Effect of Different Ablative Doses of Radioactive Iodine in Patients with Differentiated Thyroid Carcinoma and Cervical Lymph Node Metastasis

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Abstract:

Background: Thyroid cancer is the most prevalent endocrine malignancy accounting for 2% of all cancers in Egypt. Differentiated thyroid cancer (DTC) is the most histopathological subtype. Surgery with postoperative radioactive iodine (RAI) ablation is the standard treatment. Cervical lymph node metastasis is most popular site of metastasis.

Objective: The study aims to assess the effect of different doses of RAI 131I on progression free survival (PFS) and overall survival (OAS) in patients with DTC and cervical LN metastasis.

Patients and Methods: Seventy patients with DTC with cervical lymph node metastasis who had been seen at the Clinical Oncology Department, Mansoura University Hospitals between 1st of 2015 to the end of 2020 were included in this retrospective analysis.

Results: Male to female ratio was 1:1.8. The mean age was 40.98 (SD ± 14.34) years ranging from 18-69 years. Papillary thyroid carcinoma (PTC) represented 62 patients (88.6%). Fifty-seven (81.4 %) of patient were presented with stage I disease. Mean OAS was 64.01 (SD ± 14.18) ranging from 15-92 months. The 2-year PFS was 88.6% with mean PFS 46 (SD ±19.7). OAS prognostic factors were stage, tumor size (T-stage), presence of ECE or patient performance status (p-value = <0.001, 0.002, 0.041, and 0.024 respectively).

Conclusion: The high postoperative TG, PNI, ENE and higher number of involved LNs have negative clinical outcome. RAI ablation is essential for the right patient after confirming the risk category to improve the course of the disease, increase survival rates, and stop additional recurrences.

Keywords: RAI 131; Ablative dose; DTC; cervical lymph node; thyroid cancer

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Introduction:

Thyroid cancer is the most prevalent endocrine malignancy in the world, accounting for 2% of all cancers in Egypt [1]. Most differentiated thyroid carcinoma (DTC) forming either papillary, follicular, or hurthle cell carcinoma [2].

Surgery (total or near-total thyroidectomy with or without lymphadenectomy), radioactive iodine therapy (RAI) to destruct the thyroid remnant tissue, and molecular-targeted therapies with several tyrosine kinase inhibitors (TKIs) are treatment options for thyroid cancer which depend on the cancer type and stage [3,4].

As part of the head and neck, thyroid cancer spreads to the cervical LN, especially in the central compartment to levels 6 and 7, then in the lateral compartment to levels 2 and 5, and then to the contralateral side. Skip metastases to lateral LNs without central compartment disease have been reported in up to 20% of cases [5].

RAI is indicated after total thyroidectomy depend on multiple factors as primary tumor size, histology, degree of lymphatic invasion, lymph node metastases, postoperative thyroglobulin, and age at diagnosis for many reasons such as remnant ablation to achieve an undetectable serum thyroglobulin concentration and to decrease the risk of recurrence [6].

We aim in our study to assess the effect of different doses of RAI 131I on progression free survival (PFS) and overall survival (OAS) in patients with DTC with cervical LN metastasis.

Patients and Methods:

This is a retrospective study of 70 patients has DTC with cervical LN metastasis who presented to Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital, between first of 2015 to the end of 2020 inclusive. Physical examination, laboratory work up, radiological assessment, pathological diagnosis, and treatment (surgery, radioactive 131I ablative doses) were collected from patients' electronic records.

Inclusion criteria included pathologically confirmed DTC with cervical lymph node metastasis confirmed either pathologically or with RAI 131 whole body scan. Patients were more than 18 years old. Patients who were older than 70 years old and younger than 18 years, with double malignancy, distant metastasis at time of diagnosis and with any pathology rather than DTC were excluded.

We studied the effect of different doses of RAI 131 on progression free survival (PFS) and overall survival (OAS) in patients with DTC and cervical LN metastasis.

This study was approved by ethical committee (IRB) Institutional Review Board of Mansoura University, Faculty of medicine with Code Number: MS.21.03.1411.

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 or failed response: defined as indeterminate response, biological and structural failure, according to ATA.
- Overall survival (OAS): Calculated in months from the surgery/pathology date till end of study or event.
- Progression free survival (PFS): Calculated in months from start of treatment till progression.
- Follow up: Calculated from end of treatment till end of study or last visit.

