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RESEARCH ARTICLE

CLINICO-PATHOLOGICAL FEATURES OF DIFFERENTIATEDTHYROID CANCER AND THEIR IMPACTSON PROGNOSIS

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ABSTRACT

Background: Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer, with increasing incidence in last years, especially in female with three to four times in female comparing to male, also the relative increasing incidence of DTC in the mulitnodular goiter which was clearly observed in this study. **Aim of the Work:** This is a retrospective study which aims to analyze the clinical and pathological features of DTC and their impacts on the prognosis for patients with differentiated thyroid cancer who attended the Department of Clinical Oncology and Nuclear medicine in Ain Shams University Hospital between the years (2011-2016).**Subjects and Methods:** Data were collected and analyzed retrospectively from the files of the patients with DTC between the years (2011-2016), who attended the Clinical Oncology and Nuclear Medicine Department of Ain Shams University Hospital, Cairo – Egypt. Out of 102 patients with DTC, 21 patients were excluded due to insufficient data and loss of follow up, results obtained from 81 patients who were followed up until the end point of study. The mean period of follow up was 39.85±18.28 months. **Results and Conclusion:** The tumor size, lymph node metastases, capsular invasion, stage and grade were most important histopathological prognostic factors in relation to relapse risk, while the role of tumor multifocality and LVI were Insignificant. The role of different ablative doses of RAI^{131} was not significant in relation to risk of relapse in DTC patients. **Recommendations:** The use of proper risk stratification system by reassessing of relapse risk using the level of serum Tg and results of follow-up diagnostic images as markers of the response to initial surgery and radioactive iodine (RAI) remnant ablation. Further studies with larger number populations are needed to confirm the results obtained by the current work and to evaluate the role of gene mutations and other molecular markers which may affect the prognosis of DTC.

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INTRODUCTION

Thyroid cancer is the most common endocrine malignancy and presenting the fifth most common cancer among women and incidence has been increased in the last three decades [(1)]. Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer, accounting for >90% of all cases and usually has an excellent prognosis .DTC include two subtypes, papillary thyroid cancer (PTC) which is the commonest and follicular thyroid cancer (FTC) [(2)]. DTC is usually asymptomatic for long periods of time. However solitary thyroid nodule is the common presentation, where thyroid cancer could be found in 7%–15% of these nodules, depending on age, sex, radiation exposure history, family history, and other factors [(3)].

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The thyroid stimulating hormone (TSH) level, ultrasound results and clinical features are used to determine whether is it necessary to do fine-needle aspiration (FNA) of the nodule or whether there is a low risk of malignancy, where FNA consider the procedure of choice for evaluating suspicious thyroid nodule [(4)]. Surgery is the mainstay of the treatment of DTC patients with or without radioactive iodine therapy and lifelong TSH suppression [(5)]. Histological type of carcinoma and the extent of local and regional spread determine the recommended extent of primary surgical resection of DTC, in contrast, secondary factors that could affect the individual prognosis, such as age of the patient or the molecular status of the tumor play no role in the current guidelines' recommendations for the surgical treatment of DTC [(6)]. Disparity can be found in the guidelines in their recommendations about adjuvant radioactive iodine therapy for low-risk thyroid carcinomas, however [(5)], it is clearly indicated for the treatment of metastases that take up iodine and are not amenable to curative resection like in lungs and bone metastases [(7)].

Despite the fact that many advances were achieved in the diagnosis and therapy of both thyroid nodules and DTC, but clinical controversy still exists in many areas. A long history of insufficient peer reviewed research funding for high quality clinical trials in the field of thyroid neoplasia may be an important contributing factor to existing clinical uncertainties [8].

Aim of the Work: This is a retrospective study which aims to analyze the clinical and pathological features of DTC and their impacts on the prognosis for patients with differentiated thyroid cancer who attended the Department of Clinical Oncology and Nuclear medicine in Ain Shams University Hospital between the years (2011-2016).

Subjects and Methods: Data were collected and analyzed retrospectively from the files of the patients with DTC between the years (2011-2016),who attended the Clinical Oncology and Nuclear Medicine Department of Ain Shams University Hospital, Cairo – Egypt. Out of 102 patients with DTC, 21 patients were excluded due to insufficient data and loss of follow up, results obtained from 81 patients who were followed up until the end point of study. The mean period of follow up was 39.85±18.28 months.

Inclusion Criteria

- Patients with pathological evidence of well differentiated thyroid cancer.
- Presence of full data as much as possible for the patient which include the following:
- Demographic data
- Full pathological data
- Neck sonography
- Thyroid stimulating hormone
- Thyroglobulin
- Radioactive iodine 131 whole body scan
- Cumulative doses of Radioactive iodine 131

Exclusion Criteria

- Patients withpoor differentiated thyroid cancer (medullary and anaplastic).
- 2-Patients with DTC but with incomplete data.
- 3- Patients with doubleprimary malignancies.
- Staging of cancer was done according to the American Joint Committee on Cancer (AJCC)/TNM staging for thyroid cancer (7^{th}ed., 2010).

Patients were managed according to their risk stratification, which based on patients' demographic, clinical, and histopathological data. Post-operative RAI ablation therapy was given as indicated in the empiric (fixed) method in range of (30-180 mCi) with higher doses for patients with higher risk stratification. In the follow-up period, patients were kept on TSH suppression therapy, follow up visits were every (6-12) months and based mainly on clinical examination, TSH, TG, neck sonography, and RAI^{-131}Dx-WBS, other Investigations were done as indicated.

Statistical analysis: Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: Independent-samples t-test of significance was used when comparing between two means. -Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters.

