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# Comparison of Radioactive Iodine Activities in Terms of Short- and Long-term Results in Ablation Therapy in Patients with Low-risk Differentiated Thyroid Cancer

## *Düşük Risk Grubundaki Diferansiye Tiroid Kanseri Hastalarında Ablasyon Tedavisinde Radyoaktif İyot Aktivitelerinin Kısa ve Uzun Dönem Sonuçları Açısından Karşılaştırılması*

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### Abstract

**Objectives:** The aim of this study was to compare the treatment responses after ablation with 30-50 mCi radioactive iodine (RAI) and 100 mCi RAI in patients with differentiated thyroid cancer (DTC) who were in the low-risk group according to 2015 American Thyroid Associations Classification (ATA 2015) criteria.

**Methods:** Between February 2016 and August 2018, 100 patients who received RAI treatment in our clinic after total thyroidectomy and who were in the low-risk group DTC were included in this retrospective study. These patients were divided into 2 groups: low-activity (30-50 mCi) (group 1) and high-activity (100 mCi) (group 2). While 54 patients were treated with low activity, 46 patients received high activity RAI. The 2 groups were compared according to the 1st- and 3rd-year treatment response status.

**Results:** According to the first-year follow-up, 15 patients were accepted as indeterminate response and 85 patients as excellent response. Three (5.5%) of the patients who were accepted as indeterminate response were in group 1 and 12 (26%) were in group 2. According to the third year follow-up, 1 patient in group 1 and 3 patients in group 2 were accepted as indeterminate response. No biochemical incomplete response or recurrent disease was detected. In the chi-square analysis performed to investigate the relationship between the first-year treatment response and RAI activities, a significant relationship was found (p=0.004). In the Mann-Whitney U test performed to investigate the parameters that may be effective in the treatment response, only the preablative serum thyroglobulin value was shown to have a significant difference between the two groups (p=0.01). In the long-term follow-up of the patients, based on the third year treatment response data, chi-square analysis was performed to evaluate the two groups in terms of treatment responses, and no statistically significant relationship was found (p=0.73).

**Conclusion:** Ablation with 30-50 mCi can be safely applied in DTC patients who are in the ATA 2015 low-risk group and are planned for RAI ablation treatment.

**Keywords:** Differentiated thyroid carcinoma, low-risk, radioiodine, remnant ablation

### Öz

**Amaç:** Bu çalışmanın amacı, 2015 Amerikan Tiroid Dernekleri Sınıflandırması (ATA 2015) kriterlerine göre düşük risk grubunda olup radyoaktif iyot ile ablasyon (RAİ) tedavisi almış olan diferansiye tiroid kanseri (DTK) hastalarında, 30 veya 50 mCi RAİ ile 100 mCi RAİ ile ablasyon sonrası tedavi yanıtlarının karşılaştırılmasıdır.

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**Yöntem:** Şubat 2016-Ağustos 2018 tarihleri arasında kliniğimizde total tiroidektomi sonrası RAİ tedavisi alan ve düşük risk grubu DTK olan 100 hasta bu retrospektif çalışmaya dahil edildi. Bu hastalar düşük doz (30-50 mCi) (grup 1) ve yüksek doz (100 mCi) (grup 2) olarak 2 gruba ayrıldı. Elli dört hasta düşük doz ile tedavi edilirken, 46 hasta yüksek doz RAİ aldı. İki grup 1. ve 3. yıl tedavi yanıt durumuna göre karşılaştırıldı.

**Bulgular:** Birinci yıl takibine göre 15 hasta belirsiz yanıt, 85 hasta mükemmel yanıt olarak kabul edildi. İndetermine yanıt olarak kabul edilen hastaların 3'ü (%5,5) grup 1'de, 12'si (%26) grup 2'deydi. Üçüncü yıl takibine göre grup 1'de 1, grup 3'te 2 hasta indetermine yanıt olarak kabul edildi. Hiçbir hastada biyokimyasal yetersiz yanıt veya nüks hastalık saptanmadı. Birinci yıl tedavi yanıtı ile RAİ dozları arasındaki ilişkiyi araştırmak için yapılan ki-kare analizinde anlamlı ilişki bulundu (p=0,004). Tedavi yanıtında etkili olabilecek parametreleri araştırmak için yapılan Mann-Whitney U testinde sadece preablatif serum tiroglobulin değerinin mükemmel yanıt ve indetermine yanıt gösteren hasta grupları arasında anlamlı fark gösterdiği tespit edildi (p=0,01). Hastaların uzun dönem takiplerinde üçüncü yıl tedavi yanıt verilerine göre iki grubu tedavi yanıtları açısından değerlendirmek için ki-kare analizi yapıldı ve istatistiksel olarak anlamlı bir ilişki bulunamadı (p=0,73).

