Thyroid remnant ablation with radioiodine activity of 30, 60, and 100 mCi in patients with differentiated thyroid cancer – a prospective comparison of long-term outcomes

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Abstract

Introduction: The aim of this prospective study was to evaluate long-term outcomes in differentiated thyroid cancer (DTC) patients postoperatively treated with distinct RAI activities of 30 mCi, 60 mCi, and 100 mCi.
Material and methods: The analysis involved 277 low-risk and 46 intermediate-risk patients, who underwent radioiodine (RAI) ablation with 30 mCi, 60 mCi or 100 mCi under prospective, randomized clinical trials. Seventy-eight patients from the low-risk group received 30 mCi, whereas 125 and 74 patients received 60 mCi and 100 mCi, respectively. Regarding the intermediate-risk group, 20 patients were given 60 mCi, and 26 subjects were given 100 mCi. The mean time of follow-up was 11 years.
Results: An excellent treatment response was obtained in 88%, 89% and 90% of low-risk patients treated with 30 mCi, 60 mCi, and 100 mCi, respectively, and in 85% of intermediate-risk patients, who were administered 60 or 100 mCi. An indeterminate response was achieved in 9.4% and 6.5%, whereas an incomplete structural response was obtained in 1.4% and 6.5% of low-risk and intermediate-risk patients, respectively. An incomplete biochemical response was observed only in 2.2% of intermediate-risk patients. The differences in treatment response regarding RAI activity were not significant.
Conclusions: RAI activity of 30 mCi demonstrates a comparable efficacy as 60 mCi and 100 mCi in low-risk DTC. RAI activity of 60 mCi seems to be effective in intermediate-risk DTC.

Key words: differentiated thyroid cancer, low-risk thyroid cancer, radioiodine, remnant ablation, radioiodine treatment, radioiodine activity

Introduction

Differentiated thyroid cancer (DTC) is a malignant neoplasm, arising from the follicular cell, characterized by an indolent course and a good prognosis. A risk of DTC progression or relapse results from its clinic-patho-

logical features, on which basis the American Thyroid Association (ATA) distinguishes three groups: low, intermediate and high risk [1, 2]. Low-risk patients present intrathyroidal DTC with no evidence of extrathyroidal extension, vascular invasion, or metastases. The intermediate-risk group is characterized by microscopic extrathyroidal extension, vascular invasion, cervical lymph node metastases, radioiodine (RAI)-avid disease in the neck outside the thyroid bed, vascular invasion, or aggressive tumor histology. High-risk patients demonstrate gross extrathyroidal extension, incomplete tumor resection, distant metastases, or inappropriate postoperative serum thyroglobulin (Tg) concentrations. Considering the response to the treatment administered, DTC patients are stratified into one of the following categories: excellent, incomplete biochemical, incomplete structural or indeterminate response [1].

DTC treatment is based on surgery involving total/near total thyroidectomy or lobectomy completed by neck lymphadenectomy, if indicated. Until recently the operation was followed by RAI treatment in the vast majority of DTC patients. However, routine use of RAI therapy has been contested in ATA low-risk patients, whereas in the ATA intermediate-risk group the indications for postoperative RAI treatment are personalized and depend on tumor clinic-pathological features and the extent of surgery [1, 2].

The aim of postoperative RAI ablation in low-risk patients is to destroy thyroid remnants to facilitate DTC monitoring by Tg measurements or whole-body scintigraphy (WBS). The purpose of RAI adjuvant therapy is to destroy potential DTC micrometastases and perform disease staging on the basis of post-therapeutic WBS [3]. The administered RAI activity is not unequivocally defined. ATA recommends 30 mCi for remnant ablation, whereas in the case of adjuvant treatment higher RAI activities up to 150 mCi are proposed [1–7].

