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Assessment of Different Radioactive Iodine Ablation Strategies in Intermediate and High Risk Papillary Thyroid Cancer

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ABSTRACT

Background: Papillary thyroid cancer (PTC) represents most of cases of differentiated thyroid cancers. Thyroidectomy followed by radioactive iodine (RAI) remnant ablation represent the cornerstone management of many intermediate and high-risk patients according to American Thyroid Association (ATA).

Objective: This study aimed to evaluate the outcome of different used I^{131} ablation doses (80, 100 and 120 mCi) in intermediate and high-risk patients in our hospital and to analyze the predictors affecting RAI failure. Besides, survival analysis was conducted as a secondary objective of the study.

Patients and Methods: This was a retrospective study conducted on 63 patients diagnosed as PTC at our hospital from January 2015 till February 2020. Our study involved only PTC pathology, mean age of 40.6 ± 13.4 years at diagnosis, and intermediate- and high-risk patients according to ATA initial risk stratification system, 2015.

Results: Among the 63 patients included in this study (17 males and 46 females), 41 were classified as intermediate-risk, while 22 were classified as high-risk based on the ATA guideline. Overall RAI ablation success, in both groups, was observed in 43/63 (68.25%) patients. Moreover, it was achieved in 31/41 (75.6%) of intermediate-risk patients and in 12/22 (54.5%) high-risk patients. Pre-ablation stimulated Tg >1ng/ml was statistically significant negative predictor of ablation failure [P-value < 0.001, odd`s ratio 61.5, 95% CI (10.8-51.5)].

Conclusion: There was no statistically significant difference between success rates of I^{131} doses in intermediate- and high-risk groups. However, the failure rates were more after 120 mCi due to the associated more aggressive underlying disease, especially higher-risk patients so higher RAI activities are recommended for this risk group.

Keywords Papillary thyroid cancer, Radioactive iodine, Remnant ablation.

INTRODUCTION

Thyroid cancers represent nearly about 3% of new cancer cases diagnosed yearly. Thyroid cancer incidence rates have increased in the last thirty years around the world but not in Africa, mainly due to insufficient screening [(1)]. In **Egypt**, thyroid cancer represents about 1.5% of all cancers and is responsible for 30% of endocrine neoplasms. Female to male ratio among Egyptians is less than 3. Thyroid cancer is generally categorized primarily on the cell of origin. PTC is the most common kind of thyroid cancer, representing roughly 80% of all patients. Follicular thyroid carcinoma (FTC) is the second frequent form, accounting for around 15% of all cases. Both papillary and follicular malignancies are classified as differentiated thyroid cancer (DTC) because they arise from thyroid follicular cells [(2, 3)].

At 2009, **the American Thyroid association (ATA)** published her first stratification system specialized to thyroid cancer with different categories according to histological type of the disease. Recently, at 2015, ATA has modified their risk system with more risk items added to the initial one published at 2009. After every publishing the oncologists preferred applying ATA system in practice with further more thorough monitoring of its implication on the disease course. Also, major cancer institutes and hospitals adopted the clinical practice according to ATA risk stratification, besides the leading guidelines included it within its recommendations. ATA risk stratification system classified DTC into three groups; low-, intermediate- and high-risk group of recurrence [(3)].

Thyroidectomy is the cornerstone surgery in management of thyroid carcinomas. Many studies have estimated the role of different types of thyroidectomies. They compared total and near-total thyroidectomy alongside the less eradicating surgical procedures. These studies advocate that higher risk patients have a significantly improved survival when they undergone a more aggressive surgery [(4, 5)]. For post-operative management in non-metastatic cases, the term **"radioiodine remnant ablation (RRA)"** is used and it is defined as "the destruction of residual macroscopically normal thyroid tissue after surgical resection of the thyroid gland [(6)]."

