Revista Española de Medicina Nuclear e Imagen Molecular 43 (2024) 500055

Original Article

Low dose radioactive iodine ablation therapy (1.11GBq) for differentiated thyroid cancer in Western Turkey

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ARTICLE INFO

Article history:
Received 26 April 2024
Accepted 14 August 2024
Available online 10 September 2024

Keywords:
Thyroid cancer
131-I therapy
Remnant ablation
Thyroglobulin

ABSTRACT

Objective: Ablation therapy is employed in low-risk differentiated thyroid cancer (DTC) cases to facilitate patient monitoring by reducing thyroglobulin (Tg) levels to measurable levels below after surgery by eliminating residual thyroid tissue. However, there is still uncertainty about the minimum activity dose required for effective ablation. Opting for low-dose [131I]-NaI for ablation offers several advantages for both patients and healthcare services. Particularly in this tumor group with a high life expectancy (approximately 90–95 % at 10 years), [131I]-NaI treatment should not pose a risk to the patient's post-treatment life and should not compromise their quality of life. However, there is a need for a well-defined identification of factors predicting successful ablation.
Methods: Clinical data, laboratory findings, and imaging tests of 287 patients with low-dose 1110 MBq (30 mCi) [131I]-NaI ablation therapy for DTC were retrospectively reviewed. Post-ablation imaging and laboratory findings categorized ablation success/failure. The successful ablation group was determined according to the excellent response criteria outlined in ATA criteria. Relationships between clinical, pathological findings, biochemical common variables, and treatment failure were analyzed.
Results: An excellent response was achieved in 77% of the entire group according to ATA criteria post-ablation. Male gender and high Tg levels on the day of ablation (Tg cut-off: 10 ng/mL and 5.35 ng/mL) were associated with unsuccessful ablation.
Conclusions: Our results indicate that a 1110MBq (30mCi) ablation dose is sufficient to achieve an excellent response in most low-risk DTC cases 6–12 months later. When selecting the dose for ablation, besides the histological markers mentioned in guidelines and age, we observed that stimulated Tg values and gender may be important in predicting ablation success.

Terapia de ablación con yodo radiactivo de baja dosis (1.11 GBq) para el cáncer de tiroides diferenciado en el oeste de Turquía

Palabras clave:
Cáncer de tiroides
Terapia 131-I
Ablación remanente
Tiroglobulina

RESUMEN

Objetivo: La terapia de ablación se emplea en casos de cáncer diferenciado de tiroides (CDT) de bajo riesgo para facilitar el seguimiento del paciente al reducir los niveles de tiroglobulina (Tg) a niveles mensurables por debajo después de la cirugía mediante la eliminación del tejido tiroideo residual. Sin embargo, todavía existe incertidumbre sobre la dosis mínima de actividad necesaria para una ablación eficaz. Optar por dosis bajas de [131I]-NaI para la ablación ofrece varias ventajas tanto para los pacientes como para los servicios sanitarios. Particularmente en este grupo de tumores con una alta esperanza de vida (aproximadamente 90–95% a los 10 años), el tratamiento con [131I]-NaI no debería suponer un riesgo para la vida post-tratamiento del paciente y no debería comprometer su calidad de vida. Sin embargo, existe la necesidad de una identificación bien definida de los factores que predicen una ablación exitosa.
Métodos: Se revisaron retrospectivamente los datos clínicos, los hallazgos de laboratorio y las pruebas de imagen de 287 pacientes con terapia de ablación con dosis bajas de 1110 MBq (30 mCi) de [131I]-NaI para el CDT. Las imágenes posteriores a la ablación y los hallazgos de laboratorio clasificaron el éxito/fracaso de la ablación. El grupo de ablación exitosa se determinó de acuerdo con los criterios de respuesta excelente descritos en los criterios de la ATA. Se analizaron las relaciones entre los hallazgos clínicos, patológicos, las variables bioquímicas comunes y el fracaso del tratamiento.