To evaluate the effectiveness between distinct RAI activities and to choose an optimal RAI dose, two randomized prospective trials have already been carried out in our center. The first one, performed between 1998 and 2001, compared the early therapeutic effect of RAI ablation with the activity of 30 mCi and 60 mCi [8]. The second one, carried out between 2003 and 2005, compared the early effect of postoperative RAI adjuvant therapy with 60 mCi and 100 mCi [9]. The first study involved 210 low-risk DTC patients, whereas the second one involved 224 low and intermediate-risk DTC patients [8, 9]. The aforementioned trials demonstrated poorer early effectiveness of 30 mCi than 60 mCi. However, the efficacy of 60 mCi and 100 mCi was comparable. Also long-term outcomes regarding three distinct RAI activities of 30 mCi, 60 mCi, and 100 mCi did not significantly differ [10].

Considering DTC biology and its low dynamics, an adequately long follow-up is essential for proper assessment of the treatment effect. Therefore, the reevaluation of long-term DTC outcomes in patients treated with distinct RAI doses of 30 mCi, 60 mCi and 100 mCi was conducted. In particular, we focused on intermediate-risk DTC patients, due to, recommended by the current ATA guidelines, personalization in the decision-making process regarding RAI administration and its activity in this group.

Material and methods

The analysis involved 323 DTC patients, among them 277 low-risk and 46 intermediate-risk subjects, who were treated with different RAI activities of 30 mCi, 60 mCi, and 100 mCi under prospective, randomized clinical trials [8, 9]. The study group included 298 women and 25 men. The mean and median age of women at the time of postoperative RAI treatment was 55 and 58 years (range: 20–91 years), whereas these values in men were 52 and 55 years (range: 25–81 years), respectively. The differences between the groups were not significant.

In 1998, when the study was started, there were no widely accepted recommendations on how to select risk groups. Therefore, we decided to use our own criteria. DTC patients staged pT1-T3N0M0 (according to the UJCC-TNM classification, 5 edition, 1997) were classified as a low-risk group, whereas M0 patients demonstrating stage pT4 or N1 were classified as an intermediate-risk group. However, this risk evaluation did not consider all histopathological criteria, currently important, including vascular invasion or the number of metastatic lymph nodes, which were not routinely assessed at that time. This analysis did not involve patients with distant metastases or those in whom surgery was not radical (R1 or R2 resection).

Papillary thyroid cancer was diagnosed in 278 patients, among them in 237 low-risk patients and in 41 intermediate-risk patients, whereas follicular thyroid cancer was diagnosed in 40 and 5 patients, respectively.

All patients underwent total thyroidectomy. Our study involved two groups of patients. The first one enrolled in 1998, included low-risk DTC patients, who were randomly assigned to one of the following radioiodine activities: 30 mCi or 60 mCi. The second one, recruited in 2006, comprised low- and intermediate-risk patients who were randomly given 60 mCi or 100 mCi of radioiodine. Seventy-eight patients from the low-risk group were treated with 30 mCi, whereas higher RAI activities of 60 mCi and 100 mCi were administered in 125 and 74 patients, respectively. Considering the intermediate-risk group, 20 patients received 60 mCi and the remaining 26 subjects

received 100 mCi. The lowest RAI activity was not administered in the intermediate-risk group. The procedure of qualification for RAI postoperative therapy, RAI therapy course, and follow-up scheme were given in detail in our previous papers [10, 11].

The mean time of follow-up in the whole analyzed group was 11 years. Considering low- and intermediate-risk groups separately the mean values were 12 years and 11 years, while the median value was 12 years (ranges: 0–19 years and 3–18 years, respectively). The number of patients followed up more than 10 years was 249 in the low-risk group (90% of all low-risk patients) and 36 in the intermediate-risk group (78% of all intermediate-risk patients).

Treatment response was evaluated according to the current ATA criteria [1] on the basis of a physical examination, serum Tg assessment during LT4 suppression, neck ultrasound or other imaging studies (if indicated).

Both clinical trials [8, 9] were approved by the local Ethics Committee. Informed consent was obtained from all individual participants included in the study "Early evaluation of treatment effectiveness using 131I iodine radiotherapy in patients with differentiated thyroid cancer" [8], which compared the efficacy of two lower RAI activities: 30 and 60 mCi. Regarding the second study – "Optimization of 131I ablation in patients with differentiated thyroid carcinoma: comparison of early outcomes of treatment with 100 mCi versus 60 mCi" [9] – informed consent was not required by the Ethics Committee as both activities were routine RAI activities, used in complementary RAI therapy, in accordance with the national guidelines in force at that time.