The Dose of post-operative RAI varies between different scenarios. A wide range of RAI activities are used in various ATA risk groups starting with 30 mCi as ablative dose for low-risk patient. As for intermediate- and high-risk setting, more activity is needed to achieve best ablation results or in adjuvant way. The recommended range starts with 50 mCi for patients having relatively lower-risk features, while it may reach up to 150 mCi for patients possessing additional riskier criterion [(4, 7, 8)]. For response evaluation after thyroidectomy with post-operative RAI, ATA guidelines recommended a strict criterion for defining the response during the follow up after finishing therapy using three main factors; (1) Neck ultrasound and clinical evidence, (2) Whole body

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iodine scan and (3) Serum thyroglobulin and TG-Ab [(4)]. The optimal dose of RAI ablation is very controversial, so the study aimed mainly to evaluate the different RAI doses outcome.

PATIENTS AND METHODS

This study included a review of 63 patients with papillary thyroid carcinoma of intermediate- and high-risk category according to ATA, presented to Mansoura Clinical Oncology and Nuclear Medicine Department during the period from January 2015 to the end of February 2020.

Data collection:

Data were collected from medical records of Mansoura University Hospital during the period from January 2015 to the end of February 2020, with studying of demographic data (Age, gender, marital status and occupation), medical history (Family history, risk factors and past history), clinical data (neck swelling, obstructive symptoms, performance status (ECOG), hoarseness of voice and retrosternal extension), histopathological data (type of tumor, tumor size, lymph node metastases with or without extranodular extension, capsular invasion, lympho-vascular invasion and multifocality), laboratory tests (TG,TG-Ab), radiology (neck ultrasonography, whole body iodine scan and computed tomography) and management types (surgery: total or subtotal thyroidectomy, RAI : activity dose, date).

Patients' classification according to risk groups:
Patients were classified according to ATA 2015 risk stratification system into intermediate-risk group and high-risk group [(4)].

Exclusion criteria: Low risk group, M_1 cases and double malignancy.

Ablation outcome and survival functions:

- Excellent response (successful ablation): defined as TG level below 1 ng/ml and negative structural disease by radiology) according to ATA.
- Incomplete response (Failed ablation): defined as indeterminate response and biological and structural failure, according to ATA.
- Overall survival (OS): calculated in months and assessed for 63 patients from the surgery/pathology date till end of study or event.
- Disease free survival (DFS): assessed for 63 patients with PTC and calculated in months from date of documentation of successful RAI ablation till date of loco or locoregional recurrence.

Ethical consent:

An approval of the study was obtained from Mansoura University Academic and Ethical Committee. 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

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 26 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant. Kaplan-Meier method was used for survival functions.

RESULTS

This study included 63 patients diagnosed with papillary thyroid cancer and they were presented to Mansoura Clinical Oncology and Nuclear Medicine Department.

The study included 46 female patients representing about 73 % of cases, with male to female ratio about 1:2.7. Fifty-two patients had ages ranging from 18 to 54 years (82.5%) and 11 aged from 55 to 70 years (17.5%). The mean age was 40.6 ± 13.4 years. Thirty-five patients (55.6%) presented with performance status 0 according to Eastern Cooperative Oncology Group (ECOG). The main presenting symptom was "neck swelling" which was observed in 57 patients (90.5%), followed by "obstructive symptoms" seen in 9 patients (14.3%) and "hoarseness of voice" was only noticed in 2 cases (3.2%) (Table 1).

Table (1): Patient characteristics

	N	%
Gender		
Male	17	27%
Female	46	73%
AGE		
< 55	52	82.5%
≥ 55	11	17.5%
ECOG		
0	35	55.6%
≥1	28	44.4%
PRESENTING SYMPTOM		
Neck swelling	57	90.5%
Hoarseness of voice	2	3.2%
Obstructive symptoms	9	14.3%
RISK GROUP		
Intermediate	41	65.1%
High	22	34.9 %

Most of cases presented with T_1 stage (49%). Twenty-eight cases (44.4%) had cervical LN metastasis. Multifocality and LVI, each was noticed in 20 cases (31.7 %). Capsule infiltration and minimal ETE were presented in 19 patients (30.2%). Forty-one patients (65.1%) were classified as intermediate risk, while 22 patients (34.9%) were in high-risk group (Table 2).

