due to irradiation of iodine-131 or from a reduced ability of viable thyroid cells to trap iodine-131 [6]. The evaluation of Park et al. [33] showed a reduced ability of thyroid cells to trap iodine-131 as a direct consequence of β-irradiation leading to a defective cellular iodine uptake without apoptosis of cells.

Stunning in malignant thyroid diseases

There are numerous studies describing the existence of thyroid stunning in DTC and administration of high therapeutic activities of iodine-131 in vivo [8, 15, 17, 23, 25, 32, 34–39]. Otherwise, there are also numerous studies demonstrating the opposite. Bajén et al. [40], for example, evaluated 378 patients with DTC who received 185 MBq of iodine-131 for diagnostic purposes prior to a RIT with 4 GBq. The authors compared pre- to therapeutic uptake in thyroid remnants and concluded that stunning does not exist for 185 MBq of iodine-131 [40]. Cholewinski et al. [10] as well did not find any evidence of thyroid stunning in a group of 122 patients with DTC after administration of 185 MBq of iodine-131 for diagnostic purposes prior to a RIT with 5550 MBq of iodine-131. McDougall [41] concluded that 74 MBq of iodine-131 for diagnostic purposes prior to RIT with 1100 to 7400 MBq did not cause any stunning in a cohort of 147 patients with DTC. In 50 patients with DTC, Silberstein [42] compared 14.8 MBq of iodine-123 to 74 MBq of iodine-131 for diagnostic purposes prior to a RIT with 3.7 GBq and did not find any significant difference between the two groups concerning successful ablation.

The limitation of all the foregoing studies is that thyroid stunning was only related to the administered activity. But, especially in DTC the stored activity is only a small fraction of the administered activity. Moreover, the quality and complexity of the surgical intervention varies and leads to a wide range of the mass of residual thyroid tissue. Therefore, the significance and inter-comparability of the foregoing studies are limited. Assuming that thyroid stunning, if it occurs, results from iodine-131 irradiation, the most reliable way of evaluating stunning is in terms of the intra-thyroidal absorbed dose (Gy). This is indeed difficult in cases of DTC especially in light of missing or unreliable estimates of the mass of remaining thyroid tissue. Estimating a remnant thyroid volume of 1 to 10 ml, an iodine-131 uptake in this volume of 1–5% of the administered activity and an EHL of 0.5 to 3 days in the thyroid remnants, the resulting radiation doses for administered diagnostic activities of iodine-131 between 37 and 185 MBq range from 100 mGy to 100 Gy (calculated using the Marinelli equation [31]). The disparity among the results of the foregoing studies with respect to thyroid stunning is therefore not surprising. Moreover, the small number of patients in many of the foregoing studies ($n = 6$, Lassmann et al. [15], $n = 12$, Yeung et al. [37], $n = 26$, Hilditch et al. [34], $n = 35$, Wu et al. [36], $n = 40$, Park et al. [35], $n = 51$, Leger et al. [32], $n = 70$, Yin et al. [25]) compromises the significance of the respective results and their inter-comparability. A further point of controversial discussion is the time between diagnostic administration of iodine-131 and RIT [43]. This time varied considerably among these studies.

Stunning in in-vitro studies

There are several in-vitro studies recognizing the radiation dose with remarkable results. Meller et al. [20] incubated FRTL-5 cells with iodine-131 and evaluated changes of cell viability. The authors examined the time-dependent course of iodine-131 uptake and found that uptake decreased significantly with time [20]. Nordén et al. [19] detected thyroid stunning in porcine thyroid cells for an iodine-131 irradiation of 7.5 Gy and explained the effect by dose-related downregulation of NIS expression. Postgård et al. [18] also incubated porcine thyroid cells and observed thyroid stunning depending on absorbed radiation dose in excess of as little as 3 Gy. Lundh et al. [21] examined primary cultured porcine thyroid cells and found a significant inhibition of iodine-131 uptake even at radiation doses as low as 0.15 Gy. However, it has to be considered that the effects of radiation on cell viability and cell uptake are presumably distinct phenomena, with stunning-related reduction of radioiodine uptake representing an effect on viable cells. The reduction of radioiodine uptake due to reduced cell viability is a different, non-specific effect.

