Eur J Nucl Med Mol Imaging (2011) 38:673–680
DOI 10.1007/s00259-010-1689-5

ORIGINAL ARTICLE

The absorbed dose to the blood is a better predictor of ablation success than the administered ^{131}I activity in thyroid cancer patients

Frederik A. Verburg · Michael Lassmann · Uwe Mäder · Markus Luster · Christoph Reiners · Heribert Hänscheid

Received: 22 September 2010 / Accepted: 15 November 2010 / Published online: 6 January 2011

Abstract

Purpose The residence time of ^{131}I in the blood is likely to be a measure of the amount of ^{131}I that is available for uptake by thyroid remnant tissue and thus the radiation absorbed dose to the target tissue in ^{131}I ablation of patients with differentiated thyroid cancer (DTC). This hypothesis was tested in an investigation on the dependence of the success rate of radioiodine remnant ablation on the radiation absorbed dose to the blood (BD) as a surrogate for the amount of ^{131}I available for iodine-avid tissue uptake.

Methods This retrospective study included 449 DTC patients who received post-operative ^{131}I ablation in our centre in the period from 1993 to 2007 and who returned to us for diagnostic whole-body scintigraphy. The BD was calculated based on external dose rate measurements using gamma probes positioned in the ceiling. Success of ablation was defined as a negative diagnostic ^{131}I whole-body scan and undetectable thyroglobulin levels at 6 months follow-up.

Results Ablation was successful in 56.6% of the patients. The rate of successful ablation correlated significantly with BD but not with the administered activity. Patients with blood doses exceeding 350 mGy (n=144) had a significantly higher probability for successful ablation (63.9%) than the others (n=305, ablation rate 53.1%, p=0.03). In contrast, no significant dependence of the ablation rate on the administered activity was observed.

Conclusion The BD is a more powerful predictor of ablation success than the administered activity.

Keywords Differentiated thyroid cancer · Dosimetry · ^{131}I Ablation · Administered activity

Introduction

For many years the recommended therapy for differentiated thyroid carcinoma (DTC), with the exception of microcarcinomas, has consisted of (near) total thyroidectomy followed by post-operative radioiodine ablation of thyroid remnant tissue.

Successful ablation leads to a better prognosis with regard to both recurrence-free and overall survival [1] and eliminates the difference in recurrence rate between pre-ablation low- and high-risk patients [2]. Even though results of randomized controlled trials are still missing, the combination of surgery and ^{131}I ablation has proven its value as a safe and very effective treatment and is an integral part of various international guidelines [3–7].

The amount of ^{131}I required to achieve successful ablation is still subject to debate, and several trials have been performed or are currently running to provide valuable answers. Thus far, various activities in a bandwidth

---

Electronic supplementary material The online version of this article (doi:10.1007/s00259-010-1689-5) contains supplementary material, which is available to authorized users.

F. A. Verburg (✉) · M. Lassmann · C. Reiners · H. Hänscheid
Department of Nuclear Medicine, University of Würzburg,
Oberdürrbacher Straße 6,
97080 Würzburg, Germany
e-mail: verburg_e@klinik.uni-wuerzburg.de

U. Mäder
Comprehensive Cancer Center Mainfranken,
University of Würzburg,
Würzburg, Germany

M. Luster
Department of Nuclear Medicine, University of Ulm,
Ulm, Germany

between 1 and 3.7 GBq ^{131}I have been reported to result in an optimal success rate of ablation. Higher activity seems to coincide with higher success rates [8], although most studies in the literature find no further improvement in success rates when ablation activities exceed 1,850 MBq (50 mCi) [9–11].

However, the cumulated activity per volume of blood might be a more adequate predictor for therapeutic success than the administered activity [12]. The amount of ^{131}I still available in the blood depends on the ^{131}I excretion rate which varies considerably between individual patients. This results in large differences in effective half-life and consequently in the residence time of the activity per volume of blood. The determinant for a successful ^{131}I ablation is the radiation absorbed dose to the target tissue; the decisive parameters for this are the administered therapeutic activity and the retention of radioiodine in the target volume [13].

Target tissue uptake must be expected to depend on the availability of ^{131}I in the blood, i.e. the ^{131}I residence time of the activity per volume of blood. This residence time correlates well with the radiation absorbed dose to the blood (BD) per administered ^{131}I activity [12]. Consequently, the absorbed dose to the target tissue and thus the probability of successful ^{131}I ablation should be associated with the BD.