Table (2): Tumor characteristics

	N	%
T		
T_1	31	49.2%
T_2	16	25.4%
T_3	14	22.2%
T_4	2	3.2%
Stage		
I	54	85.7%
II	8	12.7%
III	1	1.6%
LN		
N0	35	55.6%
N1	28	44.4%
LVI	20	31.7%
Capsule infiltration and minimal ETE	19	30.2%
Gross ETE	10	15.9%
Gross residual	9	14.3%
Positive LN	28	44.4%
Extra-nodular extension	1	1.6%
Multifocality	20	31.7%

The overall successful ablation (excellent response) after single (1st) RAI dose was 68.25 %, while the success rate was 75.6 % in intermediate group and 54% for high-risk group. The failure rate (incomplete response) was high in patients who received 120 mCi in high-risk group (70%), while in intermediate-risk group it was (40.50%) in patients who received 80 and 100 mCi doses respectively. However, the differences did not achieve statistical significance. Out of the 63 patients, 20 patients had incomplete response (31.75%) (Table 3).

Table (3): Distribution of response according to risk group and RAI doses

Group / dose	Excellent	Incomplete	P value
Intermediate risk	N=31	N=10	0.868
80 mCi	16 (51.6%)	**4 (40%)**	
100 mCi	12 (38.7%)	**5 (50%)**	
120 mCi	3 (9.7%)	1 (10%)	
High risk	N=12	N=10	0.148
80 mCi	6 (50%)	2 (20%)	
100 mCi	3 (25%)	1 (10%)	
120 mCi	3 (25%)	**7 (70%)**	

There was a statistically significant association of high strength between ablation response (excellent/ incomplete) vs. Tg level (≤ 1 / >1 ng/ml). There was association of low strength between ablation response (excellent and incomplete) and risk groups, RAI doses, sex, type of surgery, neck swelling, hoarseness of voice, T stage, LN stage, capsule infiltration/minimal ETE, and ENE. However, none of these associations achieved statistical significance (Table 4).

