Differentiated thyroid carcinoma : nuclear medicine studies

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Chapter 3

The success rate of ^{131}I ablation in differentiated thyroid cancer: comparison of uptake-related and fixed-dose strategies

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Abstract

Introduction: The aim of the study was to compare the success rate of an uptake-related ablation protocol in which the dose depends on an ^{131}I 24-h neck uptake measurement and a fixed-dose ablation protocol in which the dose depends on tumor stage.

Methods: All differentiated thyroid carcinoma patients with M0 disease who had undergone (near-) total thyroidectomy followed by ^{131}I ablation were included. In the uptake-related ablation protocol, 1100 (uptake >10%), 1850 (uptake 5-10%) and 2800 MBq (uptake <5%) were used. In the fixed-dosage ablation strategy, 3700 (T1-3, N0 stage) and 5550 MBq (N1 and/or T4 stage) were applied. We used ^{131}I uptake on whole-body scintigraphy and thyroglobulin-off values to evaluate the ablation 6-12 months after treatment.

Results: In the uptake-related ablation protocol, 60 out of 139 (43%) patients were successfully treated versus 111 out of 199 for the fixed-dose ablation protocol (56%) (p=0.022). The differences were not statistically significant for patients with T4 (p=0.581) and/or N1 (p=0.08) disease or for patients with T4N1 tumor stage (p=0.937).

Conclusion:The fixed-dose ^{131}I ablation protocol is more effective in ablation of the thyroid remnant in differentiated thyroid carcinoma patients than an uptake-related ablation protocol. This difference is not observed in patients with a N1 and/or T4 tumor stage.

Introduction

The therapy of choice in patients suffering from differentiated thyroid cancer (DTC), subdivided into papillary and follicular thyroid carcinoma, is (near-) total thyroidectomy. This is routinely followed by the administration of radioiodine-131 (^{131}I) to destroy any remaining benign or malignant thyroid tissue, so-called ablation. There are several reasons for routine ablation after surgery [1;2]: a) to be able to detect a carcinoma recurrence by radioiodine scanning; b) radioiodine can destroy microscopic foci of carcinoma in the thyroid remnant; c) possible carcinoma outside the thyroid bed may be detected and treated by radioiodine and d) to use thyroglobulin (Tg) as tumor marker of recurrent carcinoma all normal thyroid tissue has to be destroyed. Although ^{131}I has been used for many years to ablate thyroid remnants following thyroid surgery, a single optimal ablation strategy is still not established. Reports on the amount of ^{131}I required to achieve successful ablation show a considerable range [3-7].

At the Leiden University Medical Center (LUMC) and the University Medical Center Utrecht (UMCU), two academic hospitals in the Netherlands, different ablation strategies have been used over the years. At the LUMC, a relatively low-dose uptake-related ablation strategy was applied until June 2002 [8], whereas in the UMCU a fixed-dose strategy with relatively high administered ^{131}I activities has been in use since January 1990 [9;10]. The aim of this study was to compare the success rates of ablation according to these two above-mentioned protocols.

Methods

Study population

Patients were selected who received ablation treatment with ^{131}I at the LUMC or UMCU from January 1990, as this date marks the start of the fixed-dose protocol in the UMCU. Both subgroups consisted of patients in whom surgery has been performed in the University Medical Centres as well as in referring peripheral hospitals. All DTC patients with M0 disease who had undergone (near-) total thyroidectomy followed by ^{131}I ablation were included. Tumor staging was scored according to the criteria of the fifth TNM Atlas. In all patients with N1 disease, a neck dissection was performed in addition to a resection of the thyroid and prior to ablation. So, in patients with N1 disease, this stage was established before ablation. All patients with M1 disease were excluded to avoid a bias. M1 disease as exclusion criterion was based on post-ablation whole-body scans with high ^{131}I doses and radiological examinations, such as CT scanning and/or chest-X-rays, in patients with T4 and/or N1 disease. Finally, additional inclusion criteria were: a) ablation has been performed in accordance with either protocol and b) 6-12 months after ablation patients returned for follow-up studying consisting of Tg-off measurements and/or ^{131}I whole-body scintigraphy.