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https://doi.org/10.1016/j.remnie.2024.500055

Resultados: Se logró una excelente respuesta en el 77% de todo el grupo según criterios ATA post-ablación. El sexo masculino y los niveles altos de Tg el día de la ablación (límite de Tg: 10 ng/mL y 5,35 ng/mL) se asociaron con una ablación fallida.
Conclusiones: Nuestros resultados indican que una dosis de ablación de 1110MBq (30mCi) es suficiente para lograr una respuesta excelente en la mayoría de los casos de CDT de bajo riesgo entre 6 y 12 meses después. Al seleccionar la dosis para la ablación, además de los marcadores histológicos mencionados en las guías y la edad, observamos que los valores de Tg estimulados y el sexo pueden ser importantes para predecir el éxito de la ablación.

Introduction

Radioactive iodine therapy (RAIT) applications after total thyroidectomy are a fundamental cornerstone in the treatment and follow-up of differentiated thyroid cancers.[1,2] It is the most effective biological, target-specific, and oldest known theranostic agent used in diagnosis and treatment for about 70 years. RAIT application is used in cases of differentiated thyroid cancer patients who have undergone total thyroidectomy for purposes such as the ablation of residual tissue, adjuvant therapy, and treatment of persistent tumor tissues. Ablation therapy has been performed for many years to facilitate Tg monitoring by eliminating residual thyroid tissue in low-risk DTC patients, such as the cases we examined. However, there is still uncertainty regarding the minimum activity dose required for effective ablation. Activity doses ranging from 1110 MBq to 3700 MBq are used worldwide, with a wide range varying from center to center. Selecting a low dose of [131I]-NaI for ablation has many advantages for patients and healthcare services. Particularly in this tumor group with a high life expectancy (approximately 90–95% at 10 years), [131I]-NaI treatment should not pose a risk to the patient's post-treatment life and should not compromise quality of life. This choice reduces patient isolation time, lowers environmental exposure to radiation, decreases costs, and reduces short- and long-term complications related to radiation in patients.[3]

In our study, we aimed to evaluate the success and factors influencing the success of low-dose [131I]-NaI ablation therapy by examining 287 cases treated with low-dose [131I]-NaI ablation therapy between 2016 and 2019, along with clinical, laboratory, and imaging findings.

Materials and methods

Between 2016 and 2019, we evaluated 3008 cases of differentiated thyroid cancer. These cases had applied to our center for radioactive iodine treatment after undergoing total thyroidectomy. Patients with lymph node or distant metastasis, unfavorable histology (tall, columnar, solid, hobnail variants), those at T3 and T4 stage, individuals treated with doses higher than 1.1GBq, and those diagnosed before the age of 18 were excluded from the study.

