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Impact of Ablative Low Dose Radio-Active Iodine after Thyroidectomy in Low–Risk Differentiated Thyroid Cancer

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ABSTRACT
Background: Thyroid cancer (TC) is the most frequent endocrine cancer, comprising for 3-4% of all tumors.
Objective: The aim of the current study was to assess the efficacy, safety, and disease-free survival of low-dose RAI (iodine-131) in patients with low-risk differentiated thyroid cancer (DTC) who had low-dose RAI for thyroid residual ablation after full or near-total thyroidectomy.
Patients and methods: Between January 2013 and July 2019, 35 patients with low-risk well-differentiated thyroid cancer were investigated by the Clinical Oncology and Nuclear Department at Mansoura University Hospitals.
Results: The majority of our patients (94.3%) were females. A total of 34 (97.1%) patients had papillary thyroid cancer and 1 (2.8 %) patient had follicular thyroid carcinoma. All patients were *Stage I*; 13 (37.1%) patients were T1, and 22 (62.9%) patients were T2 thyroid carcinoma. All patients had pathologically negative lymph nodes and 8 (22.8%) patients had complete thyroidectomy with block neck dissection (BND), whereas the remaining 27 (77.1%) patients had total thyroidectomy without BND.
Conclusion: Low-dose radioactive iodine ablation following surgery is an effective approach for treating low-risk DTC, because it decreases the side effects while preserving a good quality of life.
Keywords: Ablative low dose radio-active iodine, Thyroidectomy, Papillary thyroid cancer, Follicular thyroid carcinoma, Thyroid cancer, Case series, Mansoura University.

INTRODUCTION

The most common endocrine malignancy, accounting for 3-4% of all cancers, is thyroid carcinoma (TC). The prevalence is increasing globally, primarily due to the increased use of advanced diagnostic methods that enable the finding of more papillary thyroid tumors (PTC) [(1)].

Differentiated thyroid carcinoma (DTC) is a histologic subtype with papillary and follicular characteristics. They make up the majority of cases, are typically given a great prognosis (90–95%), and have a good 5-year survival rate [(2)].

Low-risk thyroid cancer refers to cancers that have a low chance of recurrence, causing morbidity and death. In the last 30 years, the prevalence of low-risk DTC has tripled in the United States, the frequency of tumors ≤2 cm has increased. Worldwide, a comparable increase in occurrence has been seen [(3)]. The post-operative thyroid residual in patients with low-risk DTC can be eradicated using radioactive iodine (RAI), which is highly concentrated in the thyroid follicular cells. The conventional treatment for people with DTC has been either a whole or near-total thyroidectomy followed by radioactive iodine treatment [(4)].

After a near-complete or total thyroidectomy, low-dosage RAI is an appropriate treatment for patients with low-risk DTC. There is no discernible difference in the recurrence risk between these patients and those who received high-dose RAI [(5)].

This retrospective study aims to assess the efficacy, safety, and disease-free survival of low-dose radioactive iodine (RAI-131) therapy for patients with low-risk DTC who have undergone low-dose RAI following complete or near-total thyroidectomy.

PATIENTS AND METHODS

We included in this retrospective analysis 35 patients with low-risk DTC who were treated between January 2013 and July 2019 at the Clinical Oncology and Nuclear Medicine Department, Mansura University Hospitals. Data collected of medical records were reviewed, and information was obtained using a standard form; identifying information, such as sex, age, location, marital status, and profession. Medical history included any coexisting diseases, risk factors, previous neck irradiation, drug history, and family history. Thyroid enlargement, cervical lymph nodes (LN) enlargement, symptoms, and indications of distant metastases are all present. Histopathology, initial tumor size, the number of metastatic lymph nodes, and the presence of capsular or vascular invasion are all examples of pathological data. The following laboratory results were obtained; serum TSH, T3, T4, alkaline phosphatase, SGOT, SGPT, serum bilirubin, blood urea, serum creatinine, uric acid, total blood count, serum thyroglobulin, and, if available, antithyroglobulin antibodies. Radiological tests include a whole-body iodine scan and neck ultrasonography.

Treatment details: Surgery (total or near-total thyroidectomy with or without block neck dissection). All patients were given levothyroxine after their first RAI ablation dose in order to maintain TSH levels at or below the lower limit of the standard range. Radioiodine (I-131) ablation was performed in all patients (treatment doses, day of therapy). All patients had pre-ablation TSH concentrations more than or equal to 30 mIU/L.