Stunning in in-vivo studies concerning absorbed radiation dose

The few in-vivo studies with an emphasis on the absorbed radiation dose found thyroid stunning. Jeevanram et al. [44] reported a reduction in uptake proportional to a calculated radiation dose of 31–73 Gy. Medvedec [45] showed similar results and found significant thyroid stunning for absorbed radiation doses above 10 Gy [45]. Again, these evaluations were only performed in patients with DTC. However, translation of these results to benign thyroid disease is questionable, in part, because of the lack of reliable pre-therapeutic and therapeutic dosimetry for the former. Furthermore, patients with DTC are generally hypothyroid (thyroid-stimulating hormone (TSH) > 30 mU/l), while patients with benign thyroid diseases are normally in a subclinical or overt hyperthyroid state.

Stunning in benign thyroid diseases

There are only few publications concerning thyroid stunning in benign thyroid diseases due to considerably lower administered iodine-131 activities. These studies examined thyroid stunning in fractionated administrations of therapeutic iodine-131 activities. Krohn et al. [26] examined 200 patients with benign thyroid diseases subdivided into two groups who received two consecutive administrations of therapeutic iodine-131 (group 1: second administration 48 h after the first administration; group 2: second administration 96 h after the first administration) due to unexpectedly low therapeutic radioiodine uptake or EHL, respectively, and found a significant dose-related uptake reduction in the second administration compared to the uptake in the first administration. Sabri et al. [27] evaluated 171 patients who received a second therapeutic activity 4 days after the first administration. Patients showed significant thyroid stunning at the second administration which was dependent on the absorbed radiation dose in the first administration [27]. Currently, there is no study evaluating a possible thyroid stunning in benign thyroid diseases caused by the radiation dose of the iodine-131 administered in the pre-therapeutically performed RIUT. Depending on EMU, EHL and thyroid volume, the radiation dose caused by a pre-therapeutic standard dose of 2–4 MBq reaches several Gray. Especially elderly patients with metabolic and accompanying disease-related extended EHL of iodine-131 or patients with Graves' disease with increased iodine-131 uptake receive considerably increased radiation doses due to standard RIUT activities compared, for example, to patients with goiter with generally lower iodine-131 uptake or to younger patients with normally shorter EHL. Following the in-vitro reported results of Postgård et al. [18] and Lundh et al. [22], a radiation-induced thyroid stunning would therefore not be unexpected in these patients.

Comparison of thyroid stunning in different benign thyroid diseases

The presented data show a significant radiation-induced thyroid stunning for patients with goiter and disseminated and multifocal autonomy, caused by relatively low radiation doses of 0.03–3.88 Gy to the thyroid obtained from RIUT (Table 1). A possible explanation of why a significant correlation is only present in patients with goiter and disseminated and multifocal autonomy and is absent in the other subgroups is that there is a large target volume in these diseases that leads to a higher influence of the so-called cross-fire effect than in smaller volumes. Another possible explanation is that the thyroid cells are previously damaged in goiters due to the lack of iodine lipids caused by decreased iodine supply and therefore in particular sensitive even for lower radiation exposure. A further explanation for thyroid stunning only being present in goiter and disseminated and multifocal autonomy is a release of thyroid hormones to the blood circulation due to radiation-induced disposing of the cells. The TSH level responds to an altered hormone level in a time interval of 5 to 7 days, which is in the range of the temporal lag between RIUT and RIT. The thus reduced TSH level decreases the iodine uptake in the cells. In hyperthyroid diseases such as Graves' disease and solitary toxic nodules a reduced TSH is irrelevant because the intra-thyroidal iodine uptake is independent of the TSH level [46]. There are investigations which postulated that thyroid stunning may not be induced by the pre-therapeutic but instead by the therapeutic activity in RIT itself [24, 34]. This could be an additional explanation for reduced therapeutic uptake but could not be confirmed by the presented data.