Clinical data, laboratory findings, and imaging studies of 287 patients (238 females, 49 males) who underwent low-dose (1110MBq) [131I]-NaI ablation therapy for DTC were retrospectively analyzed. Serum TSH, Tg (defined as the primary Tg level), and anti-Tg values were noted at the earliest 1 month after total thyroidectomy. Technetium ([99mTc]TcO4) scan findings to assess the presence of residual or metastatic thyroid tissue were examined, along with ultrasound findings performed 6 weeks after total thyroidectomy. All patients received low-dose radioiodine ([131I]-NaI) ablation therapy (1.1GBq, 30mCi; capsule, po) for ablation purposes within a few months after surgery. Serum TSH, serum Tg, and anti-Tg levels were measured on the day of ablation therapy after iodine diet and discontinuation of l-thyroxine. These values were denoted as ablation TSH, ablation Tg, and ablation anti-Tg, respectively. No serious side effects occurred in the patients, except for side effects such as nausea and sialo-adenitis, which are probably related to [131I]-NaI treatment. To confirm the presence and size of thyroid remnant and to exclude or confirm other unsuspected foci, [131I]-NaI whole body scintigraphy (WBS) was obtained 3–7 days later, depending on post-treatment iodine intake. Nine to twelve months after the ablation, L-thyroxine treatment was discontinued for 4 weeks (TSH > 30 mU/L), and the patient followed a low-iodine diet for at least 2 weeks. Additionally, in the therapeutic efficacy control study, stimulated serum TSH, stimulated Tg, and anti-Tg values were determined and recorded. Subsequently, diagnostic whole body scintigraphy (DWBS) was obtained with a tracer dose of 185mBq (in liquid form). DWBS was obtained by taking anterior, posterior whole-body images and neck/chest spot views on a dual-headed gamma camera using a high-energy, general-purpose collimator. In cases where suspicious involvement was detected on DWBS, the findings were anatomically localized with additional SPECT/CT imaging. In addition, stimulated TSH, Tg (sTg) values, Anti-Tg level and ultrasonography findings were evaluated. Based on the presence of pathological findings in imaging methods during this period, and an increase in Anti-Tg value and sTg above 0.9 ng/mL, ablation success was categorized into successful/unsuccessful. The successful ablation group was determined according to the excellent response criteria specified in ATA criteria.[2] The unsuccessful ablation group was further classified based on the presence of residual tissue in DWBS and sTg levels as indeterminate near response (1−10 ng/mL), and biochemical incomplete response (>10 ng/mL).

Evaluation of clinical outcome

Clinical records containing laboratory and imaging data were reviewed and results were categorized according to the current ATA guidelines.[2]

Excellent response (Negative imaging, TSH-stimulated Tg <1 ng/mL): 221 patients (77%),

Biochemical incomplete response (Negative imaging, Stimulated Tg >10 ng/mL, Rising anti-Tg antibody levels): 6 patients (2%). 18F-FDG PET/CT imaging was also performed in this patient group, and no lesions suspicious for recurrence were found.

Indeterminate response (Non-specific findings in imaging studies - weak uptake in thyroid bed on DWBS, Stimulated Tg can be detected but <10 ng/mL): 60 patients (20%). There were no patients with structural incomplete response (persistent or newly identified locoregional or distant metastases).

Ethics committee approval was received from the Medical Research Ethics Committee of Ege University.

Table 1
TSH, Tg, anti-Tg antibodies values (mean, min- max) obtained in the patient group at 3 evolution points.

	1. Post- IQ mean (min-max)	2. Ablative treatment mean (min-max)	3. Evaluation study of therapeutic effectiveness mean (min-max)
TSH (mU/L)	95 (5.7–363)	120 (8–355)	115 (23–325)
Tg (ng/mL)	–(<0.9–68)	–(<0.9–48)	–(<0.9–21)
Anti-Tg (IU/mL)	–(<10–1300)	–(<10–498)	–(<10–701)

(1) Post-IQ (4–6 weeks after total thyroidectomy), (2) Ablative treatment (before ablation), (3) Evaluation study of therapeutic effectiveness (post-ablation 9–12. month). Displayed as mean, min-max (Since the Tg and Anti-Tg groups also included undetectable values, the average of the groups containing these values (Tg <0.9 ng/mL, Anti-Tg < 10 IU/mL) was not taken and is shown as "–").

Table 2
Receiver operating characteristic (ROC) curve analysis of evoked ablation-Tg levels to define the cut-off value for failure to achieve successful ablation in the subgroup.

Risk factor	AUC (95%)	Cut-off	P	Sensitivity (%)	Specificity (%)
Ablation Tg	0.698 (0.598–0.798	5.355	**0.01**	66	66

Statistical analysis

Relationships between clinical, pathological findings, and biochemical common variables with successful ablation were determined. Two-way relationships between categorical variables were examined using Pearson chi-square test, and P-values were noted. Statistical significance was determined with a P-value less than 0.05. Patients with Tg values less than 0.9 ng/mL or undetectable during ablation and patients with positive anti-Tg values during ablation were excluded, creating a subgroup of 123 patients. Receiver operating characteristic (ROC) curves and calibration statistics were calculated within this subgroup to define a cut-off value for ablation-Tg. AUC value recorded. Independent t-tests were conducted to identify the relationship between serum TSH and ablation success. Multiple logistic regression analysis was used for significant values obtained in univariate analyses. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Non-overlapping CIs were considered statistically significant. SPSS-22 statistical software was used for data analysis.