Statistical analysis

Statistical analysis was carried out using Statistica software, version 10 (2011; StatSoft, Inc; USA) and Stata 13.1 for Windows. For comparison between the groups Fisher's exact test was used, with a *p*-value of 0.05 being considered significant.

Results

No patient died during the study due to DTC progression. Clinical remission, defined as the lack of local recurrence or distant metastases, was obtained in 273 low-risk patients (98% of the whole low-risk group). Eighty-nine percent of low-risk patients fulfilled criteria for excellent treatment response, among them 88%, 89%, and 90% of patients treated with 30 mCi, 60 mCi, and 100 mCi, respectively. The differences between the groups were not significant (Fisher's exact test; p = 0.714). There was no difference in the efficacy of RAI ablation regarding sex. Similarly, there was no impact of patients' age on the outcomes of RAI ablation.

An incomplete biochemical response was not observed in any low-risk patient, whereas indeterminate and incomplete structural responses were observed in 9.4% and 1.4% of patients, respectively. Similarly, the differences in treatment response regarding RAI activity were insignificant (Fisher's test; p = 0.557 – 1.0; Table I).

An excellent treatment response following the first RAI ablation was achieved in 81% of low-risk DTC patients. Eight percent of low-risk subjects required subsequent RAI therapy, among them 6% an additional RAI ablation, whereas in the remaining 2% of patients therapeutic RAI activity was given due to recurrent disease or due to micrometastases. The differences between the groups were not significant (Fisher's test; p = 0.198–1.00; Table II).

An indeterminate response after first RAI ablation was observed in 9.4% of low-risk DTC patients. In one percent of patients an indeterminate response persisted despite additional RAI treatment; among them, 0.3% of patients underwent a second RAI ablation, and 0.7% of patients were treated due to DTC recurrence or distant metastases. The differences regarding RAI therapeutic activity were not significant (Fisher's test; p = 0.376 –1.00; Table III).

Clinical remission was obtained in 41 indeterminate-risk DTC patients (89% of all indeterminate-risk patients).

An excellent treatment response was noted in 85% of intermediate-risk DTC patients, among them in 85% and 85% of patients treated with 60 mCi and 100 mCi, respectively (Table IV), and the differences between the groups were not significant (Fisher's test; p = 0.713). An indetermi-

Table I. Low-risk DTC patients – treatment response

Variable	Patients number	Excellent response	Indeterminate response	Incomplete structural response
30 mCi	78	69 (88%)	8 (10%)	1 (1.2%)
60 mCi	125	111 (89%)	12 (10%)	2 (1.6%)
100 mCi	74	67 (90%)	6 (8.1%)	1 (1.3%)
Total	277	247 (89%)	26 (9.4%)	4 (1.4%)

nate response was achieved in 6.5% of intermediate-risk patients, whereas an incomplete structural response was obtained in 6.5% of patients. There was no significant difference regarding RAI therapeutic activity (Fisher's test; $p = 0.57$; Table IV).

An incomplete biochemical response was observed in 1 (2.2%) intermediate-risk DTC patient treated with 100 mCi.

After the first RAI ablation, an excellent response was obtained in 33 intermediate-risk DTC patients (72% of all intermediate-risk DTC patients). To achieve an excellent response, additional RAI therapy was required in 11% of intermediate-risk DTC patients, among whom in 6.5% of patients it was additional RAI ablation and in 4.3% the treatment of DTC recurrence or distant metastases. The differences regarding RAI activity were not significant (Fisher's test; $p = 0.49 – 1.00$; Table V).

An indeterminate response after the first RAI ablation was noted in 3 (6.5%) intermediate-risk DTC patients, and 2 (4.3%) patients initially treated with 100 mCi required additional RAI treatment due to DTC progression (Table VI).