The aim of the current study was to investigate the relation between the radiation absorbed dose to the blood and the success rate of ablation, and compare this to the relation between the administered ^{131}I activity and the ablation success rate.

Materials and methods

Patients

We retrospectively reviewed the files of DTC patients who underwent ^{131}I ablation after thyroid hormone withdrawal in our hospital in the time period from 1993 to 2007 in order to identify those without distant metastases and with a thyroid-stimulating hormone (TSH)-stimulated follow-up including available thyroglobulin (TG) level measurement and ^{131}I whole-body scan about 6 months later. Patients who received reduced activities (<1,850 MBq) in order to prevent adverse effects in the presence of large thyroid remnants (defined as showing a thyroid remnant uptake >10% with the method used at the time) were excluded. The study included 449 patients eligible according to these criteria.

Tumour staging

Surgical specimens were analysed and classified according to standards prevailing at the time of initial treatment. The present study used the histological and TNM classification given in the original pathology report (5th edition of the TNM system until 2002 [14], 6th edition from 2003 onwards [15]). Criteria for excluding patients from this study due to the presence of distant metastases were (a) histological evidence of distant metastases or (b) non-histological evidence such as elevated TG levels, a post-therapy ^{131}I whole-body scan showing ^{131}I uptake outside the neck, computed tomography scan or magnetic resonance imaging.

Initial treatment

All patients underwent a total thyroidectomy, with some patients also undergoing additional central and/or lateral lymph node dissection. After thyroidectomy patients were left without thyroid hormone substitution until ^{131}I ablation, which took place 4–6 weeks after surgery. Prior to ablation cervical ultrasound was performed and the 24-h remnant uptake was measured using a small ^{131}I tracer activity <10 MBq in order to avoid any possible thyroid remnant stunning [16–18]. The administered ablation activities ranged mainly from 1,850 to 4,300 MBq with a trend towards on average higher activities in later years. After ablation, all patients received TSH-suppressive levothyroxine (LT_4) treatment to maintain serum TSH at <0.1 mIU/l.

Estimation of the absorbed dose to the blood

Due to German regulations on radiation protection, each ^{131}I ablation had to be performed as an inpatient procedure. All patients spent between 2 and 7 days in our dedicated radionuclide therapy ward until the radiation levels fell below the advised limits for discharge. Radiation levels were monitored by ceiling dose rate metres built in 2 m above each patient's bed. The first measurement was acquired up to 2 h after administration of the ablative activity, after which measurements were performed twice daily at 12-h intervals. The 48-h whole-body ^{131}I retention was determined for each patient from a bi-exponential decay curve fitted to the measurements. This retention value was used to calculate the BD using a method recently introduced by Hänscheid et al. [19]. Briefly, a mathematical relationship between radioiodine retention in the whole body and the radiation absorbed dose to the blood was deduced based on the assumptions that the whole-body activity decays exponentially and that 14% of the whole-body residence time can be attributed to the blood [19]. The mean of the absolute deviations between blood dose estimates obtained with the formalism and actual blood doses was found to be 14% if the whole-body retention was measured 2 days after radioiodine administration [19]. A more elaborate description of the methods used in this study is given in the online Electronic supplementary material.

Follow-up TG and diagnostic whole-body scan

All patients received a TSH-stimulated follow-up evaluation approximately 6 months after ^{131}I ablation. Serum TSH levels were elevated either by LT_4 withdrawal, or in more recent years also by intramuscular injection of recombinant human TSH (rhTSH). During TSH stimulation, TG levels were measured and a diagnostic whole-body scan (dxWBS) using 150–300 MBq ^{131}I was acquired accompanied by ultrasound imaging of the neck. Success of ablation was assessed using two different criteria. For the main criterion 1, ablation was considered successful if the ^{131}I dxWBS was negative, TG levels were undetectable and no other evidence of persistent disease was present. For the secondary criterion 2 we only considered the dxWBS results. In cases of known persistent thyroglobulinemia, patients were treated with therapeutic ^{131}I activity without preceding ^{131}I dxWBS. These patients were considered to have unsuccessful ablation according to criterion 1 and were excluded from statistical evaluations in connection with criterion 2. Even though this will cause a slight overestimation of the success rate according to criterion 2, it is not possible to include post-therapy scans in this analysis as the sensitivity of a post-therapy scan is much higher than that of a dxWBS [20].