The American Thyroid Association (ATA) criteria were used to analyze the outcomes. Effective

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radioactive iodine remnant ablation is indicated by serum thyroglobulin levels <2.0 µg /l and/or the lack of thyroid residual by diagnostic WBS and/or neck US at 6 months after RAI. Toxicity was assessed using conventional adverse event terminology (CTCAE). The number of months that transpired between the surgery date and the finding of a relapse, either locally or at a different location, lost follow-up, or death was used to calculate disease free survival (DFS).

Inclusion criteria

- Pathologically proven Differentiated thyroid carcinoma (papillary and follicular).
- Pathology confirmed that patients with a low risk of metastasis and no aggressive histology had (all macroscopic tumors eliminated, papillary thyroid cancer with no proof of extra-thyroid extension, follicular thyroid cancer with capsular invasion only and no or at least four foci of vascular invasion, and papillary thyroid cancer with no vascular invasion).
- Patients with TNM stages T1 and T2, N1 and M0 of the disease.
- Presence of ≤5 Lymph node metastases measuring 2mm or less.
- Age ≥18 years.
- Thyroid removal was complete or almost complete in these patients.
- Patients with **a** performance status of 0-2.

Exclusion criteria

- Pregnant patients were excluded.
- Cases linked with other malignancies were excluded.
- Patients with T3-T4, N+ except for N1 TNM stage of the disease were also excluded.

Ethical considerations

Mansoura University's Academic and Ethical Committee gave its approval to the research. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data revising, coding, processing, and analysis were all done using in Statistical Package for Social Sciences (SPSS) version 26 (IBM SPSS Inc, Chicago, IL, USA). The Shapiro-Wilk test was used to check whether the data followed a normal distribution. Summaries of numerical information included a mean and standard deviation or a median and range, depending on the data's distribution. Percentages and frequencies were used to represent qualitative data. When investigating the association between qualitative variables, Chi-square test or Fisher's exact test was used. The Kaplan-Meier technique was used to analyze the survival rate. P value ≤ 0.05 was considered significant.

RESULTS

Table 1 summarizes patients' sociodemographic and tumor characteristics. All of our patients had pathologically negative lymph nodes. In only 4 (11.4%) patients pre-ablation Tg was positive while in 31 (88.6%) was negative. Pre-ablation Tg AB was done only in 9 patients; it was positive in 3 patients and negative in 6 patients, The 35 patients received low dose radioactive iodine, and none of them was isolated at the hospital.

Table (1): Sociodemographic and tumor characteristics of the studied patients.

Characteristic	N	%
Age (years)		
≤ 40 years	19	54.3%
> 40 years	16	45.7%
Sex		
Male	2	5.7%
Female	33	94.3%
Histopathology		
Papillary thyroid carcinoma	34	97.1%
Follicular thyroid carcinoma	1	2.9%
T stage		
T1	13	37.1%
T2	22	62.9%
Block neck dissection (BND)		
Yes		22.9%
No	27	77.1%
Pre-ablation Thyroglobulin		
Positive	4	11.4%
Negative	31	88.6%

Table 2 and Figure 1 summarize low-dose RAI (30-50 mci) with successful ablation outcome. Among the 14 patients whose 1st low dose failed to ablate thyroid remnant successfully 9 of them were given a 2nd ablative low dose of RAI 131 and all were successfully ablated, the other 5 patients received a high dose of RAI. The final ablation outcome of all patients received low dose RAI was 27 (77.1%) patients.

Table (2) Outcome among the studied group.

Characteristics	Total N	N	%	Recurrence
First ablation outcome	35			
Successful		21	60%	3
Failure		14	40%	
Second ablation outcome	9			
Successful		9	100%	0
Failure		0	0%	
Final ablation outcome	35			
Successful		27	77.1%	
Failure		8	22.9%	