Statistical analysis:

The available data were coded, tabulated and analyzed. IBM SPSS software package version 26 for Windows (Statistical Package for Social Sciences) was used. The appropriate statistical tests were used. Qualitative data were presented as numbers and percent. Quantitative data was presented with median and range. OAS was analyzed using Kaplan Meier survival curves. Cox proportional hazards models used to calculate the univariate and multivariate analyses for prognostic factors which affected the survival. The level of significance was considered statistically significant for the analysis when p was ≤ 0.05.

Results:

Our study included 70 patients diagnosed with DTC presented to Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital during the period from the start of 2015 to 2020 inclusive.

As regard patient characteristics, the mean age of the study was 40.98 (SD ± 14.34) years ranging from 18 to 70 years most of them aged 18-54 years (81.4%). Females was 45 patients, represent 64.3% of cases, with male to female ratio about 1:1.8. Twenty-nine patients (41.4%) presented with performance status 0 according to Eastern Cooperative Oncology Group (ECOG) and 39 patients presented with ECOG score 1 (55.7%).

Regarding tumor characteristics, we found that most of our cases were at early stage (57 patients) with 81.4%. PTC represents the most common histopathological subtype (62 patients) with 88.6%. All of cases have cervical LN metastasis. We noticed that multi-focality were found in 25 Patients (35.7 %), LVI in 19 patients (27.1%), Capsule infiltration in 17 patients (24.3%), and gross extra thyroid in 14 patients (20%). More than half were classified as intermediate risk in 43 patients (61.4%), while 27 patients (38.6%) were in high-risk group.

At the end of the study 66 patients (94.3%) were alive and 4 patients lost follow up after variable periods but after ending their treatment. The mean follow-up period was 46.7 months (SD ± 17.598) ranging between 8-87 months.

Mean OAS was 64.01 months (SD ±14.18) ranging from 15- 92 months. The 2-year PFS was 88.6% with mean PFS 46 months (SD ± 19.7) as presented in Figure (1), The 5-years overall survival in this study was 91.4% as shown in figure (2).

The univariate analysis of survival prognostic factors shown at Table (3). Regarding OAS, the disease stage, tumor size (T-stage), presence of ECE or patient performance status were significant prognostic factors (P-value = <0.001, 0.002, 0.041, and 0.024 respectively).

The successful ablation in cases without gross ETE, or ENE was (42%, 48% respectively), and in patient with Thyroglobulin level <10 ng/ml versus ≥10 ng/ml was 40% to 8%. Successful ablation at intermediate versus high-risk cases was 36% vs 12%.

More detailed representation of different degrees of response shown at Table (4). It shows PNI, ENE, number of involved LNs, TG level, and risk classification were are statistically significant with (P-value 0.009, 0.026, 0.027, 0.010 respectively) but comparing between different RAI category doses was statistically insignificant.

The multivariate analysis to prognostic factors of treatment response was done, we found that there are no independent factors, but gender (odds ratio: 2.516, CI: 0.574-11.021) and stage (odds ratio: 1.028, CI: 0.228-4.637) had a strong effect on response to treatment.

Table 1: Patient characteristics

Factor		NO. (70)	%
Age	18-54	57	81.4
	55-70	13	18.6
Gender	Male	25	35.7
	Female	45	64.3
ECOG	0	29	41.4
	1	39	55.7
	2	2	2.9