**Sonuç:** ATA 2015 düşük risk grubunda yer alan ve RAİ ablasyon tedavisi planlanan DTK hastalarında 30-50 mCi ile ablasyon güvenle uygulanabilir.

**Anahtar kelimeler:** Diferansiye tiroid kanseri, düşük risk, radyoaktif iyot, remnant ablasyonu

## Introduction

Differentiated thyroid carcinomas (DTC) usually show a slow course of progression and patients diagnosed with DTC have a long life expectancy. A significant increase has been observed in the incidence of DTC with the widespread use of imaging modalities recently (1,2). An important reason for this is thought to be the incidental detection of small-sized nodules, which would not normally cause any symptoms in the patient, in imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (USG), and positron emission tomography (PET)/CT applied to the patient for other reasons. This has led to a significant increase in the incidence of especially low-risk thyroid cancer through the early diagnosis of slow-progressing malignant thyroid nodules.

According to the 2015 American Thyroid Associations Classification (ATA 2015), patients without risk factors such as extrathyroidal extension, distant metastasis, or aggressive histological subtype are defined as low-risk (3). In these patients, the recurrence of the disease or disease-related mortality after treatment is extremely rare. It has been reported that when patients with DTC undergo successful radioactive iodine (RAI) remnant ablation after total thyroidectomy, less than 1-4% of patients have disease recurrence (4,5,6,7). The very slow course of the disease and the very low rate of recurrence have led to the emergence of very different clinical approaches, and there is no consensus among physicians yet on the necessity of RAI in these patients and the activity to be administered if necessary. This situation often leads to overtreatment of these patients, resulting in undesirable results such as unnecessary radiation exposure, an increase in the frequency of side effects and secondary malignancies, and cost increase (8,9). The aim of this study was to compare the treatment responses after ablation with low-activity (30-50 mCi) RAI and high-activity (100 mCi) RAI in patients with DTC who were in the low-risk group according to ATA 2015 criteria.

## Materials and Methods

### Patients

Between February 2016 and August 2018, 100 patients (97 patients with papillary, and 3 patients with follicular carcinoma) who received RAI treatment in our clinic after total thyroidectomy and who were in the low-risk group DTC were included in this retrospective study.

The inclusion criteria were as follows: age at diagnosis ≥18 years; patients undergoing total or near-total thyroidectomy; low-risk DTC; and primary RAI therapy after surgery. The exclusion criteria were the presence of aggressive histologic subtypes, high preablative serum anti-thyroglobulin (anti-Tg) levels, vascular invasion, microscopic or gross extrathyroidal extension, metastatic lymph nodes of any size, any RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan indicating distant metastasis, and secondary malignancy. These patients were divided into two groups: low-activities (30-50 mCi) (group 1) and high-activity (100 mCi) (group 2). While 54 patients were treated with low activity (6 patients with 30 mCi and 48 with 50 mCi), 46 patients received high activity RAI. The 2 groups were compared according to the 1$^{st}$- and 3$^{rd}$-year treatment response status.

### Radioactive Iodine Administration

Patients admitted to our clinic in the 1-6 months postoperative period were prepared with thyroid hormone withdrawal for 4 weeks and a low-iodine diet for 2 weeks. Patients with thyroid-stimulating hormone (TSH) level ≥30 mU/L were evaluated for RAI activity determination by serum Tg and anti-Tg levels, neck USG, and technetium-99m pertechnetate thyroid scintigraphy. Four to 7 days after RAI treatment, a post-therapy I-131 whole-body scan (WBS) was performed using a Mediso Anyscan SC-SN-

3s-60R high energy parallel hole collimator. Scan images were reviewed by 2 consultant nuclear physicians before reporting.

### Response to Therapy

The ATA 2015 guideline has a dynamic risk assessment system that classifies the patient based on the response to therapy (excellent, indeterminate, biochemical incomplete, and structural incomplete response) using serum Tg level, anti-Tg antibodies, USG, diagnostic wholebody scan, CT, PET/CT, and MRI (3). In this study, response to therapy assessment was performed twelve months and three years after RAI treatment based on the ATA 2015 risk assessment system.

Thus, an excellent response was defined as negative imaging with TSH-stimulated Tg <1 ng/mL or suppressed Tg <0.2 ng/mL.