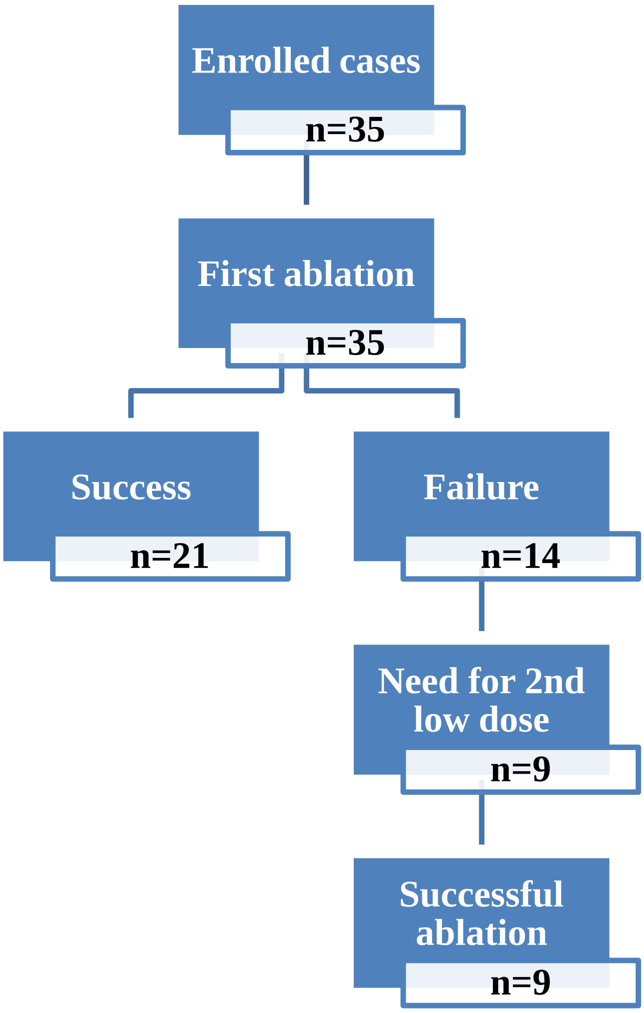

Figure (1): Flow chart of ablation outcome in studied cases.

Patients who had successful ablation with low dose RAI were followed with a median follow-up 39 months up by neck ultrasound, whole body iodine scan (WBIs), and thyroglobulin, only 3 patients developed recurrence 1 at thyroid bed and 2 patients at cervical lymph nodes. Toxicity of RAI 131 was determined using standard terminology criteria for adverse events (CTCAE), low dose RAI was tolerable with minimal side effects including 10% nausea, 8% taste problems, and 20% malfunction in the salivary glands. All the patients received their doses without hospital isolation.

Error! Reference source not found.**-6)** show the 5-years DFS and the impact of different factors on it. In this study, the 5-year DFS was 78% as shown in Error! Reference source not found.**)**.

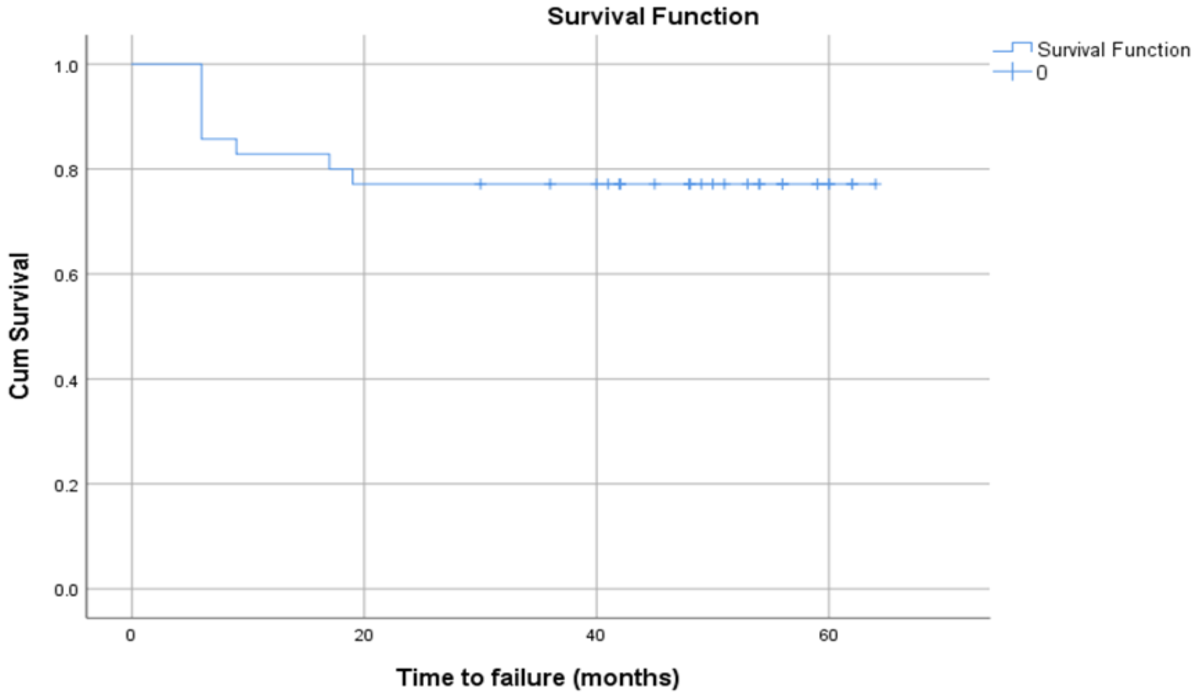

Figure (2): Kaplan Meier curve of 5 years DFS.