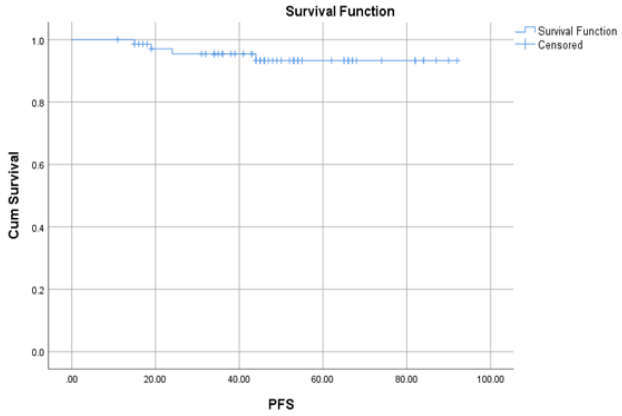

Figure 1: Kaplan Meier curve of DFS

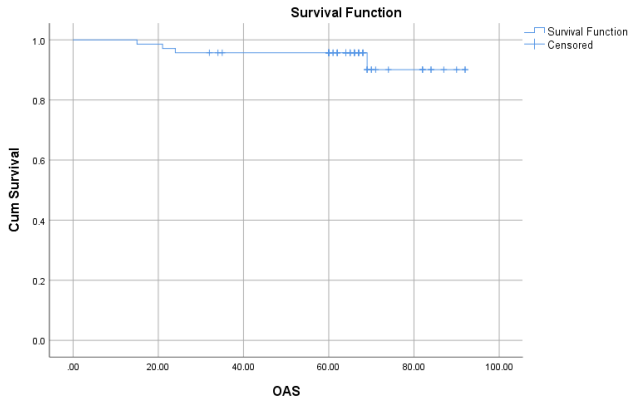

Figure 2: Kaplan Meier curve of OAS

Table 2: Tumor and treatment characteristics

Factor		NO. (70)	%
Stage	I	57	81.4
	II	11	15.7
	III	2	2.9
T	T1	34	48.6
	T2	22	31.4
	T3	13	18.6
	T4	1	1.4
N	N0	0	0
	N +ve	70	100
Pathological type	PTC	62	88.6
	Follicular	7	10
	Hurthle	1	1.4
Multi-focality	Uni-focal	45	64.3
	Multi-focal	25	35.7
LVI	-ve	30	42.9
	+ve	19	27.1
	Unknown	21	30
PNI	-ve	37	52.9
	+ve	7	10
	Unknown	26	37.1
ECE	-ve	53	75.7
	+ve	17	24.3
Gross ETE	No	56	80
	Yes	14	20
ENE	No	67	95.7
	Yes	3	4.3
Involved LNs	≤ 5LNs	48	68.6
	>5LNs	22	31.4
Gross residual	No	66	94.3
	Yes	4	5.7
Surgery	Total thyroidectomy	70	100
	Others	0	0
TG	<10 ng/ml	53	75.7
	≥10 ng/ml	17	24.3
Risk category	Intermediate	43	61.4
	high	27	38.6
RAI category	< 100	11	15.7
	≥ 100	59	84.3
Response to TTT	Successful ablation	48	68.6
	Failed ablation	22	31.4
Patient status at end of study	Alive	66	94.3
	Dead	0	0
	Missed follow up	4	5.7

(T: Tumor, N: Nodal, LVI: lymphovascular invasion, PNI: perineural invasion, ECE: extracapsular extension, ENE extranodal extension, TG: thyroglobulin)

Table 3: Univariate analysis of survival prognostic factors

Factor		Ratio	P-value (OAS)	P-value (PFS)
age	18-54	81.4	0.295	0.117
	55-70	18.6		
gender	Male	35.7	0.654	0.287
	Female	64.3		
ECOG	0	41.4		
	1	55.7	0.024**	0.047*
	2	2.9		
stage	I	81.4		
	II	15.7	<0.001**	0.437
	III	2.9		
T	T1	48.6	0.002**	
	T2	31.4		0.651
	T3	18.6		
	T4	1.4		
Pathological type	PTC	88.6		
	Follicular	10	0.544	0.367
	Hurthle	1.4		
multifocality	Unifocal	64.3	0.411	0.146
	Multifocal	35.7		
LVI	-ve	42.9		
	+ve	27.1	0.458	0.405
	unknown	30		
PNI	-ve	52.9		
	+ve	10	0.773	0.124
	Unknown	37.1		
ECE	-ve	75.7	0.041**	0.195
	+ve	24.3		
Gross ETE	No	80	0.689	0.186
	Yes	20		
ENE	No	95.7	0.832	0.001**
	Yes	4.3		
Involved LNs	≤ 5LNs	68.6	0.475	0.345
	>5LNs	31.4		
Gross residual	No	94.3	0.433	0.337
	Yes	5.7		
TG	<10 ng/ml	75.7	0.233	0.074
	≥10 ng/ml	24.3		
Risk category	Intermediate	61.4	0.297	0.162
	High	38.6		
RAI category	< 100	15.7	0.419	0.691
	≥ 100	84.3		
Response to 1st TTT dose	Successful ablation	68.6	0.807	0.018**
	Failed ablation	31.4		
progression	No	74.3	0.609	----
	Yes	25.7		