Results

The study group was predominantly composed of females (n: 238; 81%). The mean age of the patients was 47.2 ± 11.8 years (range: 18–74); 203 patients (70%) were younger than 55 years old, and 84 patients (30%) were 55 years old or older. Histopathological diagnoses were 6 follicular, 279 papillary, and 2 mixed thyroid carcinomas. According to histological subtypes; 100 were follicular variant, 128 were classic type, 25 were classic + follicular variant, and 34 were unspecified. Multifocality was present in tumor cells in 122 cases (42%), while 165 cases (57%) were unifocal. Lymphovascular invasion was present in 48 cases (16%), while absent in 231 cases (80%). The lymphovascular invasion status was not specified in 8 cases. According to the 8th edition UICC/AJCC classification, 281 patients (%98) had stage 1 disease; 6 patients (%2) were stage 2. There were no patients with stages 3 and 4. The mean follow-up duration was 11.9 ± 3.1 months. The mean TSH values examined at post-op 4 weeks were 95 (min-max: 5.7–363) mU/L. The TSH level of one of the patients did not increase due to pituitary pathology. One hundred fifty-eight patients had negative Anti-Tg levels, while four patients had levels exceeding 500 IU/mL. Other values were between 33–99 IU/mL. Technetium ([99mTc]TcO4) scan at 4–6 weeks post-surgery showed residual thyroid tissue activity in 192 cases, with ultrasound confirming this in 55 cases at post-op 6 weeks. L-thyroxine treatment was discontinued 4 weeks before the 1110MBq [131I]-NaI therapy, and on the treatment day, serum TSH, Tg, and anti-Tg levels were measured again. The mean TSH values on the treatment day were 120 (range: 8–355) mU/L. There were no cases of suspicious involvement outside the thyroid bed in the whole body scan obtained 3–7 days after RAIT. The average time between ablation treatment and scanning was 11 months (range: 4–32 months). In the therapeutic efficacy assessment study, the mean stimulated TSH value was 115 (range: 23–325) mU/L. The Tg and anti-Tg values ranged from <0.9 to 21 ng/mL and <10 to 701 IU/mL, respectively (Table 1). A residual scan with 185MBq [131I]-NaI showed no residue in 243 patients, while 44 patients had residual tissue. In this group of patients with persistent tissue, SPECT/CT confirmed persistent tissue in 32 cases. SPECT/CT could not be remaining in the other 12 cases for technical reasons. Suspicious involvement was seen in 4 cases; however, these findings were ultimately attributed to non-primary disease factors such as inflammatory dental pathology, esophageal activity and contamination. No cases of locoregional or distant metastases were observed.

After ablation, an excellent response was achieved in 77% of the entire group according to ATA criteria.

When a Tg cut-off value of 10 ng/mL was taken for the entire group (based on ATA guidelines); a significant difference was observed between groups with Tg values below and above 10 ng/mL in terms of ablation success (p: 0.001). According to ROC analysis in the subgroup, when a cut-off value of 5.35 was determined, a significant difference was found between entire group (p: 0.000). The results of the ROC analysis performed in the subgroup are shown in Table 2. The highest AUC value occurred when ablation-Tg was 0.698 (0.598–0.798). Therefore, the ablation Tg value has a weak discriminatory power in its effect on ablation success.

There was no significant relationship found for age younger or older than 55, presence or absence of multifocality, presence or absence of lymphovascular invasion, or tumor subtypes according to histological subtypes within papillary carcinoma cases for ablation success. There was no significant relationship found between serum TSH values examined during ablation and ablation success (Table 3).