Age, T-stage, and doing BND with total thyroidectomy have no significant impact on DFS as shown in Error! Reference source not found.**.** P values were 0.287, 0.45, and 0.449, respectively.

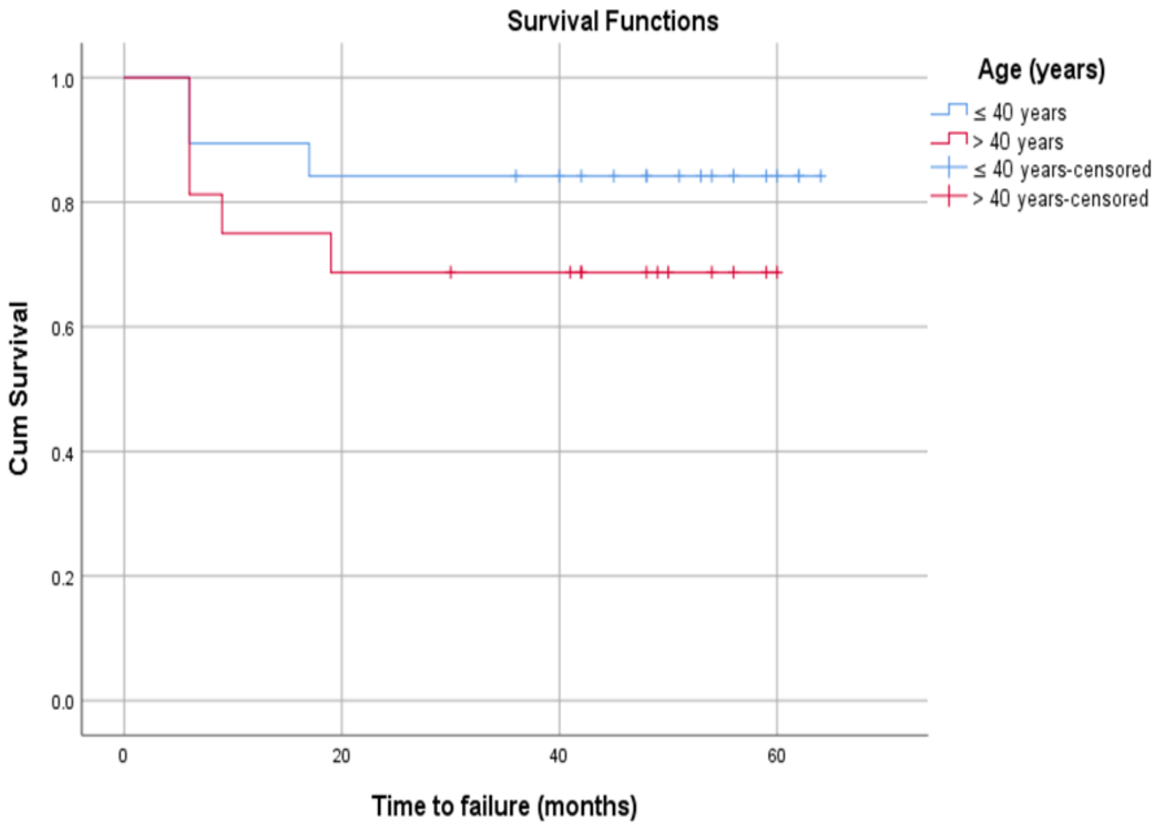

Figure (3): Age as a risk factor for time to failure of ablation.