Laboratory analyses

Because different TG assays were used over the inclusion period of this study, classification of TG levels as "undetectable" was based on the lower detection limit of the assay used in a given follow-up exam rather than on a single cutoff value for all assays. The lower detection limit was 1, 0.3 and 0.2 µg/l in 11, 22 and 67% of the patients, respectively. The presence of antibody interference, e.g. from anti-TG antibodies (TGAb) or heterophile antibodies, was excluded through determination of TG recovery rates (normal range 70–130%). Since undetectable serum TG levels cannot be interpreted as evidence of remission in the presence of antibody interference [21], patients would have been excluded from the study in the presence of insufficient TG recovery during follow-up; no patients however showed either of these two conditions.

Statistics

A p value<0.05 was considered to indicate statistical significance. The tests used are reported with the results. When normally distributed, data are given as mean ± standard deviation, otherwise median values are used.

Results

Of the 449 patients aged 47±15 years (median 47, range 11–84 years), 122 were male and 327 were female; 98 patients had a follicular and 351 patients a papillary thyroid carcinoma. There were 296 patients initially staged as pN0, 61 as pNx and 92 as pN1.

The median administered ^{131}I activity was 3.38 GBq (range 0.98–7.0 GBq). Three patients received less than 1.85 GBq and three patients with poor histology or locally invasive disease were treated with more than 4.3 GBq (up to 7.0 GBq). The median BD was 304 mGy (range 86–943). BD <200 mGy and BD >450 mGy were observed in 8% of the patients each.

Criterion 1

At the time of follow-up, which was performed a median of 5.9 months after ^{131}I therapy, 254 of 449 (56.6%) patients had successful ablation according to criterion 1. In order to investigate the effects of BD and administered activity on the ablation rates, patients were stratified to intervals of 50 mGy and 0.1 GBq, respectively. Subgroups with less than 30 patients were pooled to decrease statistical variation and to harmonize group sizes. Results listed in Table 1 and

Table 1 Rates of successful ablation after stratification to intervals of absorbed dose to the blood. Criterion 1 was matched if in addition to visually negative diagnostic whole-body scintigraphy the concurrent TSH-stimulated serum TG level was undetectable. Successful ablation according to criterion 2 was assumed in cases of visually negative diagnostic whole-body scintigraphy only

Absorbed dose to the blood		Criterion 1			Criterion 2		
Interval in mGy	Median in mGy	No. of patients		Rate in %	No. of patients		Rate in %
		Total	Ablated		Total	Ablated	
<200	174	34	17	50.0	33	23	69.7
200–250	227	65	35	53.8	62	50	80.6
250–300	278	114	61	53.5	111	78	70.3
300–350	321	92	49	53.3	86	61	70.9
350–400	376	76	48	63.2	71	55	77.5
400–450	421	31	19	61.3	27	24	88.9
>450	520	37	25	67.6	35	32	91.4
Total	304	449	254	56.6	425	323	76.0

illustrated in Fig. 1a (filled dots) indicate that the success of ablation increases with increasing BD (Pearson's r=0.94). Spearman's ρ=0.82 as a non-parametric measure of statistical dependence shows significance with p=0.03. Probability for successful ablation is significantly higher for patients with BD >350 mGy (2×2 chi-square test: p=0.03) as compared to lower BDs. In contrast, no dependence of the ablation rate on the administered activity is demonstrable [Table 2, Fig. 1b (filled dots)]. The observed tendency to higher ablation rates for administered activities exceeding 3.2 GBq does not reach statistical significance (2×2 chi-square test: p=0.1).

Criterion 2

Of the 449 patients, 24 received an immediate second ^{131}I therapy without preceding ^{131}I dxWBS. Of the remaining 425 patients, 323 (76.0%) had successful ablation according to criterion 2. After stratification to identical intervals as described before, results are similar to those obtained with criterion 1 [Tables 1 and 2, Fig. 1 (open circles)]: ablation rates increase with BD (Pearson's r=0.78, Spearman's ρ=0.79, p=0.04) but not with the administered activity, and the probability for successful ablation is significantly higher for patients with BD >350 mGy (2×2 chi-square test: p=0.02).

