Differentiated thyroid carcinoma : nuclear medicine studies

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Chapter 4

The success rate of ^{131}I ablation in thyroid cancer patients is significantly reduced after a diagnostic activity of 40 MBq ^{131}I

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Abstract

Objective: Dosimetry studies have shown that activities of ^{131}I as small as 10-20 MBq may cause a stunning effect. A result of this stunning effect may be a lower success rate of the ablative ^{131}I therapy for differentiated thyroid carcinoma (DTC). The aim of this study was to determine whether pre-therapeutic uptake measurement with 40 MBq ^{131}I causes a lower success rate of ablation.

Design: retrospective chart review study.

Patients, methods: In two hospitals the ablation protocols differed in one respect only: in the one hospital no diagnostic ^{131}I was applied before ablation (group 1, n=48), whereas in the other hospital a 24-h uptake-measurement with 40 MBq ^{131}I was performed (group 2, n=51). Included were all DTC patients without distant metastases who had undergone ^{131}I ablation between July 2002 and December 2005, and who had returned for ^{131}I follow-up. Successful ablation was defined as absence of pathological ^{131}I uptake on diagnostic whole-body scintigraphy and undetectable thyroglobulin-levels under TSH stimulation.

Results: Overall, ablation was successful in 31/48 patients (65%) in group 1 and in 17/51 patients (33%) in group 2 (p=0.002). Multivariate analysis showed that pre-therapeutic uptake measurement using 40 MBq ^{131}I was an independant determinant for success of ablation (p=0.002).

Conclusions: After applying a diagnostic activity of 40 MBq ^{131}I before ablation, the success rate of ablation is severely reduced. Consequently, the routine application of ^{131}I for diagnostic scintigraphy or uptake measurement prior to ^{131}I ablation is best avoided.

Introduction

The therapy of choice in patients suffering from differentiated thyroid carcinoma (DTC) is (near-) total thyroidectomy. To DTC patients except for those with a papillary carcinoma ≤1 cm in diameter it is recommended to subsequently administer a high activity of ^{131}I, with the intent to ablate remnant thyroid tissue [5]. There is still some discussion whether follicular thyroid carcinoma patients with a tumour diameter ≤1 cm should receive the ^{131}I ablation treatment [29,34]. In many centres this ^{131}I ablation is preceded by pre-therapeutic uptake measurement using a small activity of ^{131}I [41,42]. A potential disadvantage of this is the presumed stunning effect to thyroid remnants [16,35], i.e. a diminished uptake of ablative ^{131}I activity after the application of a diagnostic ^{131}I activity.

This stunning effect may be noticed either by a lower than expected ^{131}I uptake on a post-ablation scintigram, or as a higher failure rate of ablation. The precise definition of stunning in the context of ^{131}I ablation has not been established, with many authors only reporting a visual difference in ^{131}I uptake by the thyroid remnant and only few offering quantitative evidence. Whereas not all authors agree that this phenomenon occurs [22,25,36], it has been demonstrated by others in malignant [12,16,17,26,30] and benign thyroid disease [14].

Dosimetry studies have shown that activities of ^{131}I as small as 10-20 MBq may deliver a significant radiation dose to thyroid cells [16,23], suggesting that the stunning effect may be due to direct radiation damage to thyrocytes. This is also supported by a study from Postgard *et al*. which showed that absorbed radiation doses as little as 3 Gy already reduced iodine transport by 50% [33]. Evidence was presented of downregulation of the sodium iodine symporter expression in reaction to diagnostic activities [27], thus reducing the uptake of ^{131}I [19].

At the University Medical Center Utrecht (group 1) and at the Leiden University Medical Center (group 2), two academic hospitals with geographically partially

overlapping patient populations, comparable fixed activity ablation protocols were used since July 2002 [4]. However, there is one difference:

- Group 1: no pre-therapeutic uptake measurement is performed,
- Group 2: a pre-ablative 24-h uptake measurement is performed (40 MBq ^{131}I).

Our aim was to determine whether this pre-therapeutic procedure with 40 MBq ^{131}I causes a lower success rate of ablative ^{131}I therapy in post-operative DTC patients.

Patients, material, methods

Study population

All DTC patients after thyroidectomy and without distant metastases (known before initial treatment or demonstrated by post-ablation scintigraphy or computed tomography / magnetic resonance imaging studies during initial treatment), who received ^{131}I ablation treatment in one of our centres between July 2002 and December 2005, were included in a retrospective study. Further inclusion criteria were:

- ablation had been performed in accordance with the hospitals' protocols;
- 6-12 months after ablation, patients had returned for diagnostic scintigraphy or additional treatment with ^{131}I and for measurements of thyroglobulin (Tg) levels during TSH stimulation.