Table (4): Comparisons between response after 1st RAI

Factor	Excellent response N=43	Incomplete response N=20	Association strength	P-value
Risk category				
Intermediate	31 (72.1%)	10 (50%)	Phi = 0.216	0.087*
High	12 (27.9%)	10 (50%)		
RAI dose				
80 mCi	22 (51.2%)	6 (30%)		
100 mCi	15 (34.9%)	6 (30%)	Cramer's V= 0.299	0.075$
120 mCi	6 (14%)	8 (40%)		
Age group				
18 – 54 years	35 (81.4%)	17 (85%)	Phi = 0.044	1.000$
55 – 70 years	8 (18.6%)	3 (15%)		
Sex				
Male	9 (20.9%)	8 (40%)	Phi = 0.200	0.112*
Female	34 (79.1%)	12 (60%)		
Surgery				
Total thyroidectomy	42 (97.7%)	18 (90%)	Phi = 0.168	0.234$
Subtotal thyroidectomy	1 (2.3%)	2 (10%)		
ECOG				
0	25 (58.1%)	10 (50%)	Phi = 0.076	0.545*
≥1	18 (41.9%)	10 (50%)		
Thyroglobulin				
≤1 ng/ml	41 (95.3%)	5 (25%)	**Phi = 0.738**	**<0.001***
>1 ng/ml	2 (4.7%)	15 (75%)		
Neck swelling	37 (86%)	20 (100%)	Phi = 0.221	0.164$
Hoarseness of voice	0 (0%)	2 (10%)	Phi = 0.266	0.097$
Obstructive symptoms	7 (16.3%)	2 (10%)	Phi = 0.084	0.706$
T				
T_1	22 (51.2%)	9 (45%)		
T_2	9 (20.9%)	7 (35%)	Cramer's V= 0.185	0.612$
T_3	10 (23.3%)	4 (20%)		
T_4	2 (4.7%)	0 (0%)		
LN	21 (48.8%)	7 (35%)	Phi = 0.130	0.304*
Tumor size (cm)				
< 2.5 cm	21 (48.8%)	9 (45%)	Phi = 0.036	0.777*
≥ 2.5 cm	22 (51.2%)	11 (55%)		
Stage				
Stage I	37 (86%)	17 (85%)		
Stage II	5 (11.6%)	3 (15%)	Cramer's V = 0.097	0.799$
Stage III	1 (2.3%)	0 (0%)		
Multifocal tumor	15 (34.9%)	5 (25%)	Phi = 0.099	0.433*
LVI	13 (30.2%)	7 (35%)	Phi = 0.048	0.705*
Capsule infiltration and minimal ETE	11 (25.6%)	8 (40%)	Phi = 0.146	0.246*
RSE	1 (2.3%)	1 (5%)	Phi = 0.071	0.538$
Gross ETE	6 (14%)	4 (20%)	Phi = 0.077	0.713$
ENE	0 (0%)	1 (5%)	Phi = 0.186	0.317$
Gross residual	6 (14%)	3 (15%)	Phi = 0.014	1.000$

Notes: Test of significance is Chi-square*, or Fisher's exact test$ for categorical data.

In univariate analysis, thyroglobulin level more than 1 ng/ml, and RAI dose of 120 mCi were significant predictors of ablation failure. Also, high-risk group and male sex were marginally significant predictors. So, the multivariate analysis included these factors (Table 5). High-risk group had an incomplete response rate 2.6 times than intermediate group with marginal significance. RAI dose of 120 mCi had failure rate 4.9 times than reference dose with statistically significant result, while 100 mCi dose had 1.5 times failure rate than the reference without statistically significance. Male gender also had higher failure rate than female gender about 2.5 times and it showed no statistically significance. Thyroglobulin (before ablation) level was higher than 1 ng/ml, which showed significant high incidence of failure of ablation about 61 times than lower levels of Tg and this result was statistically significant. These results showed nearly the same significance in the multivariate model. This model was statistically significant (χ^2 = 41.609, P < 0.001). The model correctly classified 88.9% of cases with 75% sensitivity, and 95.3% specificity for prediction of incomplete response (Table 5).

Table (5): Predictors of the likelihood of incomplete response

Factor	Univariate		Multivariate	
	COR (95% CI)	P value	AOR (95% CI)	P value
Risk category				
Intermediate	r(1)		r(1)	
High	2.6 (0.86-7.8)	0.091	1.2 (0.16-8.3)	0.883
RAI dose				
80 mCi	r(1)		r(1)	
100 mCi	1.5 (0.4-5.4)	0.566	1.3 (0.14-11.5)	0.826
120 mCi	4.9 (1.2-19.7)	**0.025**	10.1 (1.1-93.7)	**0.042**
Sex				
Female	r(1)		r(1)	
Male	2.5 (0.79-8)	0.118	0.36 (0.03-4.4)	0.426
Thyroglobulin				
≤1 ng/ml	r(1)		r(1)	
>1 ng/ml	61.5(10.8-51.5)	**<0.001**	147.4 (12.7-711)	**<0.001**

In this study the overall survival (OS) was 98.4%. Mean OS was 36.4 months (Figure 1). OS was worst in the age group ≥ 55 years (90.9%). This was statistically significant (P = 0.014) (Figure 2), while the rest of prognostic factors did not show statistical significance. The disease-free survival (DFS) was 96.8% (Figure 3). Male gender (P = 0.027) (Figure 4), incomplete response of ablation (P = 0.027) (Figure 5) and thyroglobulin level >1 ng/ml (P = 0.023) (figure 6) all were statistically significant prognostic factors for DFS.