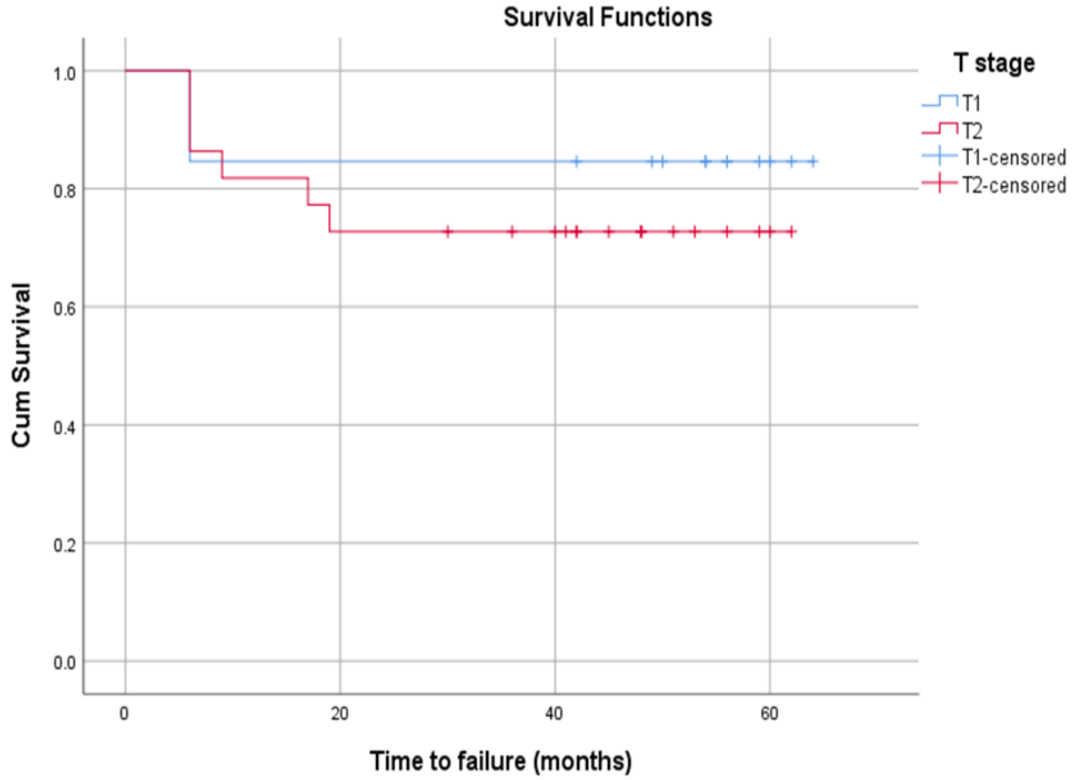

Figure (4): T stage as a risk factor for time to failure of ablation.

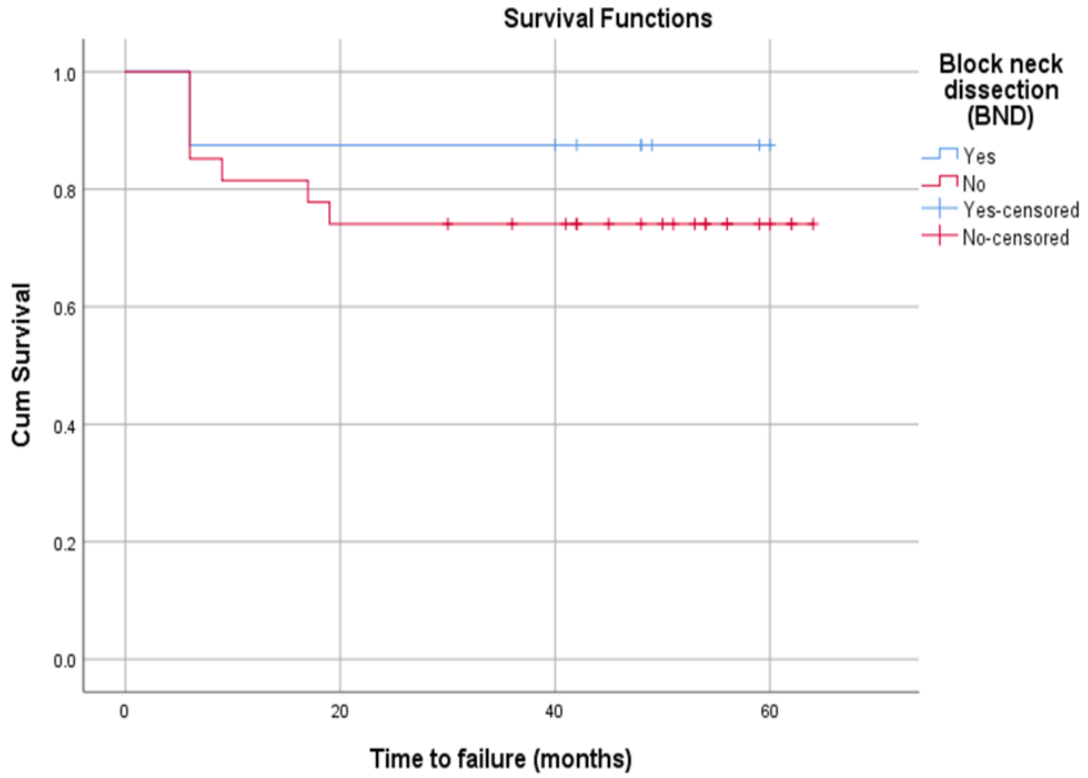

Figure (5): BND as a risk factor for time to failure of ablation.