Pre-ablative 24-h ^{131}I uptake

In group 1 the ablative activity was administered without prior diagnostic scintigraphy. In group 2 pre-ablative 24-h ^{131}I uptake measurements were performed in order to assess the percentage of ^{131}I taken up by the thyroid remnant using standard techniques: a capsule with 40 MBq ^{131}I was given orally, followed by planar scintigraphy of the neck region 24 h later.

A standard of 40 MBq ^{131}I, calibrated on the day of administration and measured in a neck phantom after 24 h, was used as a reference. The ablative ^{131}I activity was administered on the day after the uptake measurement. Patients with a ^{131}I uptake >15% would have been referred to the surgical department for evaluation of additional surgical treatment, but this never occurred.

Fixed activity ablation protocol

A fixed activity ablation protocol was used in the University Medical Center Utrecht from January 1990 onward and at the Leiden University Medical Center from July 2002 onward. All patients underwent ^{131}I ablation 4-6 weeks after (near-) total thyroidectomy. Patients did not receive L-T4 medication between surgery and ablation. In both centres TSH-levels had to be equal to or greater than 30 mU/l before ablation could take place. Since the Netherlands is an iodine-sufficient country, in both centres patients had been instructed to keep a low-iodine diet for one week prior to ablation [8,32].

An activity of 3700 MBq ^{131}I was administered to patients without (known) metastases or 5550 MBq to patients with nodular involvement (detected pre- or peri-operatively). Node negative patients with extensive extrathyroidal tumour growth (n=8) or Hürthle carcinomas (n=6) also received 5550 MBq.

Follow-up, laboratory analyses

6-12 months after ablation, patients returned to their respective hospitals for follow-up. At the UMCU this was performed with rhTSH stimulation using 370 MBq of ^{131}I while at the LUMC levothyroxin was withdrawn for 4 weeks and 185 MBq of ^{131}I was given. In both centres TSH-levels were checked before administration of ^{131}I and had to be ≥30 mU/l. At this follow-up blood was drawn for the measurement of TSH-stimulated Tg-levels. Concurrently, scintigraphy with a large-field-of-view camera and high-energy collimators in

both centres was performed, acquiring a scan of the entire body and separate planar acquisitions of the cervical region.

In group 1 the BRAHMS Dynotest Tg-pluS kit for measurement of Tg-levels and levels of Tg-antibodies was used (BRAHMS Diagnostica GmbH, Berlin, Germany). The lower detection limit of this kit was 0.2 µg/l. In group 2 the BRAHMS Dynotest Tg-S kit for measurement of Tg-levels and levels of Tg-antibodies was used (BRAHMS Diagnostica GmbH, Berlin, Germany), with a lower detection limit of 0.5 µg/l.

In the presence of antibodies, test results for Tg are not reliable [21,39]. As the assays used in both hospitals were IRMA assays, interference from antibodies against Tg generally would have resulted in underestimation of Tg-levels. Hence, eight patients with Tg test results below the cut-off level and with negative whole body scintigraphy were excluded from analysis because Tg antibodies were present in their serum.

Successful ablation, statistics

As our primary definition, ablation was considered successful if 6-12 months after the initial ^{131}I therapy patients fulfilled all of the following criteria:

- no additional therapy of any kind for thyroid cancer between ^{131}I ablation and first TSH-stimulated follow-up;
- TSH-stimulated levels below the detection limit of the assay;
- absence of pathologic ^{131}I accumulations on whole-body scintigraphy, including absence of a visually discernable uptake focus in the thyroid bed as rated by the nuclear medicine physician at the time.

In literature further measures are advised if Tg-levels meet certain cut-off levels, usually 1 µg/l [28] or 2 µg/l [6]. In order to study the clinical relevance of our findings we also analysed the overall success rate of ablation using both these cut-off levels combined with the other two criteria mentioned.

For statistical analysis we used SPSS version 12.0 for Windows (SPSS inc., Chicago, Illinois, USA). Statistical significance was defined as $p<0.05$. The quantitative data (continuous parameters) were analysed using the Mann-Whitney *U* test. For categorical data the Chi-squared test was used. Multivariate analysis was performed using binary logistic regression with a forward selection method based on likelihood ratios.

Results

Study population, cut-off

The 48 patients in group 1 received ^{131}I ablation without a pre-ablative uptake measurement, whereas the 51 patients in group 2 first underwent a 24-h-^{131}I-uptake measurement. Patient characteristics for both groups as well as tests for differences between the two groups are given in table 1; none of these differences were statistically significant.

Tg-levels undetectable

Overall, ablation was successful in

- 31/48 patients (65%) in group 1, and
- 17/51 patients (33%) in group 2.