Table 4: Predictive factors of response to treatment

Factor		Successful ablation	Indeterminate	Biological failure	Structural failure	Both failure	p-value
Age	18-54	41(58.6%)	4(5.7%)	3(4.2%)	7(10%)	2(2.8%)	0.184
	55-70	7(8.6%)	0	1(1.4%)	5(7.1%)	0	
Gender	Male	14(20%)	2(2.8%)	2(2.8%)	7(10%)	0	0.249
	Female	34(48.6%)	2(2.8%)	2(2.8%)	5(7.1%)	2(2.8%)	
ECOG	0	21(30%)	2(2.8%)	2(2.8%)	3(4.2%)	1(1.4%)	
	1	27(38.6%)	2(2.8%)	2(2.8%)	7(10%)	1(1.4%)	0.215
	2	0	0	0	2(2.8%)	0	
Stage	I	41(58.6%)	4(5.6%)	3(4.2%)	7(10%)	2(2.8%)	
	II	7(10%)	0	1(1.4%)	3(4.2%)	0	0.123
	III	0	0	0	2(2.8%)	0	
T	T1	25(35.7%)	1(1.4%)	3(4.2%)	5(7.1%)	0	
	T2	13(18.6%)	3(4.2%)	1(1.4%)	4(5.6%)	1(1.4%)	0.386
	T3	10(14.3%)	0	0	2(2.8%)	1(1.4%)	
	T4	0	0	0	1(1.4%)	0	
Pathological type	PTC	43(61.4%)	4(5.6%)	4(5.6%)	9(12.8%)	2(2.8%)	
	Follicular	4(5.6%)	0	0	3(4.2%)	0	0.790
	Hurthle	1(1.4%)	0	0	0	0	
multifocality	Unifocal	34(48.6%)	4(5.6%)	1(1.4%)	5(7.1%)	1(1.4%)	0.70
	Multifocal	14(20%)	0	3(4.2%)	7(10%)	1(1.4%)	
LVI	-ve	23(32.8%)	3(4.2%)	3(4.2%)	1(1.4%)	0	
	+ve	12(17.14%)	1(1.4%)	1(1.4%)	5(7.1%)	0	0.052
	unknown	13(18.6%)	0	0	6(8.4%)	2(2.8%)	
PNI	-ve	29(41.4%)	4(5.6%)	3(4.2%)	1(1.4%)	0	
	+ve	3(4.2%)	0	0	3(4.2%)	1(1.4%)	0.009*
	Unknown	16(22.8%)	0	1(1.4%)	8(11.4%)	1(1.4%)	
ECE	-ve	37(52.8%)	3(4.2)	4(5.6%)	8(11.4%)	1(1.4%)	0.629
	+ve	11(15.7%)	1(1.4%)	0	4(5.6%)	1(1.4%)	
Gross ETE	No	42(60%)	3(4.2%)	2(2.8%)	8(11.4%)	1(1.4%)	0.167
	Yes	6(8.4%)	1(1.4%)	2(2.8%)	4(5.6%)	1(1.4%)	
ENE	No	48(68.5%)	4(5.6%)	3(4.2%)	10(14.3%)	2(2.8%)	0.026*
	Yes	0	0	1(1.4%)	2(2.8%)	0	
Involved LNs	≤ 5LNs	35(50%)	2(2.8%)	0	9(12.8%)	2(2.8%)	0.027*
	>5LNs	13(18.6%)	2(2.8%)	4(5.6%)	3(4.2%)	0	
Gross residual	No	46(65.7%)	4(5.6%)	4(5.6%)	10	2(2.8%)	0.479
	Yes	2(2.8%)	0	0	2(2.8%)	0	
TG	<10 ng/ml	40(57.14%)	4(5.6%)	1(1.4%)	6(8.4%)	2(2.8%)	0.010*
	≥10 ng/ml	8(11.4%)	0	3(4.2%)	6(8.4%)	0	
Risk category	Intermediate	36(51.4%)	2(2.8%)	1(1.4%)	2(2.8%)	2(2.8%)	0.001*
	high	12(17.14%)	2(2.8%)	3(4.2%)	10(14.3%)	0	
RAI dose	<80	2(2.8%)	0	0	1(1.4%)	0	
	80	7(10%)	0	0	0	1(1.4%)	
	100	19(27.1%)	0	1(1.4%)	6(8.4%)	1(1.4%)	0.259
	120	16(22.8%)	4(5.6%)	2(2.8%)	2(2.8%)	0	
	150	4(5.6%)	0	1(1.4%)	3(4.2%)	0	