While **Figure (6)** shows that the 3-year DFS in patients with positive pre-ablation Tg was 25% versus 83% in patients with negative pre-ablation Tg, This was statistically significant (P =0.0025).

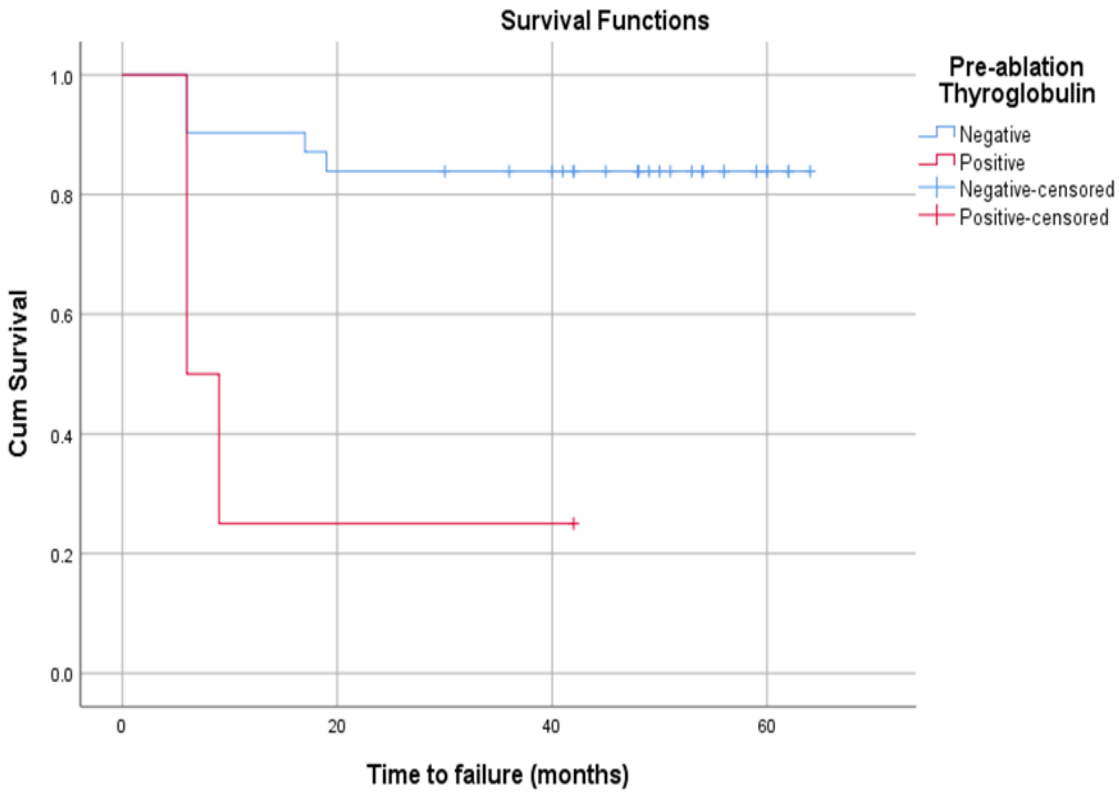

Figure (6): Pre-ablation thyroglobulin as a risk factor for time to failure of ablation.

Only pre-ablation thyroglobulin levels were shown to be statistically significant predictors of ablation failure. The hazard ratio for participants with positive pre-ablation thyroglobulin against those with negative pre-ablation thyroglobulin was 53.2. Participants who did not undergo BND had a 1.9-fold increased risk of adverse events, compared with participants who underwent BND. The hazard ratio for participants with T2 was 1.80, compared to 1.20 for those with T1. Participants aged >40 years exhibited a 2.2-times hazard ratio vs. those aged <40 years. However, none of these 3 risk variables attained statistical significance (**Table 3**).

Table (3): correlation of different prognostic factors with DFS.

Risk factor	Number events		Log rank test	
	N	%	χ^2	p-value
Age			1.1322	0.2873
≤ 40 years (N=19)	3	15.8%		
> 40 years (N=16)	5	31.3%		
'T' stage			0.5713	0.4497
T1 (N=13)	2	15.4%		
T2 (N=22)	6	27.3%		
Block neck dissection			0.5670	0.4514
Yes (N=8)	1	12.5%		
No (N=27)	7	25.9%		
Pre-ablation thyroglobulin			9.1095	**0.0025**
Negative (N=31)	5	16.1%		
Positive (N=4)	3	75%		

Table 4 displays the results of a univariate Cox proportional hazards analysis, which revealed that pre-ablation thyroglobulin was the sole statistically significant risk factor for the time to failure, with an HR of 6.6.