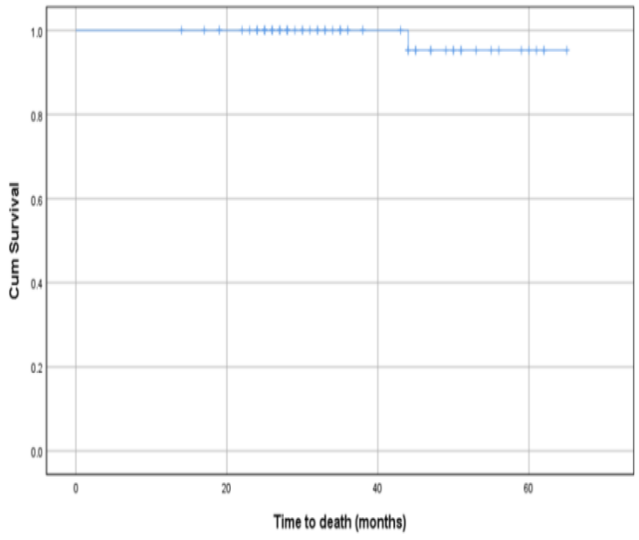

Figure (1): Kaplan Meier OS curve for all cases included

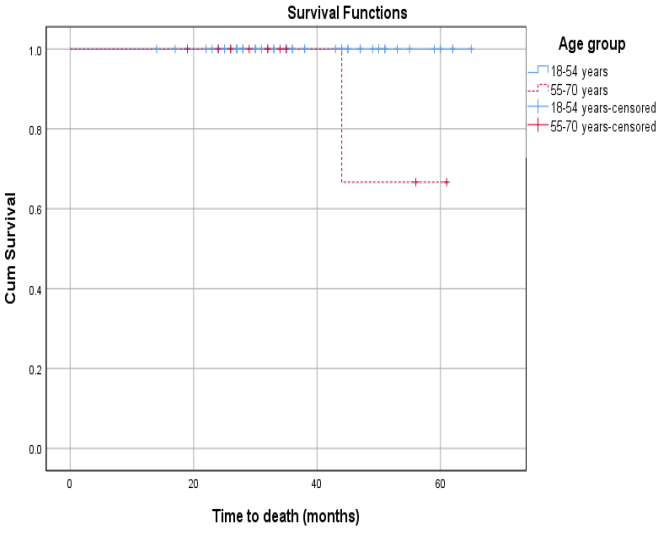

Figure (2): Kaplan Meier OS curve for age groups

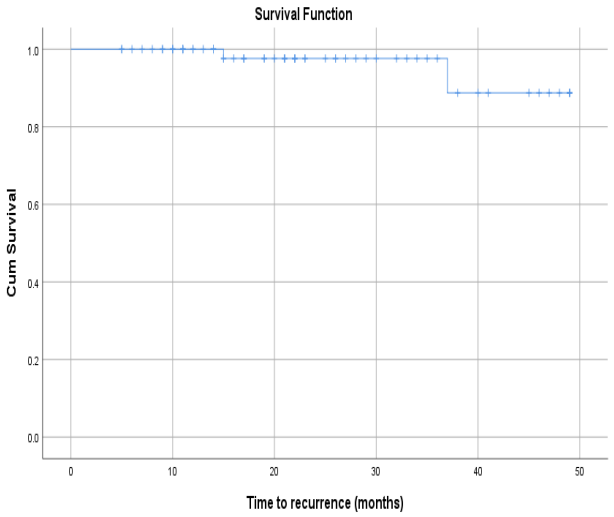

Figure (3): Kaplan Meier DFS curve for all cases included

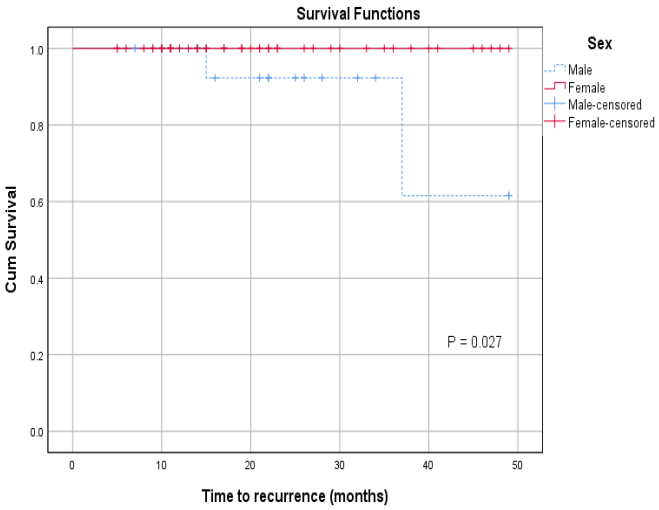

Figure (4): Kaplan Meier DFS curve for Sex

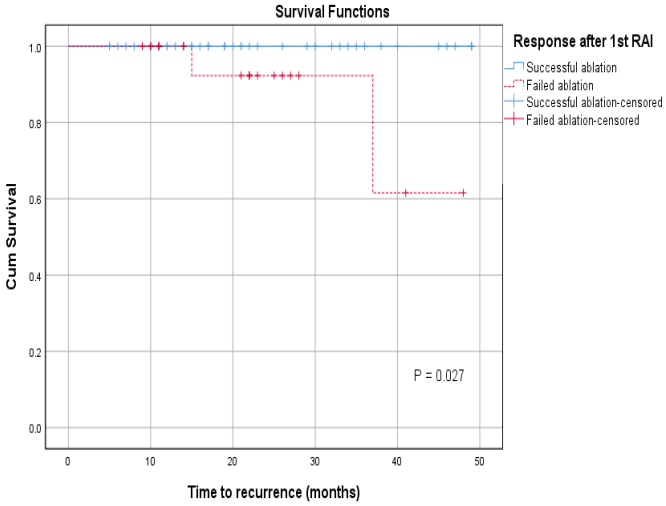

Figure (5): Kaplan Meier DFS curve to RAI ablation response

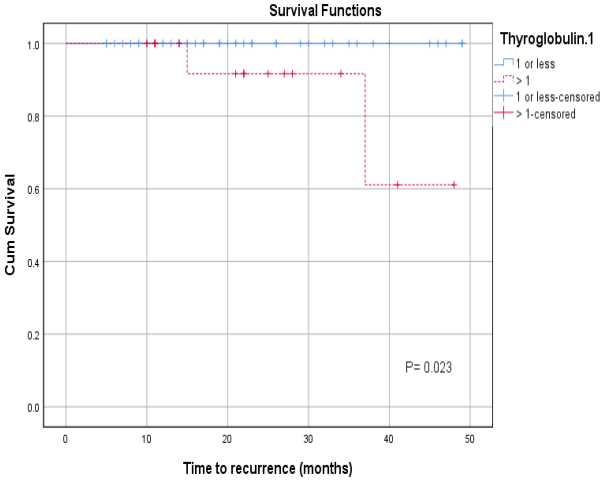

Figure (6): Kaplan Meier DFS curve for Thyroglobulin level groups

DISCUSSION

In this study, the total number of patients included with the predefined inclusion criteria were 63 patients diagnosed with PTC. In our study the majority of cases were below the age of 55 years (82.5%) while (17.5%) of cases were above 55 years old. The mean age in the study was 40.6 years. This age remains lower than the median age, 51 years, in USA, according to SEER 22 (2015-2019). The median age in our study was around 43 years, which is found by another study done at Mansoura University [9-10]. The younger age at diagnosis could be attributed to the relatively younger age of most of both genders at Egypt than USA which expresses a longer lifespan and average age.