Uptake-related ablation protocol

This treatment strategy was used at the LUMC until June 2002. All patients had undergone (near-) total thyroidectomy, followed by ^{131}I ablation 4-6 weeks after surgery. During this interval, no suppressive treatment with L-thyroxine was initiated. Furthermore, low-iodine diets were prescribed to optimize the therapeutic outcome [11;12]. The 24-h pre-treatment radioiodine uptake percentage in the neck region was measured using standard techniques: 40 MBq of ^{131}I was given orally, followed by planar scintigraphy of the neck region 24 h later. A standard of 40 MBq ^{131}I that was calibrated on the day of admission and measured in a neck phantom after 24 h was used as a reference. An uptake of less than 5%, between 5 and 10%, and more than 10% was followed by 2800, 1850 and 1110 MBq of ^{131}I in one administration respectively. The rationale of this quantitative approach was to avoid unnecessary exposure [13] and local side effects from radioiodine [14;15]. In this regimen, no adjustments were made in the case of cervical lymph node metastases.

Fixed-dose ablation protocol

This strategy was used in the UMCU from 1990 onwards. All patients had undergone (near-) total thyroidectomy, followed by ^{131}I ablation 4-6 weeks after surgery. A standard activity of 3700 MBq was administrated in cases without any (known) metastases. In case of pre- or peri-operatively detected lymph node involvement or T4 tumor stage, an activity of 5550 MBq was given. Between surgery and ablation patients did not receive L-thyroxine supplementation, and they had been instructed to keep a low-iodine diet for approximately 1 week [11;12]. No pre-ablative diagnostic scintigraphy was performed.

Follow-up strategy

Between 6 and 12 months after ^{131}I ablation, patients were evaluated by the measurement of Tg-off values, i.e. Tg values under thyrotrophin (TSH) stimulation. For this purpose, hormonal supplementation was withdrawn for 4 weeks, whereas in a minority of the UMCU cohort recombinant human TSH was applied. In the UMCU study group, all patients underwent ^{131}I whole body scintigraphy (WBS), whereas in the LUMC cohort ^{131}I WBS was performed in case of Tg <1 μg/l. In both hospitals, scintigraphy was performed at least 3 days after administration of ^{131}I. In case of increased Tg values or an abnormal WBS, additional treatment was given followed by WBS within 7 days after the administration of a therapeutic dose. Follow-up results 6-12 months after this treatment were not studied. Despite the increased use of ultrasonography in the follow-up of DTC patients, it was not routinely used in this study.

Laboratory analysis

From 1990, in both hospitals, various kits were used for the measurement of Tg and Tg antibodies. Test results for Tg cannot be considered reliable in the presence of Tg antibodies [16;17]. As all assays were IRMA assays, the presence of Tg antibodies would have resulted in unreliable Tg values. Therefore, Tg values were excluded from analysis in the presence of measurable Tg antibodies and a corresponding Tg value below the cut-off level. As results of Tg measurements are not interchangeable between kits [18], Tg values in any patient were considered undetectable if they were below the lower detection limit of the kit used (i.e. cut-off level). Until 1997, serum Tg was measured using an IRMA, the Dynotest TG (Brahms Diagnostica GmBH, Berlin, Germany), with a detection limit of 1 µg/l. From 1997 onwards, the Dynotest TG-s (Brahms Diagnostica GmBH) was used, with a detection limit of 0.5 µg/l. Recurrent disease, however, was defined as Tg values >1µg/l. TSH values were measured by means of an immunofluorometric assay with the Delfia (Wallac, Turku, Finland) until 1997. Thereafter, an immunoluminometric assay was used with the Elecsys (Boehringer Mannheim). Serum Tg-antibodies were determined by the Ab-HTGK-3 IRMA test (DiaSorin Biomedics, Saluggia (VC) Italy).

Criteria for successful ablation

Ablation was considered successful if 6-12 months after ablation when patients fulfilled the following criteria: Tg-off values below the cut-off level of the assay used and negative ^{131}I whole-body scintigraphy.

Statistical analysis

For statistical analysis, we used SPSS version 12.0.1 for Windows (SPSS Inc., Chicago, Illinois, USA). The quantitative data (continuous parameters) were analysed using the Mann-Whitney *U*-test. For categorical data, the χ^2 -test was used. A statistically significant difference was considered when $p<0.05$.

Results

Study population

In this study, a total of 359 patients were included. According to the uptake-related and fixed-dose ablation protocols, 153 and 206 patients were treated respectively. In Table 1, the patient characteristics and results of tests for differences between the two groups are displayed. Papillary microcarcinomas were not observed in the groups studied. In the uptake-related protocol, 20% of patients were treated with 1110 MBq ^{131}I, 19% with 1850 MBq and 61% with 2800 MBq. The mean 24-h ^{131}I uptake value in this group was 6.86% (range: 0.03-12.0%). In the fixed-dose protocol, 69% of patients were treated with 3700 MBq ^{131}I and 31% with 5550 MBq. In this group, 24-h uptake values were not measured.