Table (4): Univariate analysis for prognostic factors with DFS.

Risk factor	Hazard ratios		P-value
	HR	95% CI for HR	
Age **≤ 40 years (N=19)** **> 40 years (N=16)**	r(1) 2.08	r(1) 0.5 – 8.7	0.317
Age (years)	1.04	0.98 – 1.1	0.156
'T' stage **T1 (N=13)** **T2 (N=22)**	r(1) 1.8	r(1) 0.36 – 8.9	0.473
Block neck dissection **Yes (N=8)** **No (N=27)**	r(1) 2.13	r(1) 0.26 – 17.3	0.479
Pre-ablation thyroglobulin **Negative (N=31)** **Positive (N=4)**	r(1) 6.6	r(1) 1.5 – 28.7	**0.0122**

Notes: HR = hazard ratio. CI = confidence interval.

Only pre-ablation thyroglobulin was a statistically significant independent risk factor for the duration of time until ablation failure was seen by multivariate analysis employing the Cox-proportional hazards ratio (Table 5).

Table (5): Multivariate analysis for prognostic factors with DFS.

Risk factor	Hazard ratio		p-value
	HR	95% CI for HR	
Age **≤ 40 years (N=19)** **> 40 years (N=16)**	r(1) 1.66	r(1) 0.36 – 7.6	0.516
'T' stage **T1 (N=13)** **T2 (N=22)**	r(1) 2.8	r(1) 0.52 – 14.9	0.235
Block neck dissection **Yes (N=8)** **No (N=27)**	r(1) 1.42	r(1) 0.16 – 12.8	0.754
Pre-ablation thyroglobulin **Negative (N=31)** **Positive (N=4)**	r(1) 6.5	r(1) 1.3 – 33	**0.025**

Notes: HR = hazard ratio. CI = confidence interval.

DISCUSSION

Low-risk differentiated thyroid tumors such as intrathyroid tumors are very rare to recur or produce serious side effects if treated. When it came to residual ablation, high-dosage RAI (80-100 mci) was the standard in the past. Multiple trials, however, have demonstrated that in low-risk DTC, a dosage of RAI between 30 and 50 mci is equally as beneficial as a higher dose [5].

A total of 35 people with low-risk DTC participated in the present study. Women accounted for the majority of our patients (94.3%). This is consistent with the findings of the Surveillance, Epidemiology, and End Results (SEER) Program, where the prevalence of thyroid cancer in women is four times that of men.

At presentation, 19 (54.2%) patients were under the age of 40, while 45.7% were older. The median age of participants in our research was 40 years old, according to the findings of a descriptive study of Brazilian population-based cancer registries (PBCRs), which included cases of thyroid cancer in young adults. Among Brazilian young adults, the prevalence of thyroid cancer between the years 2000 and 2013 was 76.7% for the 25–29 year age group [6].

Our research revealed that in practically all of the individuals who were diagnosed with low-risk DTC, 97.1% had papillary thyroid carcinoma, whereas just 2.9% of them had follicular thyroid carcinoma. This is quite similar to the findings of Miranda et al., who found that 90% of all thyroid malignancies are papillary thyroid carcinoma and 4% are follicular thyroid carcinoma [7].

In the present study, low-dose RAI (30-50 mci) was administered to all participants. Successful ablation was shown by a negative diagnostic WBS and undetectable blood thyroglobulin at 6 months in 21 of the 35 patients. All 9 patients who received a second dose of low RAI were successfully ablated. High-dose RAI was administered to the remaining 5 patients, the final successful ablation outcome with low-dose RAI was 27 (77.1%). Results from a prospective, randomized trial of 45 individuals with low-risk DTC are quite similar to these. In this group, 26/45 (57.8%) received 30 mci, whereas 19/45 (42.2%) received 80 mci. 15 of 19 arms (78.9%) with 80 mci were ablated successfully, whereas 15 of 26 arms (60%) with 30 mci were ablated successfully (P =0.13). This was found by Ibrahim et al. 2016 [8].

A cohort study comparing 173 people found no significant changes between the 30 mCi and 100 mCi radioiodine groups. In all, 170 (98.3%) of the 173 patients who underwent ablation had positive outcomes. Ablation success rates after the first dose were 78.2% in the low-dosage group and 73.3% in the high-dose group (P =0.36). Final success was 97.6% of those given the low dose and 98.9% of those given the high dose (P =0.54) [9].