**Meanwhile, an incomplete response was defined as one of the following:**

1. Biochemical incomplete response was defined as negative imaging with abnormal suppressed Tg (≥1 ng/mL) and/or stimulated Tg values (≥10 ng/mL) or rising anti-Tg.

2. Structural incomplete response was defined as locoregional or distant metastases on USG and/or WBS (independent of Tg and anti-Tg).

Lastly, indeterminate response was defined as non-specific findings on imaging studies, non-stimulated Tg between 0.2 and 1 ng/mL, stimulated Tg between 1 and 10 ng/mL, or anti-Tg stable or declining in the absence of structural or functional disease.

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### Statistical Analysis

Data were analyzed using IBM SPSS Statistics 26.0 for Windows. Results were expressed as mean ± standard deviation. Comparisons of the data were performed by Mann-Whitney U and chi-square tests. Results were considered statistically significant when the two-tailed p value was less than 0.05.

## Results

Of the 100 patients included in the study, 79 were female and 21 were male. The mean age of the patients was 47±13 (range 19-75 years), while the mean tumor diameter was 19.40±10.68 millimeters. The mean preablative Tg value was calculated as 2.92 (0.04-82.55) in all patients in the study group. While there were 7 T1a, 38 T1b, 8 T2, 1 T3 stage patients in group 1, which consisted of patients who received low-activity (30-50 mCi) RAI treatment, there were 3 T1a, 21 T1b, 19 T2, 3 T3 stage patients in group 2, which consisted of patients who received high-activity (100 mCi) RAI treatment. In group 1, 25 patients had unifocal and 29 patients had multifocal disease, while in group 2, 23 patients had unifocal and 23 patients had multifocal disease. While the mean primary tumor diameter was 21.62±7.39 (4-45) mm in group 1, it was 23.11±12.69 (3-65) mm in group 2. Preablative serum Tg value was 1.81 (0.04-34) ng/mL in group 1 and 4.25 (0.05-82.55) ng/mL in group 2. The demographic and clinical features of the patients in this study are summarized in Table 1.

According to the first-year follow-up, 15 patients were accepted as indeterminate response and 85 patients as an excellent response. Three (5.5%) of the patients who were accepted as indeterminate response were in group 1 and 12 (26%) were in group 2. According to the 3rd year follow-up, 1 patient in group 1 and 3 patients in group 2 were accepted as indeterminate response. No biochemical incomplete response or recurrent disease was detected in any patient in either patient group. The treatment responses of the patients at the end of the 1st and 3rd years according to the administered RAI activities are summarized in Table 2.

In the chi-square analysis performed to investigate the relationship between the first-year treatment response and RAI activities, a significant relationship was found (p=0.004). Accordingly, group 2 had significantly more patients who were accepted as indeterminate response than group 1 at the end of the first year. It was investigated which parameters had a statistically significant difference between patients with excellent response and patients

**Table 1. Patient characteristics**

| Parameters | n | |
|---|---|---|
| Gender | Female | 79 |
| | Male | 21 |
| Age | 47±13 years | |
| Mean tumor diameter | 19.9±10.68 milimeters | |
| Mean preablative Tg | 2.92 ng/mL | |
| T stage | T1a | 10 |
| | T1b | 59 |
| | T2 | 27 |
| | T3 | 4 |
| Tumor multifocality | Unifocal | 48 |
| | Multifocal | 52 |

Tg: Thyroglobulin

**Table 2. The treatment responses of the two patient groups at the end of the 1st and 3rd years, according to the administered RAI activities**

| | 1st year treatment response | | 3rd year treatment response | |
|---|---|---|---|---|
| | Excellent | Indeterminate | Excellent | Indeterminate |
| Group 1 (30-50 mCi) | 51 | 3 | 53 | 1 |
| Group 2 (100 mCi) | 34 | 12 | 40 | 6 |

RAI: Radioactive iodine

with indeterminate response. In the Mann-Whitney U test performed for this purpose, only the preablative serum Tg value was shown to have a significant difference between patients with excellent and indeterminate response (p=0.010), and tumor size, patient age, and preablative anti-Tg levels were found to be not statistically significant factors (p=0.083; 0.38; 0.80; respectively).

The mean preablative serum Tg value was 2.14 (0.04-85.55) ng/mL in patients with excellent response at 1st year after treatment and 6.21 (0.83-41) ng/mL in patients with indeterminate response. In the long-term follow-up of the patients, based on the third year treatment response data, chi-square analysis was performed to evaluate the two groups in terms of treatment responses, and no statistically significant relationship was found (p=0.73).