A possible arithmetical correction of the thyroid stunning could be the administration of disease-adapted RIUT activities to avoid disproportionate radiation doses to the thyroid prior to RIT. Unfortunately, iodine bio-kinetics are unknown prior to the RIUT and can therefore not be taken into account that easily. In contrast, an adaption of the therapeutic iodine-131 activity depending on the obtained iodine-131 radiation dose to the thyroid during RIUT should be the method of choice. Based on the results of this study, an indication-specific correction of radiation-induced thyroid stunning seems to be advantageous. Correction factors could be used to correct the calculated EMU depending on pre-therapeutic absorbed dose. This may lead to a stunning corrected RIT activity. Using these corrections, the standard deviation of the values should be significantly reduced. Moreover, prediction of therapeutic uptake could be improved for the individual patient that directly leads to an improvement of RIT.

Discussion of alternatives

A potentially meaningful alternative to a RIUT with iodine-131 could be the pre-therapeutic use of other iodine isotopes such as iodine-123 or iodine-124 as described in several studies [32–34, 40, 47–49] due to their equal physiological bio-kinetics compared to iodine-131. As a gamma emitter, iodine-123 causes nearly no radiation damage to thyroid cells and to other organs, and thyroid stunning should not occur. However, there are several disadvantages of iodine-123 such as a lower sensitivity [33], higher costs [32], a relatively short half-life of only 13 h [40] and the fact that it is not available in all countries of the world. Moreover, it has to be considered that there are studies that found thyroid stunning even for iodine-123. The authors explained the phenomenon by the emission of Auger electrons [34] but this is likely not a realistic explanation. Auger electrons

typically have such low energies and short ranges that once localized within the thyroid follicles, they would not significantly irradiate follicular or other functioning thyroid cells. To clarify the possible advantages of iodine-123 in the RIUT for RIT of benign thyroid diseases, further studies in larger cohorts of patients have to be performed. As a further alternative, some authors discuss the use of iodine-124 in pre-therapeutic diagnostic [9, 23, 49] which, however, provides similar disadvantages as iodine-123 with the additional disadvantage being a positron emitter and therefore leading to methodical problems. Moreover, the decay schemes of iodine-124 and iodine-131 show the energy emitted per decay in the forms of beta-particles (positrons and electrons, respectively) and are nearly identical, meaning that the dose to thyroid tissue per unit administered activity would likewise be nearly identical. The use of technetium-99m (^{99m}Tc) for RIUT was likewise discussed by some authors [9, 22, 50, 51]. $^{99m}TcO_4^-$ is a gamma emitter that accumulates in the thyroid follicles due to its similar ion radius to iodine. However, the use of ^{99m}Tc for RIUT is critical due to its lower, and not in all cases proportional, intra-thyroidal uptake compared to the iodine isotopes [9]. Moreover, Lundh et al. [22] found stunning effects even for ^{99m}Tc. The authors explained this effect by a downregulation of NIS expression and low energy Auger electrons [22].

Conclusion

The presented data suggest a significant dependence of thyroid stunning on pre-therapeutically absorbed dose in patients with goiter and disseminated and multifocal autonomy. To achieve the desired therapeutic radiation dose to the thyroid, administered RIT activity should be adapted depending on the dose in RIUT. The results from this study may help to deepen our understanding of thyroid stunning to consider this effect by disease-specific correction factors and thus may enhance effectiveness of RIT in benign thyroid diseases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