Discussion

Long-term follow-up in the analyzed group confirmed the relevance of proper stratification

Table II. Low-risk DTC patients – excellent treatment response

Variable	Number of patients who did not require additional treatment	Number of patients who required additional treatment	Number of patients who required additional treatment – reason for treatment	
			Additional RAI ablation	Treatment of progressive DTC
30 mCi	64 (82%)	5 (7.8%)	4 (5.1%)	1 (1.2%)
60 mCi	103 (82%)	8 (6.4%)	7 (5.6%)	1 (0.8%)
100 mCi	58 (78%)	9 (12%)	6 (8.1%)	3 (4.0%)
Total	225 (81%)	22 (7.9%)	17 (6.1%)	5 (1.8%)

Table III. Low-risk DTC patients – indeterminate treatment response

Variable	Number of patients who did not require additional treatment	Number of patients who required additional treatment	Number of patients who required additional treatment – reason for treatment	
			Additional RAI ablation	Treatment of progressive DTC
30 mCi	7 (8.9%)	1 (1.2%)	1 (1.2%)	
60 mCi	11 (8.8%)	1 (0.8%)		1 (1.2%)
100 mCi	5 (6.7%)	1 (1.3%)		1 (1.2%)
Total	23 (8.3%)	3 (1.0%)	1 (0.3%)	2 (0.7%)

Table IV. Intermediate-risk DTC patients – treatment response

Variable	Patients number	Excellent response	Indeterminate response	Incomplete structural response
60 mCi	20	17 (85%)	2 (10%)	2 (10%)
100 mCi	26	22 (85%)	1 (3.8%)	1 (3.8%)
Total	46	39 (84.8%)	3 (6.5%)	3 (6.5%)

Table V. Intermediate-risk DTC patients – excellent treatment response

Variable	Number of patients who did not require additional treatment	Number of patients who required additional treatment	Number of patients who required additional treatment – reason for treatment	
			Additional RAI ablation	Treatment of progressive DTC
60 mCi	14 (70%)	2 (10%)	2 (10%)	–
100 mCi	19 (73%)	3 (12%)	1 (3.8%)	2 (7.6%)
Total	33 (72%)	5 (11%)	3 (6.5%)	2 (4.3%)

Table VI. Intermediate-risk DTC patients – indeterminate treatment response

Variable	Number of patients who did not require additional treatment	Number of patients who required additional treatment	Number of patients who required additional treatment – reason for treatment	
			Additional RAI ablation	Treatment of progressive DTC
60 mCi	2 (10%)	–	–	–
100 mCi	1 (3.8%)	2 (7.6%)	–	2 (7.6%)
Total	3 (6.5%)	2 (4.3%)		2 (4.3%)

of DTC patients into different risk groups [1, 2] due to a higher risk of cancer progression in intermediate-risk DTC. According to the current ATA Guidelines, the postoperative risk stratification should be based on very precise histopathological features [1] that were not included in the routine histopathological evaluation at the time when our patients underwent thyroid surgery. Therefore, we were not able to strictly follow the 2015 ATA risk stratification. DTC patients staged pT1-T3N0M0, were classified as a low-risk group, whereas M0 patients with extrathyroidal tumor extension or lymph node metastases were considered as intermediate risk. After the mean time of follow-up of 11 years an incomplete structural treatment response was obtained in nearly 1.4% of low-risk DTC patients, whereas DTC relapse or distant metastases occurred despite treatment being applied in 6.5% of intermediate-risk DTC patients.

A similar opinion, regarding the necessity to properly stratify the patients at qualification for treatment and further follow-up, was presented by other papers [12, 13]. Such stratification is particularly important because of ongoing discussion concerning the indications for RAI ablation in low-risk DTC patients. The authors of the current ATA guidelines allow the non-performance of RAI ablation in low-risk DTC. However, the quality of evidence is low [1, 14, 15]. Currently ongoing studies probably will justify the lack of RAI ablation in a low-risk group [16]. However, at least in some patients, RAI activity used for ablation seems to be important. Our previous study, which summarized the results of 6–12-year follow-up in DTC patients treated with different RAI activities of 30, 60, and 100 mCi, did not demonstrate any treatment benefit with the increase of RAI activity [10]. Similar data were published by Bal *et al.* who reported no advantages related to a higher RAI activity [6]. Also Mäenpää *et al.* did not observe better outcomes of RAI ablation after the administration of higher RAI activity (100 mCi) in comparison to a lower RAI dose (30 mCi) [7]. According to Mallick *et al.* RAI ablation with low activities is similarly effective as with a high RAI dose of 100 mCi [4]. These data were confirmed by subsequent meta-analyses showing a comparable effect of low RAI activities with lower treatment-related side effects [17, 18]. The authors of another meta-analysis did not precisely state an RAI ablation activity level, but they confirmed similar efficacy of 30 mCi, 60 mCi and 100 mCi [19].