No significant difference was observed between groups when a cut-off value of 10 ng/mL was taken in the subgroup (p: 0.06). When a cut-off value of 5.35 was taken in the subgroup; a significant difference was found between groups below and above this value in terms of ablation success (p: 0.001).

Variables that were significant in univariate analyses (gender, ablation Tg above and below 10 ng/mL, ablation Tg above and below 5.35 ng/mL) were included in multivariate analysis.

A significant relationship was observed between male gender and ablation failure (p: 0.000), with males having a 3.2 times higher risk of ablation failure compared to females (Table 4).

In multivariate analysis (Table 4), female gender (entire group p: 0.001, subgroup p: 0.000) and ablation Tg below 5.35 (entire group p: 0.004, subgroup p: 0.012) were found to affect ablation success. Gender-OR estimates were consistent in the entire group and sub-

Table 3
Univariate analyzes of factors on ablation success.

	Entire group			Subgroup		
Variable	Successful ablation (n:221)	Unsuccessful ablation (n:66)	P value	Successful ablation (n:90)	Unsuccessful ablation (n:33)	P value
Age						
<55	155 (%54)	48 (%16.7)	0.40	68 (%55.3)	25 (%20.3)	0.59
≥55	66 (%23)	18 (%6.3)		22 (%17.9)	8 (%6.5)	
Gender						
Female	193 (%67.2)	45 (%15.7)	**0.001***	78 (%63.4)	18 (%14.6)	**0.000***
Male	28 (%9.8)	21 (%7.3)		12 (%9.8)	15 (%12.2)	
Tumor type						
Papillary	214 (%74.6)	66 (%23)	0.15	87 (%70.7)	33 (%26.8)	0.38
Others	7 (%2.4)	0 (%0)		3 (%2.4)	0 (%0)	
Papillary carcinoma tumor subtype						
Classical	47 (%16.4)	13 (%4.5)	0.46	16 (%13)	5 (%4.1)	0.48
The others	174 (%60.6)	53 (%18.5)		74 (%60.2)	28 (%22.8)	
Multifocality						
Yes	96 (%33.4)	26 (%9.1)	0.33	28 (%22.8)	15 (%12.2)	0.10
No	125 (%43.6)	40 (%13.9)		62 (%50.4)	18 (%14.6)	
Lymphovascular invasion (LVI)						
Yes	39 (%13.6)	8 (%2.8)	0.19	17 (%13.8)	2 (%1.6)	0.06
No	182 (%63.4)	58 (%20.2)		73 (%59.3)	31 (%25.2)	
Ablation Tg						
≥10	14 (%4.9)	14 (%4.9)	**0.001***	12 (%9.8)	9 (%7.3)	0.06
<10	207 (%72.1)	52 (%18.1)		78 (%63.4)	24 (%19.5)	
Ablation Tg						
≥5.35	37 (%12.9)	29 (%10.1)	**0.000***	31 (%25.2)	22 (%17.9)	**0.001***
<5.35	184 (%64.1)	37 (%12.9)		59 (%48)	11 (%8.9)	
Ablation TSH	221 (x = 123.6)	66 (x = 111.4)	0.025	90 (x = 122.6)	33 (x = 112.7)	0.07

x, mean.
* Statistically significant, P < 0.05.

Table 4
Multivariate analyzes of factors on ablation success.

	Entire group		Subgroup	
Variable	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Gender				
Female	3.26 (1.64–6.47)	**0.001***	6.08 (2.26–16.34)	**0.000***
Male				
Ablation Tg				
≥10	1.68 (0.61–4.65)	0.31	1.33 (0.40–4.42)	0.64
<10				
Ablation Tg				
≥5.35	3.10 (1.44–6.65)	**0.004***	3.73 (1.33–10.48)	**0.012***
<5.35				

P < 0.05; CI, confidence interval.
* Statistically significant.

group (OR = 3.26, 95% CI: 1.64–6.47, p: 0.001) and (OR = 6.08, 95% CI: 2.26–16.34, p: 0.000). Ablation Tg-OR estimates were consistent in the entire group and subgroup (OR = 3.10, 95% CI: 1.44–6.65, p: 0.004) and (OR = 3.73, 95% CI: 1.33–10.48, p: 0.012).