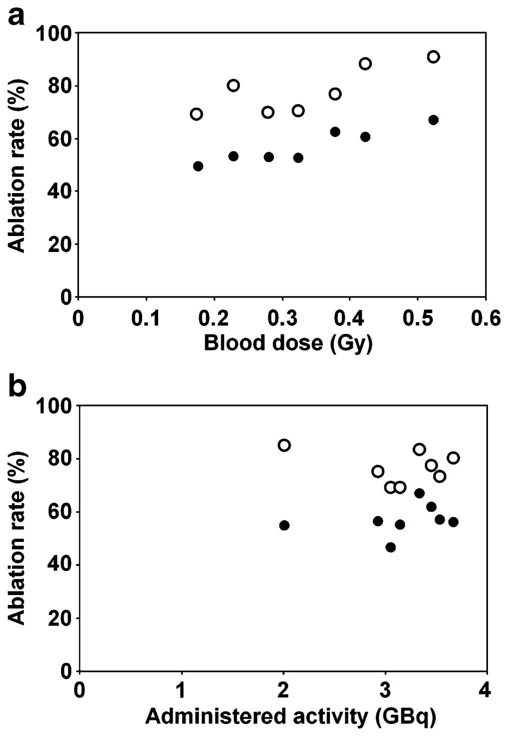

Fig. 1 Rates of successful ablation in subgroups of patients after stratification to intervals of absorbed dose to the blood (**a**) and administered activity (**b**). Criterion 1 (*filled dots*) was matched if in addition to visually negative diagnostic whole-body scintigraphy the concurrent TSH-stimulated serum TG level was undetectable. Successful ablation according to criterion 2 (*open circles*) was assumed in cases of visually negative diagnostic whole-body scintigraphy only. Values are drawn at the median of the correspondent interval

Patients with identical activity

In order to rule out a potential effect of the selection of the administered activity on the results, the analysis was repeated for a subgroup of 209 patients with almost identical therapeutic activities of 3.5 GBq ± 5% of ^{131}I (Table 3). The distribution of the BD is shown in Fig. 2 (bars) together with the observed ablation rates according to criterion 1 (filled dots). The BD ranged from 164 to 943 mGy (median 325 mGy) showing minor deviations from a normal distribution. The results obtained for all patients are confirmed in the subgroup of patients receiving 3.5 GBq ± 5%: ablation rates increase with BD (Pearson's r=0.93, Spearman's ρ=0.90, p=0.02) and the probability for successful ablation is significantly higher for patients with BD >350 mGy (2×2 chi-square test: p=0.03).

Multivariate analysis using a binary logistic regression with a forward selection based on likelihood ratios showed that for successful ablation according to criterion 1 an absorbed dose to the blood ≥350 mGy (p=0.032) and the presence of lymph node metastases (p=0.01) were independent significant predictors of ablation success, whereas T stage (p=0.12) and histology (p=0.06) were not significant and the age at the time of ablation (p=0.85) was unimportant. For ablation success according to criterion 2 the absorbed dose to the blood was the only significant predictor of ablation success (p=0.018); neither the lymph node status (p=0.18) nor T stage (p=0.41), histology (p=0.72) or age (p=0.98) were relevant in this analysis.

Discussion

Many studies have already tried to determine the optimal ablation activity, either under withdrawal or under rhTSH stimulation [9, 10, 22–24]. In most of these studies it was generally found that lower activities of about 1,100–1,850 MBq did not result in a significantly worse rate of successful ablation than did a higher activity of around 3,700 MBq. Accordingly no effect of increasing activity on the ablation rate is verifiable in our collective of 449 patients, 446 of whom received activities of 1,850 MBq or more. An effect of the blood dose on the ablation rate is apparent, which however is in contradiction with findings published recently by Flux et al. [25]. They found that BD was lower in patients with successful ablation than in those with unsuccessful ablation in a study of 23 DTC patients. A potential explanation of this discrepancy could be that the

Table 2 Rates of successful ablation after stratification to intervals of administered activity. Criterion 1 was matched if in addition to visually negative diagnostic whole-body scintigraphy the concurrent TSH-stimulated serum TG level was undetectable. Successful ablation according to criterion 2 was assumed in cases of visually negative diagnostic whole-body scintigraphy only