The difference is statistically significant ($p=0.002$). Table 2 displays the results of analyses of various subgroups. In most subgroups, there was a significant difference between group 1 and group 2 with regard to success of ablation. In some subgroups (e.g., male patients or patients with follicular thyroid carcinoma) for which the group size was insufficient to show a significant difference, the distribution of successful vs. unsuccessful ablation approximated that of the total group. Remarkable was the lack of a significant difference between group 1 and group 2 for those patients who received 5550 MBq ^{131}I.

In order to exclude tumour size affecting the results, we compared all node negative patients without extrathyroidal tumor invasion (T1-3N0M0 according

to the 5th edition of the TNM system) [38] from group 1 (n=30), as no uptake data were available, with only those patients (n=18) from group 2 with an uptake of <5 %, reflecting a smaller thyroid remnant. In this analysis too group 1 did significantly better (p=0.024). Also we compared 6 node negative patients with extrathyroidal tumour invasion from group 2 with an uptake percentage ≥8% with 11 patients who showed an uptake ≤2 %, representing the highest and lowest uptake percentages, respectively. The difference between the two groups was not significant (p=0.62).

For each group we also compared the results of those patients receiving 3700 MBq with those receiving 5550 MBq. This resulted in p=0.047 for group 1, and p=0.83 for group 2.

Multivariate analysis showed that having received a diagnostic ^{131}I activity was the most significant factor influencing the chance of successful ablation (p=0.002). The only other significant influence was having extrathyroidal tumour growth (p=0.007).

Tg-levels <1 µg/l and <2 µg/l

Ablation was deemed successful by using as cut-off

- Tg-levels <*1* µg/l
  - 35/48 patients (73%) in group 1, and
  - 26/51 patients (51%) in group 2
- Tg-levels <2 µg/l
  - 37/48 patients (77%) in group 1, and
  - 27/51 patients (53%) in group 2

The differences are statistically significant: p=0.025(Tg <1 µg/l); p=0.012(Tg <2 µg/l).

Table 1. Baseline characteristics of patients treated without (group 1) and with (group 2) pre-ablative diagnostic ^{131}I scintigraphy and differences between the two protocols.

	Group 1		Group 2		p value
No. Patients	48		51		
Mean age in years (range)	45.2 (19-80)		43.8 (13-79)		0.57
Gender					0.98
Male	14	(29%)	15	(29%)	
Female	34	(71%)	36	(71%)	
Histology					0.40
Papillary carcinoma	40	(83%)	39	(76%)	
Follicular carcinoma	8	(17%)	12	(24%)	
Extrathyroidal invasion					0.57
Not present	44	(92%)	45	(88%)	
Present	4	(8%)	6	(12%)	
Lymph node metastases					0.10
Not present	30	(59%)	40	(78%)	
Present	18	(41%)	10	(20%)	
Unknown	0		1	(2%)	
Administered activity					0.40
3700 MBq	34	(71%)	32	(63%)	
5550 MBq	14	(29%)	19	(37%)	

Table 2. Comparisons the rates of successful ablation (defined as undetectable Tg-levels, no visible pathologic ^{131}I uptake and no intermittent further treatment) of various subgroups in group 1 and group 2.

	Group 1 successful ablation	**Group 2 successful ablation**	**p value**
Total group	31/48 (65%)	17/51 (33%)	0.002
Males	9/14 (64%)	5/15 (33%)	0.10
Females	22/34 (65%)	12/36 (33%)	0.009
Papillary carcinoma	25/40 (63%)	11/39 (28%)	0.002
Follicular carcinoma	6/8 (75%)	6/12 (50%)	0.26
No extra-thyroidal invasion and node negative	23/30 (77%)	15/37 (41%)	0.003
Extra-thyroidal tumor invasion and/or node positive	8/18 (44%)	2/13 (15%)	0.09
3700 MBq	25/34 (74%)	11/32 (34%)	0.001
5550 MBq	6/14 (43%)	6/19 (32%)	0.51

Discussion

Our study shows substantial differences in efficacy of ^{131}I ablation, correlated with pre-therapeutic administration of 40 MBq ^{131}I: the success rate of ablation in the group without pre-ablative scintigraphy is nearly twice that of the group who underwent pre-therapeutic ^{131}I uptake measurement.

Stunning remains controversial

Thyroid stunning remains a controversial issue. Jeevanram *et al*. [12] were the first to report a 25-75% decrease in uptake of therapeutic ^{131}I activities after diagnostic scanning with 111-185 MBq ^{131}I. Subsequently, several authors have

reported various degrees of stunning of thyroid remnants after the administration of ^{131}I activities ranging from 74 MBq [16], to 111 MBq [26], 185 MBq [11,17], and 370 MBq [30], all resulting in a less successful outcome than a control group that was scanned either with a much lower (37 MBq) ^{131}I activity [26], with ^{123}I [17,30], or without any pre-therapeutic ^{131}I before ablation [11].