The data demonstrating comparable long-term outcomes, following low (30 mCi) and high (100 mCi) RAI activity, may justify the lack of the necessity of RAI ablation in low-risk DTC patients. If we assume that 30 mCi is only an ablative dose, we do not protect low-risk DTC patients against potential microdissemination. Nevertheless, a long-term prognosis in low-risk DTC does not differ regarding the administered RAI activity.

The present study focused on the assessment of long-term treatment outcomes. The data concerning serum Tg concentration, measured before and after RAI ablation, could provide additional information regarding the efficacy of RAI ablation. However, due to the lack of complete data for all subjects, we were not able to perform such an analysis.

According to the published data, the risk of DTC progression in intermediate-risk patients is nearly 20% [3, 13]. Therefore, our decision not to use the low RAI activity of 30 mCi proved to be right. Based on our data, RAI activity of 60 mCi seems to be sufficient to treat intermediate-risk patients. However, some authors used higher RAI activities [1, 20]. Nevertheless, one should remember that in our study, in contrast to the low-risk group, the intermediate-risk group included a small number of patients. Moreover, 20% of intermediate-risk patients were lost to follow-up. That may affect the results. Therefore, we have to be cautious when drawing any conclusion. Notably, Castagna *et al.* did not observe any treatment benefit using higher RAI activity in intermediate-risk DTC, either [21].

Given the prospective nature of this study and the presence of confounders, the results should be interpreted with caution. We summarize the outcomes of a long-term follow-up, more than 10 years, mean 11 years. Such long observation is the most important value of this analysis. Our data may be interpreted as almost final results, but one should remember that DTC recurrence may occur even years after diagnosis [22]. On the other hand, this long-term follow-up is also a disadvantage of our study due to the lack of a very accurate histo-

pathological report fulfilling current requirements. Therefore, it is not possible to precisely assign the patients to a particular risk group and the distinction between low- and intermediate-risk DTC was not so strict. Our conclusions regarding the postoperative RAI treatment would be much more accurate if we also analyzed a group of non-treated patients. We are aware of this limitation. However, we were convinced about the necessity of postoperative RAI treatment in 1998, and the comparison between treated and non-treated patients seemed to be non-ethical at that time. So, RAI was given to nearly all DTC patients.

Due to the lack of unequivocal data confirming that RAI ablation is not necessary in low-risk DTC and that it does not influence the long-term prognosis, the decision-making process regarding further therapy is personalized. One should remember that, even if RAI is given only to destroy thyroid remnants, it facilitates precise DTC monitoring and, in some cases, in which an excellent response was not obtained, it allows confirmation of an appropriate therapeutic decision. In some patients an excellent response was achieved only after the treatment of progressive disease. However, we are not sure whether such good outcomes were noted without accurate diagnostics based on serum Tg measurements and WBS. An improvement of disease monitoring results in a decrease in the number of imaging studies and in a lower frequency of follow-up visits, which may have a beneficial effect on patients' quality of life. For supporters of RAI ablation in low-risk DTC the decision-making process should be personalized and consider the impact on the quality of life, disease follow-up, and long-term outcomes.

In conclusion, RAI activity of 30 mCi demonstrates comparable efficacy as 60 mCi and 100 mCi in low-risk DTC. RAI activity of 60 mCi seems to be effective in intermediate-risk DTC.

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Conflict of interest

The authors declare no conflict of interest.

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