Administered activity		Criterion 1			Criterion 2		
Interval in GBq	Median in GBq	No. of patients		Rate in %	No. of patients		Rate in %
		Total	Ablated		Total	Ablated	
<2.5	2.02	18	33	54.5	33	28	84.8
2.5–3.0	2.94	32	57	56.1	56	42	75.0
3.0–3.1	3.06	31	67	46.3	64	44	68.8
3.1–3.2	3.15	17	31	54.8	29	20	69.0
3.2–3.4	3.34	32	48	66.7	48	40	83.3
3.4–3.5	3.46	45	73	61.6	66	51	77.3
3.5–3.6	3.54	45	79	57.0	74	54	73.0
>3.6	3.68	34	61	55.7	55	44	80.0
Total	3.38	449	254	56.6	425	323	76.0

median absorbed doses to blood observed by Flux et al. are substantially lower than the absorbed doses observed by other authors [12, 26, 27]. Although Flux et al. made direct measurements of serum ^{131}I activity, no samples were collected within the first 24 h after administration. Disregard of unnoticed short components in the blood activity functions potentially affecting the blood dose calculation might be a reason for low and unreliable BD values.

As many different criteria have been used in the literature to define successful ablation, absolute values for ablation rates are often difficult to compare. Mostly we can compare our results for criterion 2 (negative ^{131}I dxWBS). Our rate of successful ablation of 76% is of the same order as those reported by e.g. Pacini et al. [28] and Verkooijen et al. [29] or in two studies by Barbaro et al. [30, 31], in which the rate of successful ablation in different groups ranged from 58 to 85%. It is, however, somewhat lower than that reported in studies by e.g. Pilli et al. [23], Chianelli et al. [32], Robbins et al. [33] or de Klerk et al. [34], who reported rates of successful ablation according to criterion 2 ranging from 88 to 100%. Criterion 1 can only be compared to a limited number of studies. The rate of successful ablation of 57% is comparable or slightly better than in a study by Verkooijen et al. [29], who reported a success rate of 43–56%, depending on the ablation protocol used, and two studies by Verburg et al., which reported a success rate of 33–65%, depending on whether or not a pre-ablation diagnostic ^{131}I activity of 37 MBq was given [18] or 61% in total [1].

The current study has used a number of different TG assays over time and whole-body scans were acquired using a number of different cameras; also the method of TSH stimulation for follow-up has, especially in later years, varied. This heterogeneity in data may affect the comparability with external data but not the conclusion of the present study.

Another source of uncertainty is the method of blood dose calculation. Hänscheid et al. [19] were able to prove a good correlation between the BD and blood dose estimates from a single whole-body retention measurement in an investigation mainly based on remnant ablation data in patient groups similar to the collective included in the present study. Therefore, it is unlikely that our results are biased, e.g. by the presence of ^{131}I accumulations in the thyroid remnants. The inherent uncertainty introduced by the blood dose estimate is 14% under study conditions. Retrospective application of this method to data gathered less attentively in routine daily practice will probably

Table 3 Rates of successful ablation of patients treated with 3.5 GBq ± 5% ^{131}I after stratification to intervals of absorbed dose to the blood. Criterion 1 was matched if in addition to visually negative diagnostic whole-body scintigraphy the concurrent TSH-stimulated serum TG level was undetectable. Successful ablation according to criterion 2 was assumed in cases of visually negative diagnostic whole-body scintigraphy only

Absorbed dose to the blood		Criterion 1			Criterion 2		
Interval in mGy	Median in mGy	No. of patients		Rate in %	No. of patients		Rate in %
		Total	Ablated		Total	Ablated	
<250	219	34	18	52.9	31	22	71.0
250–300	277	49	27	55.1	49	32	65.3
300–350	322	41	22	53.7	37	27	73.0
350–400	382	43	29	67.4	39	30	76.9
>400	466	42	31	73.8	38	35	92.1
Total	325	209	127	60.8	194	146	75.3

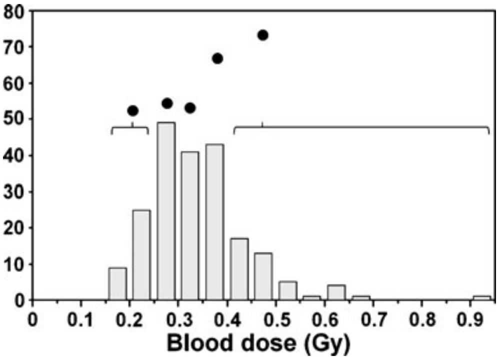

Fig. 2 Distribution of blood doses in 209 patients receiving therapeutic activities of 3.5 GBq ± 5%. The ordinate shows both numbers of patients and percentage of successful ablation (*filled dots*) in five blood dose intervals

enlarge this error. However, statistical errors in blood dose calculation will more likely blur rather than introduce a bias to the effect of the BD on the ablation rates.