Discussion:

This study was conducted to estimate the effect of different ablative doses of RAI as regard OAS and PFS in patients with DTC and cervical lymph node metastasis. Through using clinical evaluation, US, CT, frozen biopsy with or without WBI scan, we suggested that the tumor had progressed to the cervical lymph nodes. Despite reports indicated the most significant and reliable variables to determine lymph node metastases were clinical assessment and US inspection of cervical lymph nodes [7].

The idea of risk stratification is very crucial for determining the biological behavior of the disease and choosing a course of therapy. The ATA guidelines classified thyroid cancer patients into low, middle, and high-risk groups based on their relative risk of mortality and recurrence [8]. Those at high risk might have sever extrathyroidal spread, insufficient tumor excision, or distant metastases. Those at intermediate risk have

microscopic extrathyroidal extension, vascular invasion, aggressive histology (e.g: tall cell, hobnail variant, columnar cell carcinoma) or regional lymph node metastases. Patients with low risk had no vascular invasion, extrathyroidal extension, aggressive histology, local or distant metastases. So, there is no benefit to low-risk patients from RAI treatment and there is little risk of disease-specific mortality or persistent/recurrent disease [9].

Adjuvant RAI therapy after total thyroidectomy is generally not recommended for patients with low-risk PTC. Although the efficacy of RAI in intermediate-risk PTC patients is unknown, studies have shown that it can reduce the risk of recurrence and prolong overall survival in these patients. Our data support routine, strong recommendations for RAI treatment for high-risk PTC patients [8].

As regard patient characteristics, in this study, the total number of patients included were 70 patients all of them diagnosed with DTC. The majority of cases were below the age of 55 years (81.4%). The mean age in the study was 40.98 year and regarding sex, the majority of patients were females (64.3%) with male to female ratio 1:1.8 and this was differed from the study done by Haugen et al. *at 2016*, where the mean age was (44.1), the majority were female (72.7%) with male to female ratio was 1: 2.6. this can be attributed to sample size as they include 16212 patients received RAI [8]. Although, this result coincides with the study by Iizuka et al, they conducted among 119 patients. They concluded that the female percent was (67.2%) while, male percent was (32.7%) with male to female ratio was 1:2. In their study compared the clinical results of individuals who underwent thyroidectomy for intermediate to high-risk differentiated thyroid cancer with radioactive iodine (RAI) ablation [10].

As regard tumor characteristics, we summarized that increased number of involved LNs more than five associated with poor predictive outcome (P=0.027), multiple studies also have suggested that increasing size and number of involved LNs are associated with greater recurrence and poorer survival. However, there is no clear consensus on the size and number threshold which is most prognostic of poorer outcome. Due to the single institution, retrospective nature of many of these studies, inclusion criteria have been heterogeneous. For example, the study conducted by Wang LY, et al *at 2016*, who considered the number of positive LNs, the significant cutoffs have similarly varied in the literature. Greater than 2 through ten positive LNs in the lateral or both neck compartments, have been suggested as markers of poorer outcome [5].

As regard sex difference in thyroid carcinoma, we summarized that gender has strong effect on response to treatment, in the multivariate analysis prognostic factors of treatment response (odds ratio: 2.516, CI: 0.574-11.021), but P-value was not statistically significant (P=0.221), in another study done by Lee et al 2017, They included a large sample size of approximately 2930 patients who underwent surgery and compared clinicopathologic features from patient medical records for male and female PTC patients, and found that male gender is an independent prognostic factor in PTC >1cm, associated with poor prognosis (12.6 vs 9.6%, p = 0.03 and 2.2 vs 0.6%, p 0.001) [11].

This retrospective study included cases with differentiated thyroid carcinoma who received different doses of radioactive iodine ablation after total thyroidectomy, response to treatment in the form of successful versus failed ablation in univariate analysis of survival prognostic factors was statistically significant (P=0.018), in comparison with another study done by Eui Young Kim et al 2011, who compares ablation success and disease-free survival (DFS) on the basis of different ablation doses, large number of patients were included so more detailed data was obtained, Successful ablation was accomplished in 81.7%, 89.5%, and 94.8% of the 1024 patients who received radioactive iodine dosages of 30 mCi (group A), 80 mCi (group B), and 150 mCi (group C) (P 0.001). In total, 100 patients (9.8%) experienced clinical recurrences throughout the course of the median follow-up of 6.6 years. According to the success of the ablation in each dose group, DFS was assessed, but with no significant differences [12].