## Discussion

The ATA 2015 guideline does not recommend routine RAI ablation in low-risk thyroid cancer patients but recommends the application of low-activity RAI if ablation is required. Similarly, there are multiple studies that have shown that a low activity of RAI is as effective as a high activity for thyroid remnant ablation in low- and intermediate-risk patients. However, due to changes in definitions of response to treatment and patient selection criteria, the rate of ablation success may differ between these studies.

In this study, we found that 85 out of 100 patients with low-risk DTC showed excellent response to treatment 1 year after RAI treatment. Similarly, in a single-center randomized study by Dong et al. (10), it was found that RAI ablation was successful at 6 months after RAI in 412 of the 474 (87.5%) low-intermediate risk patients. In the same study, it was reported that the successful ablation rates between the patients who received high- and low-activity RAI were similar (87.5% vs. 86.5%; respectively). Comparably, in another study that included 34 patients by Yasmin et al. (11), it was reported that no statistically significant difference concerning the treatment response was found between high- and low-activity RAI receiving patients at 1 year after RAI treatment [82% vs. 76%, respectively (p=0.671)]. As opposed to these studies, in the present study, there was a statistically significant difference between the two groups 1 year after RAI treatment. In this study, the successful ablation rates 1 year after treatment were 94.5% at low- and 74% at high-activity RAI receive patients (p=0.004). This variability among these past studies and this study could be due to different study populations and different definitions of treatment response. In the Mann-Whitney U test performed to investigate the parameters that may be effective in the significant difference in treatment responses in the current study, only the preablative serum Tg value was shown to have a significant difference between the two groups (p=0.01); and tumor size, patient age, preablative anti-Tg levels were found to be not statistically significant factors (p=0.083; 0.38; 0.80; respectively).

In the present study, the mean preablative serum Tg value was 2.14 (0.04-85.55) ng/mL in patients with excellent response at 1st year after treatment and 6.21 (0.83-41) ng/mL in patients with indeterminate response. In a different study by Ha et al. (12), it was reported that 121 of 176 (68.8%) patients with low-risk DTC had successful ablation after receiving low-activity RAI. Although the successful ablation rate was lower in the study by Ha et al. (12), it was also discovered similarly to our study that the pre-ablative serum Tg levels were the only independent factor related to the treatment response (1.2±2.3 ng/mL in successful, vs. 6.2±15.2 ng/mL in unsuccessful ablation, p=0.027).

In two major open-label, randomized, controlled trials, there was no statistically significant correlation found between high- and low-activity RAI receiving low-intermediate risk patients, considering the treatment response in long-term follow-up. In the HiLo study including 434 patients by Dehbi et al. (13), the successful ablation rates were similar between the high- and low-activity RAI groups at 3-5 years after treatment (98.5% vs. 97.9% at 3 years and 97.9% vs. 97.3% at 5 years after RAI, respectively). Likewise, in the ESTIMABL1 study including 752 patients by Schlumberger et al. (14), 98% of the low-risk DTC patients had excellent response to treatment at 5 years after RAI. Of the 11 patients who showed evidence of disease 5 years after RAI, 5 had previously received high-activity and 6 had received low-activity RAI treatment. Similar to these studies, in this study, no statistically significant difference was found

between the high- and low-activity RAI groups at 3 years after treatment (98% vs. 87%, respectively, p=0.73).

### Study Limitations

The limitations of this study were the retrospective design, limited number of patients, and relatively short follow-up time of 3 years. As previously stated, DTC is a disease that can progress over a long period of time. Thus, extending this period may have some positive impacts on patient outcome.

## Conclusion

In conclusion, although the data obtained in our study revealed that there was a statistically significant difference between the high- and low-activity RAI groups at the end of the first year, there was no statistically significant difference in long-term follow-up. Therefore, considering the unwanted effects of high-activity RAI treatment such as side effects, cost increase, and secondary malignancy, ablation with 30-50 mCi can be safely applied in DTC patients who are in the ATA 2015 low-risk group and are planned for RAI ablation treatment.

### Ethics

**Ethics Committee Approval:** University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee approval was obtained on 09.05.2022 with decision number 147 for this clinical study, which was designed retrospectively.

**Informed Consent:** All patients signed written informed consent.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: S.K., S.S.K., Concept: S.K., Design: T.Ö., Data Collection or Processing: S.S., G.B.B., Analysis or Interpretation: O.G., Literature Search: S.E., Writing: S.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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