There were only three recurrences among the 35 patients in this trial; one in the thyroid bed and two in the cervical lymph nodes. This is quite similar to the findings of the non-inferiority, parallel, open-label, randomized controlled trial known as the Hilo study, which was conducted in the United Kingdom at 29 sites between January 16, 2007, and July 1, 2010. The trial had 438 participants who were split into two groups at random: 1.1 GB was given to 217 people. On December 31, 2017, the median follow-up time for 434 patients was 6.5 years. With 21 confirmed recurrences, 11 occurred in the low-dose group and 10 occurred in the high-dose group [10].

A retrospective study of Chinese patients diagnosed with DTC between 1990 and 2016 with a median follow-up of 6.5 years. 4292 persons were identified as having DTC based on ATA criteria. After a median of 57.8 months of follow-up, 60% of individuals with a low-risk profile remained disease-free [11].

The DFS was correlated with the prognostic variables. Our research found that the 5-year DFS for patients younger than 40 was 84%, whereas the DFS for patients older than 40 was 69%. As one gets older, their DFS decreases. This aggress with the results of a cohort study including 15,675 participants conducted by Kauffmann et al. Twenty-one percent were older than 60 years old, while 46.3% were between the ages of 18 and 44. DSS and DFS are worse for PTC patients younger than 60 years old at all disease stages. These findings provide credence to the use of age as an independent predictor of survival and recurrence in the current staging criteria for patients, since survival rates decline precipitously beyond age 45 [12].

The 5-year DFS rate in our research was 85% for patients with T1, and 72% for individuals with T2 (P =0.45). This mirrored the results of a retrospective study of 2323 individuals diagnosed with DTC at Texas University in the United States, which found that those with larger tumors (>4 cm) had shorter DFS rates [13].

Patients in our research who had complete thyroidectomy with BND had a DFS of 98% at 5 years, whereas those who did not have BND had a DFS of 74%. No statistically significant difference (P =0.45) was found between total thyroidectomy alone, ipsilateral, and bilateral prophylactic central neck dissection in a retrospective study of patients hospitalized with clinically node-negative differentiated thyroid carcinoma between January 2008 and December 2010. People with no lymph nodes accounted for 163 occurrences of DTC. Patients were classified into one of three groups based on the procedures they had. There were 103 (63.2%) patients in Group A who underwent a complete thyroidectomy (TT) but no lymph nodes removed. In Group B, 30 (18.4%) patients had TT with ipsilateral node dissection, while in Group C, 30 (18.4%) patients underwent TT with bilateral node dissection. **Cal et al., 2017** found that total thyroidectomy was a successful treatment for patients with clinically node-negative DTC. In terms of regional recurrence, there were no statistically significant differences between the three groups [14].

A retrospective, non-randomized observational analysis of 477 individuals who had total thyroidectomy with or without pCND for clinically node-negative PTC measuring 4 cm comprised 341 participants who underwent pCND and 136 patients who did not. Between individuals with and without pCND, the recurrence rate was 2.96% and 1.48%, respectively (P =0.684). The number of years between occurrences was patterned similarly in both groups [15].

Our research showed that the 3-year DFS for patients with a positive pre-ablation Tg was 25%, whereas the DFS for individuals with a negative pre-ablation Tg was 83%. The statistical significance of this difference was found to be significant (P =0.002). This was the finding of research that followed up 103 persons with DTC who had a complete thyroidectomy. According to ATA risk prediction criteria, patients were ranked according to their likelihood of experiencing a recurrence: low, moderate, or high. Pre-ablation Tg was predictive of persistence in 94.7% of patients having long-term follow-up data, whereas a negative pre-ablation Tg was linked with a low likelihood of long-term illness recurrence. Except for the five patients diagnosed with papillary microcarcinoma, all patients were treated with RAI [16].

None of the patients required hospital isolation, and they were all able to tolerate radioactive iodine without any unpleasant side effects. There is nothing but nausea, flavor changes, and discomfort in the salivary glands. According to Andresen et al., "In patients with low-risk differentiated thyroid carcinoma who have had a complete thyroidectomy, the percentage of effective residual ablation is comparable between doses of 30-50 mCi and dosages of 100 mCi," the latter group experiencing more chronic side effects, including nausea (13% versus 4%), neck pain (17% versus 7%), lacrimal gland dysfunction (10-24% versus 8-20%), and salivary gland dysfunction (5-16% versus 6-8%) **[17].**

In conclusion, low-dose RAI for postoperative radioiodine ablation may be a beneficial therapeutic option for low-risk DTC because it reduces the likelihood of adverse effects without affecting quality of life.

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Author contribution: Authors contributed equally in the study.

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