According to the evaluation with ^{131}I WBS as single tool (Table 2), 89 out of 153 (58%) patients had no iodine uptake in the neck at the first follow-up scintigraphy in the uptake-related ablation protocol. In 174 out of 206 patients (84%) treated according to the fixed-dose ablation, scintigraphy did not show radioiodine uptake in the neck. This difference was statistically significant ($p<0.001$). The scintigraphic ablation results in various subgroups as well as the differences between the protocols are displayed in Table 2, demonstrating significant differences between the different protocols in all subgroups with the exception of T4 tumor stages.

Regarding the combination of ^{131}I WBS and Tg measurement as evaluation tools, it was decided to exclude patients with Tg antibodies and a negative diagnostic ^{131}I WBS to avoid a bias leaving 338 patients available for analysis. Of those treated according to the uptake-related ablation protocol, 60 out of 139 (43%) patients were successfully treated. For patients treated according to the fixed-dose ablation protocol, 111 out of 199 (56%) patients had successful ablation. Again, this difference was statistically significant ($p=0.022$). The results of ablation in various subgroups and tests for differences between the protocols are also displayed in Table 2. We found significant differences between the protocols for almost all subgroups defined. However, differences were not statistically significant for patients with papillary thyroid cancer (p=0.23) and for patients with N1 (p=0.08) and/or T4 (p=0.581) disease. In addition, 10 patients in the uptake-related dose group and 9 patients in the fixed-dose group had T4N1 disease (p=0.006). In both subgroups, only one patient had a successful ablation (p=0.937) revealing a high failure rate in these tumor stages. All patients with radioiodine uptake in the neck and/or elevated Tg values 6-12 months after ablation, the so-called failures, underwent subsequent treatment with a high therapeutic ^{131}I dose. The results of the post-therapy scans were not part of the present study, but all patients with uptake on the diagnostic follow-up WBS also demonstrated uptake on the post-therapy scan. The post-therapy scans of patients with increased Tg values were not evaluated.

Table 1. Differences in population characteristics for the ablation protocols studied.

	Uptake-related	Fixed-dose	p value
Total number of patients	153	206	
Mean age in years (range)	42.6 (15-87)	43.1 (19-82)	0.675
Gender			0.07
Male	33 (22%)	62 (30%)	
Female	120 (78%)	144 (70%)	
Histology			0.294
Papillary carcinoma	123 (80%)	156 (76%)	
Follicular carcinoma	30 (20%)	50 (24%)	
24-hr ^{131}I -uptake (range)	6.86% (0.03-12)	NA	
N-stage			0.008
N0	125 (82%)	140 (68%)	
N1	27 (18%)	66 (32%)	
NX	1 (<1)	0 (0)	
T-stage			0.005
T1-3	131 (86%)	194 (94%)	
T4	22 (14%)	12 (6%)	

N-stage, lymph node stage (N0, without clinically lymph node metastases; N1, with histopathologically proven lymph node metastases); T-stage, primary tumor stage; NA, not available.

Table 2. Successful ablation results in the entire population and various subgroups according to ^{131}I WBS and ^{131}I WBS with Tg measurements.

Group	^{131}I Whole body scan			^{131}I Whole body scan and Tg		
	Uptake-related (n=153) (%)	Fixed-dose (n=206) (%)	p value	Uptake-related (n=139) (%)	Fixed-dose (n=199) (%)	p value
All patients	89 (58)	174 (84)	<0.001	60 (43)	111 (56)	0.022
PTC	73 (59)	133 (85)	<0.001	47 (43)	75 (50)	0.230
FTC	16 (53)	41 (82)	0.006	13 (45)	36 (72)	0.016
N0	76 (61)	119 (85)	<0.001	55 (48)	86 (63)	0.017
N1	12 (44)	55 (83)	<0.001	5 (20)	25 (40)	0.080
T1-3N0	70 (62)	117 (85)	<0.001	53 (51)	86 (65)	0.034
T4	10 (45)	12 (75)	0.236	3 (15)	1 (8)	0.581

Twenty-one patients with positive Tg-antibodies were excluded in the evaluation using ^{131}I WBS and Tg measurements. PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; N, lymph node stage; T, tumor stage.