Despite the limitations of our study, it is obvious that in our large series of patients the BD is a better predictor of the success of ablation than the administered ablative ^{131}I activity. This is only to be expected; theoretical considerations imply that the residence time of the activity in the blood is a determinant for the remnant uptake and thus the dose to the target tissue [12]. Particularly in patients with a high renal iodine clearance rate, any circulating ^{131}I will be excreted quickly, eliminating its availability for any iodine-avid tissue, whereas, in a patient with slow clearance, the thyroid remnant will have a considerably higher amount of ^{131}I circulating in the blood at its disposal, in turn resulting in a larger thyroid remnant absorbed dose.

The results of the present study, which need to be confirmed in independent investigations, have a multitude of clinical implications. In the debate on the dosage necessary for successful ^{131}I ablation, attention has been focused too much on the amount of fixed activities of ^{131}I that should be administered. The radiation absorbed dose to the thyroid remnant must be considered to be the principal determinant of outcome. It is closely related to the amount of circulating ^{131}I, i.e. the number of radioactive decay events in the blood, which is the main determinant of the BD. The absence of significantly improved ablation rates for higher ablation activities in most studies might be due to the considerable variation in iodine kinetics. This variation degrades the correlation between BD and administered activity, which was found to be only $r=0.36$ for the patients included in this study, and deteriorates the correlation between administered activity and remnant absorbed dose.

The question has recently been asked about how low the ablative activity may be when performing rhTSH-stimulated ablation [35]. Although it has been shown that there was no significant difference in ablation rates between levothyroxine withdrawal and rhTSH stimulation [28, 36], it has also been shown that iodine clearance is considerably faster under rhTSH stimulation, resulting in a significantly lower absorbed dose to the blood [12, 26, 37]. On the other hand, the ^{131}I half-life in thyroid remnants is longer under rhTSH stimulation [12, 26, 37]. These differences in ^{131}I kinetics makes it impossible to apply the values from the present study to rhTSH-stimulated ^{131}I ablation.

Individualized therapy ideally targets at the optimal radiation absorbed dose to the thyroid remnant and is based on a pre-therapeutic dosimetry of both red marrow and target dose per activity administered. Usually target dosimetry is not feasible as it requires ^{131}I activities potentially inducing stunning and information on the target mass, the S factor of self-irradiation and the homogeneity of the activity concentration in the remnant. Hänscheid et al. [12] suggested that therapy be individualized by generally adjusting the administered activity according to the residence time of the activity per volume of blood or, as a surrogate, that one aim at a fixed radiation absorbed dose to the blood rather than administering fixed activities. As an initial guess, 400 mGy was stated to be adequate as BD for remnant ablation [12]. This value was modified to 300 mGy in a recalculation published in [19]. The current study suggests that the maximum ablation effect will be attained if the BD is at least 350 mGy. Further improved ablation rates at higher doses cannot be excluded from our data, which indicates that the optimal BD might be a compromise between ablation rate and radiation exposure.

Figure 3 shows the distribution of activities necessary to target a blood dose of 350 mGy for the patients included in this study. Values range from 1.1 to 7.3 GBq with the median at 3.7 GBq. Activity exceeds 5 GBq in 13% of the patients. Using the method described by Hänscheid et al. [19], the activity required to achieve this BD can easily and reliably be determined in a simple pre-ablation dosimetry procedure using <10 MBq of ^{131}I in order to determine the 48-h whole-body ^{131}I retention.