Most of patients were females (73%) while males were (27%) with male to female ratio 1:2.7. This result coincides with SEER at USA, which found that male to female ratio was 1:2.76 [10].

The incidence of LN metastasis in our study was (44.4%) which nearly agrees with a retrospective study of 859 patients with papillary thyroid cancer done at Mayo Clinic. This study found that about 37% of cases had LN metastasis during management. Also, PTC has LN involvement range mostly from 35% to 50% [11]. In another study conducted by **Shah *et al.*** [11], they found that LN metastasis was found at 451 cases (48%).

The RAI ablation success rate after one RAI dose for both groups, at our department, was 68.2%. This result nearly matches another study by **Iizuka *et al.*** [12], who conducted study over 119 patients with intermediate- to high-risk thyroid cancer and found that 86 (72%) patients had successful ablation. Despite that there was low strength of association between RAI dose and ablation response, it did not reach statistical significance. However, in univariate and

multivariate analysis it showed statistical significance, 0.025 and 0.042 respectively for 120 mCi dose vs lower dose (80 mCi). This significant failure with the higher dose could be attributed to association between the high dose RAI (120 mCi) and underlying aggressive disease with more complicated behavior and risk features and this setting of disease needs more study to fully understand the negative and positive predictors of the disease. We also concluded that ablation success rate did not vary through different doses of RAI as an independent factor for ablation response. This is in agreement with **Watanabe *et al.* [13],** who found that high dose RAI was not superior to low dose RAI in intermediate- to high-risk differentiated thyroid cancer.

Throughout the study, we found that high pre-ablative/post-operative TG was statistically significant negative prognostic factor with high strength of association and higher failure incidence more with TG level above 1 ng/ml. This notice is observed also by **Lubin *et al.* [14],** who found that following surgery but before RAI, if the patient was found to have elevated serum levels of Tg, this was more likely to be associated with ablation failure (P = 0.011).

Also, **Rosario *et al.*** [15] found that all patients with stimulated Tg ≤ 1 ng/mL and normal ultrasonography before ablation continued to show the same results up to a year after initial therapy irrespective of the administration of low or high I^{131} dose.

Our study found that male sex has higher incidence of ablation failure than female sex with an odd's ratio of 2.5. Despite it did not reach statistical significance, most of studies showed the same conclusion. However, only 37% of studies found close correlation between them. This could be attributed to the more delay in seeking medical help from men than women, so most of male cases reach higher stages at presentation and as a result, a higher failure rate.

In the present study, risk groups were analyzed with other factors in univariate and multivariate logistic regression and we found a marginal significance between it and ablation failure. However, high-risk group had higher COR (2.6) than intermediate group with P-value = 0.091. This result is nearly matching with **Iizuka *et al.*** [12] who found also that there was no significance between intermediate- and high-risk patients with RAI response in univariate analysis (P = 0.08).

According to SEER 17 (2012-2018) the expected 5-years survival rate among differentiated thyroid cancer patients was 98.4%. This is exactly coinciding with our present study. Also, at Canada, the 5-years survival nearly matches our result (98%) [10-16].

CONCLUSION

- Early detection of the disease and proper stratification of patients according to the different stratification groups will help our selection of management besides predicting the prognosis.
- Higher RAI doses, especially in high-risk groups, more than 120 mCi should be included more in our practice for better outcome results.
- Lower doses as 50 mCi and 80 mCi should be more offered to intermediate-risk group rather than higher doses more than 100 mCi
- Strict follow up should be offered more in some cases of incomplete response especially indeterminate response.
- Computerized medical archive system is very important for patient data registration with more data included in it we could conduct more and variable studies.

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Author contribution: Authors contributed equally in the study.

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