High post-operative TG has negative clinical outcome on successful ablation, also in a study conducted by Watanabe et al. *at 2017*, They found that even with high doses of I-131, the ablation success rate was very poor due to excessive thyroglobulin levels. Those at high risk, particularly those with high thyroglobulin levels (>10 ng/ml), are unlikely to achieve levels low enough to satisfy the successful ablation criteria [13].

Our data demonstrated that PNI, ENE, number of involved LNs >5, these 3 differences were statistically significant with (P-value 0.009, 0.026, 0.027 respectively), a finding that was comparable with another study by Sang Hun Lee et al. *at 2019*, which involved 136 patients with pathologically confirmed PTC and clinically lymph node (LN)-positive lateral neck but no initial distant metastases after total thyroidectomy with therapeutic central and lateral neck dissection. They estimated the risk factors of recurrence after treatment of node positive PTC, they were the PNI, ENE, number of involved LNs >5 (P= value 0.036, 0.002, 0.058) [14].

We discovered throughout the study, high post-operative TG was a statistically significant negative prognostic factor, with a strong connection and a higher failure incidence more with TG levels above 1 ng/ml. This observation was made Lubin, et al. *at 2021*. who identified 107 adult patients, aged 18 to 79, with 73 female and 34 male individuals. This study included sixteen patient variables: age at diagnosis, sex, previous thyroid disease, type of thyroidectomy, disease grade and lymph node involvement at surgery, histopathologic variation, primary tumor size, multifocality, dose of I-131 administered, interval from surgery to RAI treatment, pre-RAI and post-RAI Tg and anti-Tg antibody serum levels and interval from RAI to follow-up. They discovered that if patients who had

elevated serum levels of Tg following surgery but before RAI, ablation failure was more likely to occur in them (P = 0.011) [15].

In our study, successful ablation was obtained in intermediate risk group 36% than in high risk groups (12%) with significant P value as regard predictive factors of response to treatment (P=0.001), In another study done by Michele Klain et al 2021, who discussed the rate of ablation in patients with differentiated thyroid cancer at intermediate or high risk of recurrence, following radioactive iodine therapy, obtained a large sample of 3,103 patients at intermediate-to-high risk of persistent/recurrent disease and found that ablation success rates were higher in intermediate-risk patients (72%) than in high-risk patients (52%).) with a relative ratio of 1.22 (p =0.008) [16].

The presence of extra nodal extension predicts negative clinical outcome with statistically significant (P=0.009) coincides with another study done by Hu Hei et al. *at 2022*, which compares presence of ENE versus none with (P- <0.001). They found 645 patients who had T1 PTC that had been initially removed, significant LN metastases in 3.9% of T1 PTC patients, and ENE in 8.1% of patients. Male sex, high tumor size, more lymph nodes positive, and extensive surgical treatment were all linked to ENE [17].

The OAS in the successful ablation group (68.6%) was higher than failed ablation group (31.4%), Although it did not reach statistical significance. This may be because the majority of the failure group was at higher risk groups, The 5- years overall survival in this study was 91.4%, in comparison with another study done by Allen S Ho et al (2020),10-year overall survival was 85.4%, the difference mainly attributed to large number of patients included in Allen's study and long period of follow up [18].

The limitation to our study is the sample size which is crucial since, with a larger sample, the percentage may be substantially higher than what we discovered.

Conclusion:

The high postoperative TG, PNI, ENE and higher number of involved LNs have negative clinical outcome. Higher TG levels before ablation is more likely to decrease the ablation success rates especially when it reaches levels above 10 ng/ml. Postoperative TG and Anti-TG is a key prognostic indicator and determined in various situations. RAI ablation is essential for the right patient to improve the course of the disease, increase survival rates, and stop additional recurrences.

In general, aggressive disease requires a higher dose, especially if risk factors are present to prevent further recurrences, but intermediate risk could be successfully controlled with lower doses as well, this should be done after the appropriate investigations to detect the true risk category before the final treatment decision.