References

1. R. Lorenz, A. Buck, C. Reiners, In-patient nuclear medicine therapy in Germany from 2010 to 2012 – analysis of structured quality reports. Nuklearmedizin **54**, 61–68 (2015)
2. M. Freesmeyer, F. Gühne, C. Kühnel, T. Opfermann, T. Winkens, A. Werner Determination of effective half-life of ^{131}I in patients with differentiated thyroid carcinoma: comparison of cystatin C and creatinine-based estimation of renal function. Endocrine (2018). https://doi.org/10.1007/s12020-018-1800-4
3. O. Dohan, A. de la Vieja, V. Paroder, C. Riedel, M. Artani, M. Reed, C.S. Ginter, N. Carrasco, The sodium/iodine symporter (NIS): characterization, regulation, and medical significance. Endocr. Rev. **24**, 48–77 (2003)
4. E. Bell, F. Grünwald. *Radiojodtherapie bei Benignen und Malignen Schilddrüsenerkrankungen* (Springer-Verlag Berlin Heidelberg, New York, 1999).
5. R.W. Rawson, J.E. Rall, W. Peacock, Limitations in the treatment of cancer of the thyroid with radioactive iodine. Trans. Assoc. Am. Physicians **64**, 179–198 (1951)
6. W. Brenner, Is thyroid stunning a real phenomenon or just fiction? J. Nucl. Med. **43**, 835–836 (2002)
7. A.J. Coakley, Thyroid stunning. Eur. J. Nucl. Med. **25**, 203–204 (1998)
8. H.Q. Dam, S.M. Kim, H.C. Lin, C.M. Intenzo, ^{131}I therapeutic efficacy is not influenced by stunning after diagnostic whole-body scanning. Radiology **232**, 527–533 (2004)
9. I.R. McDougall, A. Iagaru, Thyroid stunning: fact or fiction? Semin. Nucl. Med. **41**, 105–112 (2011)
10. S.P. Cholewinski, K.S. Yoo, P.S. Klieger, R.E. O'Mara, Absence of thyroid stunning after diagnostic whole-body scanning with 185 MBq ^{131}I. J. Nucl. Med. **41**, 1198–1202 (2000)
11. M. Filesi, M. Colandrea, T. Montesano, R. D'Apollo, G. Ronga, Thyroid stunning in clinical practice: is it a real problem? Minerva Endocrinol. **34**, 29–36 (2009)
12. J.M. Woolfenden, Thyroid stunning revisited. J. Nucl. Med. **47**, 1403–1404 (2006)
13. J.E. Kalinyak, I.R. McDougall, Whole-body scanning with radionuclides of iodine, and the controversy of "thyroid stunning". Nucl. Med. Commun. **25**, 883–889 (2004)
14. S. Walrand, M. Hesse, F. Jamar, Statistical and radiobiological analysis of the so-called thyroid stunning. EJNMMI Res. **5**, 67 (2015)
15. M. Lassmann, M. Luster, H. Hänscheid, C. Reiners, Impact of ^{131}I diagnostic activities on the biokinetics of thyroid remnants. J. Nucl. Med. **45**, 619–625 (2004)
16. L.F. Morris, A.D. Waxman, G.D. Braunstein, Thyroid stunning. Thyroid **13**, 333–340 (2003).
17. J.P. Muratet, A. Daver, J.F. Minier, F. Larra, Influence of scanning doses of iodine-131 on subsequent first ablative treatment outcome in patients operated on for differentiated thyroid carcinoma. J. Nucl. Med. **39**, 1546–1550 (1998)
18. P. Postgård, J. Himmelman, U. Lindencrona, N. Bhogal, D. Wiberg, G. Berg, S. Jansson, E. Nyström, E. Forssell-Aronsson, M. Nilsson, Stunning of iodide transport by ^{131}I irradiation in cultured thyroid epithelial cells. J. Nucl. Med. **43**, 828–834 (2002)
19. M.M. Nordén, F. Larsson, S. Tedelind, T. Carlsson, C. Lundh, E. Forssell-Aronsson, M. Nilsson, Down-regulation of the sodium/iodide symporter explains ^{131}I-induced thyroid stunning. Cancer Res. **67**, 7512–7517 (2007)