In contrast, McDougall *et al*. [22] and Cholewinski *et al*. [2] reported no visually apparent stunning after diagnostic activities of 74 MBq and 185 MBq ^{131}I, respectively. However, in neither of the latter studies the success rates of ablation were reported. Dam *et al*. [3] reported that even though visually apparent stunning was encountered in a part of their patient population, there were no differences in the success rate of ablation between those who did and those who did not show stunning on pre- or post-ablation scintigraphy. Sisson *et al*. even argued that visually apparent stunning may not be attributed to a diagnostic activity, but rather to early effects from the subsequent ablation activity [37]. However they did not compare to patients who had not received diagnostic ^{131}I activities. Silberstein [36] reported no difference in ablation success rates between patients receiving 14.8 MBq of ^{123}I or 74 MBq of ^{131}I for pre-therapeutic uptake measurement.

The activity of 40 MBq ^{131}I used in the study presented here is lower than those reported in the literature. Thus far there was only scant evidence as to whether or not stunning may be caused by such low ^{131}I activities. Medvedec [23] performed a meta-analysis by fitting a regression model on results reported in four studies, and concluded that thyroid remnant stunning might already occur after administration of ^{131}I activities as low as 10-20 MBq.

Limitations

Whether there is a time point at which a pre-therapeutic diagnostic activity does not influence the outcome of the following ablative activity is questionable and should be subject to further study; few data exist in literature and in this study

success of ablation is already diminished even if the diagnostic activity is given only 24-h before the ablative dose.

The success of ablation treatment is influenced by the size of the thyroid remnant [18]. Even though it is possible that there were some patients in group 1 with a considerably larger thyroid remnant, patients from group 2 did significantly worse even when only the smallest remnants were selected.

Follow-up

There are differences in the follow-up regime between group 1 and 2; both the method of stimulation (rhTSH vs. withdrawal) and the activity used (370 vs. 185 MBq). Neither of these differences should significantly influence the results: it was shown that the activity used for follow-up does not influence the results [31], and a large international trial established that results after rhTSH-stimulated follow-up are equivalent to those after levothyroxin withdrawal [20,40].

From the results of this study it can be deducted that patients with a favourable prognosis suffer most from performing pre-therapeutic ^{131}I uptake measurement: patients receiving 3700 MBq (who have low-risk tumours) show a difference between group 1 and group 2, whereas those receiving 5550 MBq (which are patients with higher risk tumours) do not show such a difference. In addition it turns out that in group 1 there is a large difference in success of ablation between those receiving 3700 and 5550 MBq ^{131}I; this difference is absent in group 2.

Most subgroups showed significant differences between group 1 and group 2; in those subgroups that were too small to achieve a statistically significant difference (e.g., male patients, and patients with follicular carcinoma) we found differences between group 1 and group 2 proportional to those in the entire group.

In order to establish the clinical relevance we also analysed the differences in success rate using different cut-offs for Tg-levels that have been mentioned in literature. Even though the difference was less pronounced than with the stricter criterium of undetectable Tg-levels, we still found a considerable, statistically significant difference in success rate between group 1 and group 2. This indicates that at the first TSH-stimulated follow-up patients in group 2 considerably more often showed Tg-levels at such levels that additional diagnostic or therapeutic measures are indicated, and therefore poses a clinically relevant effect.

Other conditions being equal, it is highly likely that the lower success rate of ablation in group 2, which was seen especially in those with a favourable prognosis, was caused by stunning from the pre-therapeutic uptake measurement procedure with 40 MBq ^{131}I. Consequently, in order to maximize the success rate of ^{131}I ablation and minimize the number of required additional ^{131}I therapies, 24-h uptake measurements or diagnostic scintigraphy using ^{131}I is best avoided in patients with differentiated thyroid cancer.

Conclusion

Whether pre-ablative diagnostic scintigraphy should be performed is in discussion. Pre-ablation dosimetry, especially using ^{124}I, may for instance allow a precise determination of the absorbed dose per MBq ^{131}I [7,13]; which may in turn lead to a reduction in the activity of ^{131}I given, although individual dosimetry may become difficult in patients with a thyroid remnant mass <1 g [9]. Small amounts of ^{131}I before ^{131}I therapy may be useful in determining the largest activity that can be given without a risk for hematologic toxicity [15].

The local situation, legal requirements or the frequent occurrence of large thyroid remnants may also necessitate a pre-ablative uptake measurements. In such cases ^{123}I scintigraphy may also provide a valuable alternative; to date no evidence of stunning of thyroid remnants after ^{123}I has been reported [1,10,24].

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