Discussion

In the present study, two fundamentally different ablation strategies were compared. The rationale of the quantitative uptake-related protocol was to avoid unnecessary exposure [13] and minimize local radioiodine side effects [14;15], whereas the fixed-dose ablation protocol was designed to maximize the chance of successful ablation after one administration of ^{131}I. The present study showed that the fixed-dose ablation protocol has a significantly higher rate of successful ablation compared with the uptake-related ablation strategy. However, of all subgroups, the fixed-dose ablation protocol failed to show a significant advantage in patients with extra thyroidal invasion of the primary tumor (T4 tumors) and/or lymph node involvement (N1 stage). In addition, the results also demonstrate the low sensitivity of ^{131}I WBS in the follow-up of thyroid cancer patients compared with the Tg measurements. This finding is in agreement with the recommendation presented in the European guidelines indicating that for the control of successful ablation in low-risk patients Tg measurements are the first step in the follow-up and WBS is not recommended anymore.

Several studies have shown that higher administered ^{131}I activities lead to higher ablation rates, although estimations of the optimal activity vary between authors. A randomized trial reported by Bal *et al*. [19] revealed no differences in the rates of remnant ablation for activities over 925 MBq (25 mCi). With successful ablation defined as a follow-up scintigram of the neck with less than 0.2% uptake and Tg less than or equal to 10 μg/l, they achieved in 81.6% of the cases successful ablation with activities of 925 MBq or more after one administration. The absence of activity-related differences in success rates of ablation in the study by Bal *et al*. is in sharp contrast with the differences encountered in the present study between those treated with a lower activity (with a minimum of 1110 MBq) and a higher activity (minimum 3700 MBq). The findings of Bal *et al.* are also in contrast with the results described in their earlier study [5], in which an activity of 1850 MBq (50 mCi) or more performed significantly better than an activity of 1110 MBq.

Also in contrast to our results are the findings of Johansen *et al*. [4], who found a success rate of 81% after one administration of 1073 MBq and 84% after the first administration for those receiving 3700 MBq. However, they analyzed only 63 patients in total, whereas their reported success rates have been based on scintigrams performed 3-4 months after ablation. They also reported that the elevated Tg values in the ablated subjects were not statistically significant. However, their lower detection level for Tg was 5 μg/l, which is higher than our cut-off levels (0.2-1.0 μg/l). The comparable ablation results of 1073 and 3700 MBq could be caused by less sensitive follow-up (short follow-up period after ablation and higher cut-off levels for Tg).

An interesting comparison can be made with the uptake-related protocol published by Zidan *et al*. [20], who reported results of an uptake-related protocol with used activities varying from 3145 MBq (85 mCi) for the patients with lowest uptake to 1110 MBq (30 mCi) for those with the highest uptake. Despite the fact that their definition of a successful ablation was based solely on a diagnostic ^{131}I WBS, they reported a higher overall success rate of 94%. However, compared with the uptake-related protocol as described in the present study, Zidan *et al.* used higher ^{131}I activities (approximately 1100 MBq more) for uptake values between 6 and 15%.

In two recently published articles, systematic meta-analyses were presented on the ^{131}I activity for remnant ablation in patients with DTC. In the analysis by Hackshaw *et al*. [21], 41 case notes, 12 prospective cohorts and 6 randomized trials were used to compare the outcome in patients treated with 30 mCi with those treated with 100 mCi. The pooled ablation success rates in the observational studies were 10% lower using 30 mCi compared with the higher dose. The meta-analysis of the randomized trials revealed equivocal results. Despite these findings and because of the lack of randomized trials, these authors concluded that it is not possible to reliably determine whether ablation success rates using the low activity are similar to those using the high activity. This statement was in contrast with the analysis presented by Doi *et al*. [22]. In line with their previous report, they clearly stated that the available data continue to favor higher doses of radioiodine (ranging from 2775 to 3700 MBq) for remnant ablation, especially after near-total thyroidectomy. The use of high doses in these patients results in about one-third less risk of non-ablation than low doses. Our data support the use of higher doses in thyroid cancer.

Regarding the results in the present study and the data published in the literature, it is highly important to stress the difference between the ^{131}I activity administered and the absorbed dose of radiation in thyroid tissue. The absorbed dose causes the ablation effect. This dose depends on several factors, such as uptake of ^{131}I and retention time in the remnants, the mass of the thyroid remnant, different TSH values, the initial activity given and patient's preparation. Despite the fact that a standard amount of radioactivity is used in the present study protocols, it may still result in different ablation doses.