We recommend that future studies should give a larger sample size with similar risk factors, data can be also obtained from many institutions.

Compliance with ethical standards:

Ethical approval was obtained from Institutional Research Board (IRB) at the Faculty of Medicine, Mansoura University, Egypt (MS.21.03.1411). All procedures were done in accordance with the current revision of Helsinki Declaration of medical research involving human subjects.

Conflict of interest:

The authors declare that no conflict of interest to disclose.

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References:

1. Mathur P, Sathishkumar K, Chaturvedi M, et al. Cancer statistics, 2020: report from national cancer registry program, India. *JCO global oncology*, 2020, 6: 1063-1075.
2. National Comprehensive Cancer Network (NCCN): Thyroid Carcinoma. https://www.nccn.org/guidelines /guidelines-detail?category=1&id=1470. Accessed 1/2022.
3. Nguyen QT, Lee EJ, Huang MG,, et al. Diagnosis and treatment of patients with thyroid cancer. Am Health Drug Benefits. 2015 Feb;8(1):30-40.
4. Albano D, Bonacina M, Durmo R, et al. Efficacy of low radioiodine activity versus intermediate-high activity in the ablation of low-risk differentiated thyroid cancer. Endocrine. 2020 Apr;68(1):124-131.
5. Wang LY, Ganly I. Nodal metastases in thyroid cancer: prognostic implications and management. Future Oncol. 2016 Apr;12(7):981-94.
6. Schlumberger M, Leboulleux S, Catargi B, et al. Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial. Lancet Diabetes Endocrinol. 2018 Aug;6(8):618-626.
7. Amin AT, Rezk KM, Atta H. Clinical Examination and Ultrasonography as Predictors of Lateral Neck Lymph Nodes Metastasis in Primary Well Differentiated Thyroid Cancer. Journal of Cancer Therapy 2018;9(1):55-63.
8. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016 Jan;26(1):1-133.
9. Sacks W, Fung CH, Chang JT, et al. The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a systematic analysis of the peer-reviewed literature from 1966 to April 2008. Thyroid. 2010 Nov;20(11):1235-45.
10. Iizuka YY, Katagiri T, Ogura K, et al. Comparison between the different doses of radioactive iodine ablation prescribed in patients with intermediate-to-high-risk

differentiated thyroid cancer. Ann Nucl Med. 2019 Jul;33(7):495-501.
11. Lee YH, Lee YM, Sung TY, et al. Is male gender a prognostic factor for papillary thyroid microcarcinoma? Ann Surg Oncol. 2017 Jul;24(7):1958-1964.
12. Kim EY, Kim TY, Kim WG, et al. Effects of different doses of radioactive iodine for remnant ablation on successful ablation and on long-term recurrences in patients with differentiated thyroid carcinoma. Nucl Med Commun. 2011 Oct;32(10):954-9.
13. Watanabe K, Uchiyama M, Fukuda K. The outcome of I-131 ablation therapy for intermediate and high-risk differentiated thyroid cancer using a strict definition of successful ablation. Jpn J Radiol. 2017 Sep;35(9):505-510.
14. Lee SH, Roh JL, Gong G, et al. Risk factors for recurrence after treatment of N1b papillary thyroid carcinoma. Ann Surg. 2019 May;269(5):966-971.
15. Lubin DJ, Tsetse C, Khorasani MS, et al. Clinical predictors of I-131 therapy failure in differentiated thyroid cancer by machine learning: A single-center experience. World J Nucl Med. 2021 Mar 15;20(3):253-259.
16. Klain M, Nappi C, Zampella E, et al. Ablation rate after radioactive iodine therapy in patients with differentiated thyroid cancer at intermediate or high risk of recurrence: a systematic review and a meta-analysis. Eur J Nucl Med Mol Imaging. 2021 Dec;48(13):4437-4444.
17. Hei H, Li Y, Luo Z, et al. Extranodal extension is an independent predictor of extensive nodal metastasis in T1 papillary thyroid cancer. Langenbecks Arch Surg. 2022 Jun;407(4):1647-1652.
18. Ho AS, Luu M, Barrios L, et al. Incidence and Mortality Risk Spectrum Across Aggressive Variants of Papillary Thyroid Carcinoma. JAMA Oncol. 2020 May 1;6(5):706-713.