Although the current results clearly show a beneficial effect of a higher absorbed dose to the blood on the rate of

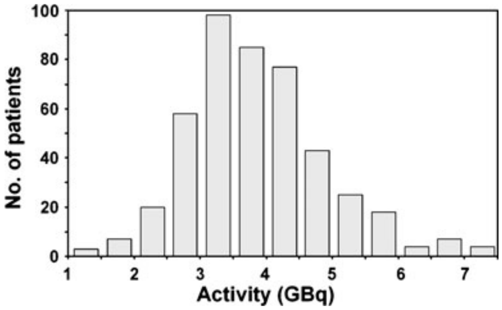

Fig. 3 Distribution of activities necessary to target a blood dose of 350 mGy in 449 patients

successful ablation, it still remains a retrospective study with all the limitations that come with such an assessment. The implications of the present study are however of a magnitude that could significantly change the way we practice nuclear medicine; the best way to ascertain the potential of the concept laid out here would be to perform a randomized trial comparing a fixed activity of e.g. 3,500 MBq vs blood dose-based dosimetry using the methodology described in this paper, aiming for a blood dose of at least 350 mGy.

Although we have no data to analyse this in the current collective, it is of course possible that an increase in blood dose will also lead to an increase in the frequency of early and late side effects such as sialadenitis and xerostomia; in the same randomized study it should of course be studied further whether these risks do not outweigh the benefits.

Conclusion

In the present retrospective study it has been observed that the radiation absorbed dose to the blood was a significant indicator of ablation success, whereas this was not the case for the administered ^{131}I activity in a population of patients receiving >1,850 MBq of ^{131}I for thyroid remnant ablation. Our findings should encourage further research into factors influencing ablation success other than the administered activity.

Conflicts of interest None.

References

1. Verburg FA, de Keizer B, Lips CJ, Zelissen PM, de Klerk JM. Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. Eur J Endocrinol 2005;152:33–7.
2. Verburg FA, Stokkel MP, Düren C, Verkooijen RB, Mäder U, van Isselt JW, et al. No survival difference after successful (131)I ablation between patients with initially low-risk and high-risk differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2010;37:276–83. doi:10.1007/s00259-009-1315-6.
3. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787–803.
4. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.
5. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJ, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2008;35:1941–59.
6. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, et al. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006;12:63–102.
7. Dietlein M, Dressler J, Eschner W, Grünwald F, Lassmann M, Leisner B, et al. Procedure guidelines for radioiodine therapy of differentiated thyroid cancer (version 3). Nuklearmedizin 2007;46:213–9.
8. Sawka AM, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A, et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin North Am 2008;37:457–80.
9. Bal C, Padhy AK, Jana S, Pant GS, Basu AK. Prospective randomized clinical trial to evaluate the optimal dose of 131 I for remnant ablation in patients with differentiated thyroid carcinoma. Cancer 1996;77:2574–80.
10. Bal CS, Kumar A, Pant GS. Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: a randomized clinical trial in 509 patients. J Clin Endocrinol Metab 2004;89:1666–73.
11. Hackshaw A, Harmer C, Mallick U, Haq M, Franklyn JA. 131I activity for remnant ablation in patients with differentiated thyroid cancer: a systematic review. J Clin Endocrinol Metab 2007;92:28–38.
12. Hänscheid H, Lassmann M, Luster M, Thomas SR, Pacini F, Ceccarelli C, et al. Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J Nucl Med 2006;47:648–54.
13. Lassmann M, Reiners C, Luster M. Dosimetry and thyroid cancer: the individual dosage of radioiodine. Endocr Relat Cancer 2010;17:R161–72.
14. Sobin LH, Wittekind C. TNM classification of malignant tumours. Berlin: Springer; 1997.
15. Sobin LH, Wittekind C, Wittekind C. TNM classification of malignant tumours. New York: Wiley-Liss; 2002.
16. Lassmann M, Luster M, Hänscheid H, Reiners C. Impact of 131I diagnostic activities on the biokinetics of thyroid remnants. J Nucl Med 2004;45:619–25.
17. Medvedec M. Thyroid stunning in vivo and in vitro. Nucl Med Commun 2005;26:731–5.
18. Verburg FA, Verkooijen R, Stokkel M, van Isselt J. The success of 131I ablation in thyroid cancer patients is significantly reduced after a diagnostic activity of 40 MBq 131I. Nuklearmedizin 2009;48:138–42.
19. Hänscheid H, Lassmann M, Luster M, Kloos R, Reiners C. Blood dosimetry from a single measurement of the whole body radioiodine retention in patients with differentiated thyroid carcinoma. Endocr Relat Cancer 2009;16:1283–9.
20. Schlumberger M, Pacini F. Thyroid tumors. 3rd ed. Paris: Editions Nucleon; 2006.
21. Spencer CA, Takeuchi M, Kazarosyan M, Wang CC, Guttler RB, Singer PA, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998;83:1121–7.
22. Mäenpää HO, Heikkonen J, Vaalavirta L, Tenhunen M, Joensuu H. Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PLoS One 2008;3:e1885. doi:10.1371/journal.pone.0001885.
23. Pilli T, Brianzoni E, Capocetti F, Castagna MG, Fattori S, Poggiu A, et al. A comparison of 1850 (50 mCi) and 3700 (100 mCi) 131-iodine administered doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. J Clin Endocrinol Metab 2007;92:3542–6.
24. Logue JP, Tsang RW, Brierley JD, Simpson WJ. Radioiodine ablation of residual tissue in thyroid cancer: relationship between