20. B. Meller, E. Gaspas, W. Deisting, B. Czarnocka, M. Baehre, B.E. Wenzel, Decreased radioiodine uptake of FRTL-5 cells after ^{131}I incubation in vitro: molecular biological investigations indicate a cell cycle-dependent pathway. Eur. J. Nucl. Med. Mol. Imaging **35**, 1204–1212 (2008)
21. C. Lundh, M.M. Nordén, M. Nilsson, E. Forssell-Aronsson, Reduced iodine transport (stunning) and DNA synthesis in thyrocytes exposed to low absorbed doses from ^{131}I in vitro. J. Nucl. Med. **48**, 481–486 (2007)
22. C. Lundh, U. Lindencrona, P. Postgård, T. Carlsson, M. Nilsson, E. Forssell-Aronsson, Radiation-induced thyroid stunning: differential effects of ^{123}I, ^{131}I, ^{99m}Tc and ^{211}At on iodide transport and NIS mRNA expression in cultured thyroid cells. J. Nucl. Med. **50**, 1161–1167 (2009)
23. F.A. Verburg, R.B. Verkooijen, M.P. Stokkel, J.W. van Isselt, The success of ^{131}I ablation in thyroid cancer patients is significantly reduced after a diagnostic activity of 40 MBq ^{131}I. Nuklearmedizin **48**, 138–142 (2009)
24. J.C. Sisson, A.M. Avram, S.A. Lawson, P.G. Gauger, G.M. Doherty, The so-called stunning of thyroid tissue. J. Nucl. Med. **47**, 1406–1412 (2006)
25. Y. Yin, Q. Mao, S. Chen, N. Li, X. Li, Y. Li, A quantitative study about thyroid stunning after diagnostic whole-body scanning with 74 MBq ^{131}I in patients with differentiated thyroid carcinoma. Q. J. Nucl. Med. Mol. Imaging **59**, 455–461 (2015)
26. T. Krohn, P.T. Meyer, C. Ocklenburg, D. Knollmann, B. Nowak, W.M. Schaefer, Stunning in radioiodine therapy of benign thyroid disease. Quantification and therapeutic relevance. Nuklearmedizin **47**, 248–254 (2008)
27. O. Sabri, M. Zimny, M. Schreckenberger, A. Meyer-Oelmann, P. Reinartz, U. Buell, Does thyroid stunning exist? A model with benign thyroid disease. Eur. J. Nucl. Med. **27**, 1591–1597 (2000)
28. E. Wudel, K. Koppenhagen, The stunned thyroid? Veränderte Radiojodkinetik der NACH-THERAPIE bei benignen Schilddrüsenerkrankungen. Nuklearmedizin **34**, A166 (1995). (Abstract)
29. M. Dietlein, J. Dressler, W. Eschner, M. Lassmann, B. Leisner, C. Reiners, H. Schicha, Procedure guideline for radioiodine test (version 3). Nuklearmedizin **46**, 198–202 (2007)
30. M. Dietlein, J. Dressler, F. Grünwald, B. Leisner, E. Moser, C. Reiners, H. Schicha, P. Schneider, O. Schober, Guideline for radioiodine therapy for benign thyroid disease (version 4). Nuklearmedizin **46**, 220–223 (2007)
31. L.D. Marinelli, Dosage determination in the use of radioactive isotopes. J. Clin. Invest. **28**, 1271–1280 (1949)
32. F.A. Leger, M. Izembart, F. Dagousset, L. Barritault, G. Baillet, A. Chevalier, J. Clerc, Decreased uptake of therapeutic doses of iodine-131 after 185-MBq iodine-131 diagnostic imaging for thyroid remnants in differentiated thyroid carcinoma. Eur. J. Nucl. Med. **25**, 242–246 (1998)
33. H.M. Park, Y.H. Park, X.H. Zhou, Detection of thyroid remnant/metastasis without stunning: an ongoing dilemma. Thyroid **7**, 277–280 (1997)
34. T.E. Hilditch, M.F. Dempsey, A.A. Bolster, R.M. McMenemin, N.S. Reed, Self-stunning in thyroid ablation: evidence from comparative studies of diagnostic ^{131}I and ^{123}I. Eur. J. Nucl. Med. **29**, 783–788 (2002)
35. H.M. Park, O.W. Perkins, J.W. Edmondson, R.B. Schnute, A. Manatunga, Influence of diagnostic radioiodine on the uptake of ablative dose of iodine-131. Thyroid **4**, 49–54 (1994)
36. H.S. Wu, H.H. Hseu, W.Y. Lin, S.J. Wang, Y.C. Liu, Decreased uptake after fractionated ablative doses of iodine-131. Eur. J. Nucl. Med. Mol. Imaging **32**, 167–173 (2005)