In both academic hospitals, the aim of surgery is to do an optimal resection of malignant tissue, which is a combination of a (near-) total thyroidectomy combined with a neck dissection in case of lymph node metastases. In T4 tumors, there seems to be, however, a high chance of residual malignant cells in the thyroid remnants. In addition, a comparable phenomenon has been described for N1 disease, in which even after a modified neck dissection micrometastases in left lymph nodes cannot be excluded. In the literature, it has been described that thyroid carcinoma cells take up and process iodine less efficiently than normal thyroid cells due to a lower expression of the sodium-iodine symporter [23-25]. In a recently published study on prognostic parameters in thyroid cancer, both N1 and T4 tumor stages significantly correlated with a high chance of local tumor recurrences [26]. Consequently, minimal residual disease could be a thorough explanation for the fact that our study did not show a statistically significant difference in ablation results between the two protocols in case of T4 and/or N1 tumors. Even a mean activity of ^{131}I up to 5000 MBq as used in the fixed ablation dose, which is twice as much as applied in the uptake-related strategy, fails to achieve a complete response in 60 and 92% of the patients with N1 and T4 tumor stage respectively. In addition, in only 1 out of 10 and 9 patients with T4N1 disease in the uptake-related and fixed-dose strategies respectively, success was achieved. These findings are in agreement with data published by Rosaria *et al.* [27]. They studied 274 patients with DTC and found a clear relationship between ablation failures and the presence of metastases and tumors larger than 4 cm in diameter. However, also thyroid remnants with an uptake >5% resulted in a higher failure rate.

It has to be realized that two factors could have influenced the treatment results in the present study. First, the two centres used different follow-up strategies. An endocrinologist of the LUMC performed the clinical follow-up of patients who underwent ablation in the LUMC. The clinical follow-up of a part of the UMCU patients is in their own (referring) hospitals by means of ^{131}I diagnostic scintigraphy and Tg measurements. This subgroup of UMCU patients only returns to the UMCU if additional radioiodine treatment is required (in case of unsuccessful ablation). This effectively may create a bias, as a number of patients with a successful ablation cannot be included in the present study. In this respect however, the missing data would have further increased the overall success rate in the fixed-dose group compared with the uptake-related protocol. Second, it has been shown that relatively low diagnostic activities of ^{131}I may lead to impaired ability of remnant thyroid tissue to concentrate the subsequent ablative dose of ^{131}I (so-called stunning effect) and thereby reduce therapeutic efficacy [28-31]. Although this phenomenon has been acknowledged for some time, the precise time interval and ^{131}I activity after which it occurs is still a subject to discussion. If an applied activity of 40 MBq causes a lower concentration of ^{131}I in the thyroid remnant, part of the effect seen in this study could have been attributed to the stunning effect with a probable bias against the uptake-related protocol. However, data on stunning effects caused by such low doses have not been reported yet.

In the present study, we evaluated patients at 6-12 months after ablation, demonstrating a significant difference in short-term outcome. However, data on long-term recurrence rates are currently not available. The number of studies evaluating differences in long-term outcome in patients treated with high or low ^{131}I doses is scarce. Data presented by Chow *et al*. clearly demonstrated the influence of radioiodine after surgery regarding the 5-, 10- and 15-year local relapse rate [32]. In patients not treated by radioiodine after surgery, the cumulative relapse rate after 15 years follow-up was 20.9% compared with 9.2% in patients treated with radioiodine. In this study, patients who were treated received a mean dose of 3400 MBq at initial stage. It was shown by Verburg *et al.*, that a successful ablation itself seems to be a highly important prognostic factor for long-term outcome [33]. They found that of the patients with a successful ablation, 87% were still free of the disease after 10 years, whereas of the patients with an unsuccessful ablation, only 50% were free of disease ($p<0.001$). According to this finding, a higher recurrence rate may be expected during follow-up in the uptake-related protocol group compared with the group of patients treated according to the fixed-dose protocol. However, this statement is not supported by data recently published by Rosario *et al*. [34]. They treated 82 patients with 3700 MBq ^{131}I and 44 patients with 1100 MBq. At the end of a 5-year follow-up period, the recurrence rate was 3.6% in patients who had received the high dose and 3.4% in those treated with the low dose (p=NS). Criteria used for patient's selection and risk factors were unfortunately not reported, which may have caused a selection bias. Therefore, more randomized trials are required to assess the short- and long-term outcome in relation to the ablation dose used in DTC ablation.

Conclusion

The fixed-dose ablation protocol, using relatively higher ^{131}I activities, is generally more effective in thyroid remnant ablation than a 24-h ^{131}I uptake-related ablation protocol that uses relatively low activities. This difference, however, is not observed in patients with T4 and/or N1 tumor stages, which can be clarified by the presence of minimal residual malignant disease. The present study addressed the issue of ablation efficacy as judged by scintigraphy and Tg measurements after 6-12 months, whereas long-term outcome was not evaluated. Therefore, follow-up studies are necessary to solve whether this lack of difference between both algorithms results in poorer long-term outcome.

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