administered activity, neck uptake and outcome. Br J Radiol 1994;67:1127–31.

25. Flux GD, Haq M, Chittenden SJ, Buckley S, Hindorf C, Newbold K, et al. A dose-effect correlation for radioiodine ablation in differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2010;37:270–5. doi:10.1007/s00259-009-1261-3.
26. Luster M, Sherman SI, Skarulis MC, Reynolds JR, Lassmann M, Hänscheid H, et al. Comparison of radioiodine biokinetics following the administration of recombinant human thyroid stimulating hormone and after thyroid hormone withdrawal in thyroid carcinoma. Eur J Nucl Med Mol Imaging 2003;30:1371–7.
27. Chiesa C, Castellani MR, Vellani C, Orunesu E, Negri A, Azzeroni R, et al. Individualized dosimetry in the management of metastatic differentiated thyroid cancer. Q J Nucl Med Mol Imaging 2009;53:546–61.
28. Pacini F, Ladenson PW, Schlumberger M, Driedger A, Luster M, Kloos RT, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 2006;91:926–32.
29. Verkooijen RB, Verburg FA, van Isselt JW, Lips CJ, Smit JW, Stokkel MP. The success rate of I-131 ablation in differentiated thyroid cancer: comparison of uptake-related and fixed-dose strategies. Eur J Endocrinol 2008;159:301–7.
30. Barbaro D, Boni G, Meucci G, Simi U, Lapi P, Orsini P, et al. Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. J Clin Endocrinol Metab 2003;88:4110–5.
31. Barbaro D, Boni G, Meucci G, Simi U, Lapi P, Orsini P, et al. Recombinant human thyroid-stimulating hormone is effective for radioiodine ablation of post-surgical thyroid remnants. Nucl Med Commun 2006;27:627–32.
32. Chianelli M, Todino V, Graziano FM, Panunzi C, Pace D, Guglielmi R, et al. Low-activity (2.0 GBq; 54 mCi) radioiodine post-surgical remnant ablation in thyroid cancer: comparison between hormone withdrawal and use of rhTSH in low-risk patients. Eur J Endocrinol 2009;160:431–6.
33. Robbins RJ, Tuttle RM, Sonenberg M, Shaha A, Sharaf R, Robbins H, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin. Thyroid 2001;11:865–9.
34. de Klerk JM, de Keizer B, Zelissen PM, Lips CM, Koppeschaar HP. Fixed dosage of 131I for remnant ablation in patients with differentiated thyroid carcinoma without pre-ablative diagnostic 131I scintigraphy. Nucl Med Commun 2000;21:529–32.
35. Barbaro D, Verburg FA, Luster M, Reiners C, Rubello D. ALARA in rhTSH-stimulated post-surgical thyroid remnant ablation: what is the lowest reasonably achievable activity? Eur J Nucl Med Mol Imaging 2010;37:1251–4. doi:10.1007/s00259-010-1402-8.
36. Elisei R, Schlumberger M, Driedger A, Reiners C, Kloos RT, Sherman SI, et al. Follow-up of low-risk differentiated thyroid cancer patients who underwent radioiodine ablation of postsurgical thyroid remnants after either recombinant human thyrotropin or thyroid hormone withdrawal. J Clin Endocrinol Metab 2009;94:4171–9.
37. Remy H, Borget I, Leboulleux S, Guilabert N, Lavielle F, Garsi J, et al. 131I effective half-life and dosimetry in thyroid cancer patients. J Nucl Med 2008;49:1445–50.