Discussion

It is known that various activities between 30–100mCi are used as ablation doses in low-risk DTC cases around the world. According to the ATA guideline, radioactive iodine ablation is not routinely recommended in low-risk differentiated thyroid carcinoma cases. However, it is stated that if ablation is necessary, it should be at a low dose.[2] We aimed to examine the effect of the 30mCi activity dose used for this purpose on ablation success in our institution, which is a thyroid center in Western Turkey. İn the recently completed randomized ESTIMABL-2 study, it was shown that in the low-risk DTC group, follow-up without [131I]-NaI was non-inferior to administration of 1.1GBq [131I]-NaI.[4] However, we think that this 3-year follow-up period needs to be supported with longer-term results in the low-risk DTC group with a benign course.

It has been stated in the literature that there is no significant difference between low doses and high doses in achieving ablation success in the low-risk patient group.[5–8] However, ablation success rates vary. This may be due to differences in the definition of ablation success and patient selection. In our study, ablation success was determined by those who responded perfectly to treatment according to the ATA guideline. It is concluded that it is a good way to avoid secondary side effects that higher doses may bring in well-selected patients.

Male gender is known as a poor prognostic factor in differentiated thyroid cancer. In the NCCN 2023 guideline, it is stated that male gender, especially those aged >40 years, should be evaluated with special concern.[9] However, although it is a simple marker, its clinical significance has not been clearly determined because it is not included in risk classifications and TNM staging system. The study conducted by Zahedi et al. on DTC patients is one of the limited studies emphasizing that the risk of recurrence is higher in men than in women.[10] Since DTC cases are generally a disease group with a benign course, we could not look at the survival times of our patient group. Apart from the evaluations in the literature in terms of mortality and recurrence, we would like to draw atten-

tion to male gender in terms of ablation failure. Therefore, we think that our study will contribute to the literature by emphasizing the importance of gender in terms of ablation success. At the same time, if the gender factor is supported by other studies and international guidelines, it can guide the clinician in the initial evaluation for the ablation dose.

[131I]-NaI therapy in low-risk DTC patients is a controversial issue. The broad definition of the low-risk group and its heterogeneity may lead to different practices in centres. It is common in ATA, ETA and SNMMI/EANM guidelines that routine use of [131I]-NaI is not recommended for patients with $\leq$1 cm intrathyroidal DTC without evidence of locoregional and/or distant metastasis. However, there are differences regarding the guiding factors regarding the use of [131I]-NaI in the low-risk group. For instance, while SNMMI/EANM states that an absolute Tg threshold requiring [131I]-NaI treatment cannot be determined in this group, the ETA guideline states that the postoperative Tg level together with postoperative ultrasound is very important. In particular, patients with Tg levels > 2 ng/mL while on thyroxine or >5–10 ng/mL after TSH stimulation have a higher risk of recurrence and [131I]-NaI therapy may be considered. However, there is no evidence that it can improve disease-free survival. However, stimulated ablation Tg levels have been associated with relapse and lack of response to low-dose [131I]-NaI ablation therapy in many studies.[11–15] Tamilia et al. demonstrated successful ablation in the majority of cases receiving 30mCi ablation therapy and indicated that stimulated-ablation Tg values were a strong predictor of ablation failure.[16] As a result of our multivariate analysis, the ablation success is supported by the effect of the Tg threshold value of 5.35.

Conclusions

Our results suggest that in most low-risk DTC cases, 1110MBq ablation dose is sufficient to achieve an excellent response 6–12 months later. When selecting a dose for ablation, besides histological markers and age as indicated in guidelines, we observed that stimulated Tg levels and gender factor could be important in predicting ablation success.

Conflict of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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