37. H.W. Yeung, J.L. Humm, S.M. Larson, Radioiodine uptake in thyroid remnants during therapy after tracer dosimetry. J. Nucl. Med. **41**, 1082–1085 (2000)
38. J.C. Reynolds, J. Robbins, The changing role of radioiodine in the management of differentiated thyroid cancer. Semin. Nucl. Med. **27**, 153–164 (1997)
39. E.C.S.C. Etchebehere, A.O. Santor, P.S. Matos, L.V.M. Assumpção, Lima MCVL, M.C.L. Lima, L.S. Ward, Is thyroid stunning clinically relevant? A retrospective analysis of 208 patients. Arq. Bras. Endocrinol. Metab. **58**, 292–300 (2014)
40. T. Bajén, S. Mañé, A. Muñoz, J.R. García, Effect of a diagnostic dose of 185 MBq ^{131}I on postsurgical thyroid remnants. J. Nucl. Med. **41**, 2038–2042 (2000)
41. I.R. McDougall, 74 MBq radioiodine ^{131}I does not prevent uptake of therapeutic doses of ^{131}I (i.e. it does not cause stunning) in differentiated thyroid cancer. Nucl. Med. Commun. **18**, 505–512 (1997)
42. E.B. Silberstein, Comparison of outcomes after (123)I versus (131)I pre-ablation imaging before radioiodine ablation in differentiated thyroid carcinoma. J. Nucl. Med. **48**, 1043–1046 (2007)
43. N.A. Damle, C. Bal, S. Ballal, Stunning in post (131)I therapy scans after low-dose (131)I diagnostic whole body scans with differentiated thyroid cancer in the Indian patient population: critical importance of interval between the two scans. Indian J. Endocrinol. Metab. **16**, 477–478 (2012)
44. R.K. Jeevanram, D.H. Shah, S.M. Sharma, R.D. Ganatra, Influence of initial large dose on subsequent uptake of therapeutic radioiodine in thyroid cancer patients. Int. J. Rad. Appl. Instrum. B. **13**, 277–279 (1986)
45. M. Medvedec, Thyroid stunning in vivo and in vitro. Nucl. Med. Commun. **26**, 731–735 (2005)
46. J. Halstenberg, W.T. Kranert, H. Korkusuz, A. Mayer, H. Ackermann, F. Grünwald, C. Happel, Influence of glucocorticoid therapy on intratherapeutic biodistribution of ^{131}I radioiodine therapy in Graves' disease. Nuklearmedizin **57**, 43–49 (2018)
47. M.K. Chen, M. Yasrebi, J. Samii, L.H. Staib, I. Doddamane, D.W. Cheng, The utility of I-123 pretherapy scan in I-131 radioiodine therapy for thyroid cancer. Thyroid **22**, 304–309 (2012)
48. A. Siddiqi, R.R. Foley, K.E. Britton, A. Sibtain, P.N. Plowman, A.B. Grossman, J.P. Monson, G.M. Besser, The role of ^{123}I-diagnostic imaging in the follow-up of patients with differentiated thyroid carcinoma as compared to ^{131}I-scanning: avoidance of negative therapeutic uptake due to stunning. Clin. Endocrinol. (Oxf.). **55**, 515–521 (2001)
49. M. Ruhlmann, W. Sonnenschein, J. Nagarajah, I. Binse, K. Herrmann, W. Jentzen, Pretherapeutic ^{124}I dosimetry reliably predicts intratherapeutic blood kinetics of ^{131}I in patients with differentiated thyroid carcinoma receiving high therapeutic activities. Nucl. Med. Commun. **39**, 457–464 (2018)
50. P. Szumowski, M. Mojsak, S. Abdelrazek, M. Sykała, A. Amelian-Fiłonowicz, D. Jurgilewicz, J. Myśliwiec, Calculation of therapeutic activity of radioiodine in Graves' disease by means of Marinelli's formula, using technetium (^{99m}Tc) scintigraphy. Endocrine **54**, 751–756 (2016)
51. K. Watanabe, T. Igarashi, H. Ashida, S. Ogiwara, T. Ohta, M. Uchiyama, H. Ojiri. Diagnostic value of ultrasound and Tl-201/Tc-99m dual scintigraphy in differentiating between benign and malignant thyroid nodules. Endocrine (2018). https://doi.org/10.1007/s12020-018-1768-0