Binary logistic regression: was used to predict the outcome of categorical variable based on one or more predictor variables.

Probability (P-value):

- P-value <0.05 was considered significant
- P-value <0.001 was considered as highly significant
- P-value >0.05 was considered insignificant.

RESULTS

Descriptive data analysis

Demographic data analysis: The mean age of patients was 39.83±14.27, the range was (11-80 years), 53 patients (65.43%) were <45 year, while 28 (34.57%) ≥45 year.64 patients (79.01%) were females as compared to 17 male (20.99%) with female to male ratio 3.7, Table (11) shows the demographic data distribution of the study group.

Table (1). Demographic data distribution of the study group

Demographic Data	Total No. (81)
Age (years)	
<45	53 (65.43%)
≥45	28 (34.57%)
Age (years)	11-80 [39.83±14.27]
Sex	
Female	64 (79.01%)
Male	17 (20.99%)

Histopathological data analysis: In regarding to histopathological analysis, the vast majority had papillary type 75 patients (92.59%), while follicular type was evident in 6 patients (7.41%). Nineteen patients (23.5%) had lymph node metastases, distal metastases found in 3 patients (3.70%).The vast majority of DTC patients were in stage I at diagnosis, where they form (75.31%), 7 patients (8.64%)were in StageII, 8 patients (9.88%) in stage III,4 patients (4.94%) in stage IVa and 1 patient (1.23%) were in stage IVc. Forty three patients (53.09%) had grade 1 disease, while 38 patients(46.91%) were with grade 2 disease. Capsular invasion found in 25 patients (30.86%),lympho-vascular invasion found in 10 patients (12.35%) and tumor multi-focality were found in 23 (28.40%). Table 12 below showing the histopathological distribution in details for the study group.

Clinical data analysis: Family history for thyroid malignancy found only in 2 patients (2.47%), while 79 patients (97.53%) present with negative history.51 patients (62.96%)presented with history of solitary thyroid nodule (STN),while 30 patients (37.04%)presented with history of multi-nodular goiter (MNG). All patients had either total or near-total thyroidectomy. Thyroidectomy was done as 1 stage surgery (total or near total thyroidectomy) in 47 patients (58%) and associated with neck dissection in 10 patients, while 2 stage surgery (hemithyroidectomy followed by 2^{nd} surgery to complete removal of thyroid gland) was done in 34 patients (42%) and associated with neck dissection in 9 patients. In regarding to late complications of thyroidectomy, Hypocalcameia was

Table 2. Histopathology distribution of the study group

Histopathology	Total No. (81)
Histology	
Follicular	6 (7.41%)
Papillary	75 (92.59%)
T	
T1a	13 (16%)
T1b	12 (14.8%)
T2	34 (42%)
T3	17 (21%)
T4a	5 (6.2%)
N	
N0	62 (76.5%)
N1	19 (23.5%)
M	
M0	78 (96.30%)
M1	3 (3.70%)
Stage	
I	61 (75.31%)
II	7 (8.64%)
III	8 (9.88%)
IVa	4 (4.94%)
IVc	1 (1.23%)
Grade	
Grade I	43 (53.09%)
Grade II	38 (46.91%)
Capsular invasion	
Positive	25 (30.86%)
Negative	56 (69.14%)
Lym. Vas Inv.	
Positive	10 (12.35%)
Negative	71 (87.65%)
Multi-focality	
Positive	23 (28.40%)
Negative	58 (71.60%)

observed in 9 patients (11.11%) during follow up, and vocal cord injury diagnosed in 4 patients (4.94%). RAI131 ablation mean dose given was (90.28±32.60mCi), and the dose range was (30-180 mCi) with the higher doses for higher risk stratification. 25 patients received adjuvant doses of RAI131, the mean dose was [139.00±119.06 mCi] in range of (30-495mCi). only 3 patients (3.7%)with metastatic disease received palliative radiotherapy for bone pain.

Investigations and imaging methods data analysis: Post-operative Tg mean was (25.66±54.29ng/ml) with range (0.01-300ng/ml).Post-op Tgwas <1ng/ml in 16 patients (19.75%), between (1-10 ng/ml)in 32 patients(39.51%), between (10-30ng/ml) in 15 patients (18.52%), >30ng/mlin 14 patients (17.28%), and not done in 4 patients (4.94%). Tg-Ab was positive in 7 patients (8.64%) and negative in 70 patients (86.42%) not done in 4 patients (4.94%).

Tg rise during follow up was observed in 19 patients (23.46%), while 55 patients (67.90%) rise wasn't observed in their Tg levels through follow up period, and Tg measurements was irregular in 7 patients (8.64%) due to irregular visits. DxWBS after (6-12) mspost operative findings was positive in 23 patients (28.40%), and negative in 47 patients (58.02%) and not done in 11 patients (1385%). U/S in 6 months post op was found to be positive in 22 patient (27.16%) and negative in 54 patients (66.67%), not done in 5 patients (6.17%). Pet-Ct was done for 2 patients only (2.47%). Table 14 below show the distribution of Investigations and imaging methods in the study group in details.

Treatment outcome: 54 patients (66.7%) had complete resolution through the duration of follow up which was 39.85±18.28 months, while 6 patients (7.4%) had a partial response and 21 patients (25.9%) had relapse disease.

Table 3. Investigations and imaging methods distribution of the study group

	Total No. (81)
Investigations	
Tg rise on Follow up	
Not done	7(8.64%)
Positive	19 (23.46%)
Negative	55 (67.90%)
Tg-Ab	4(4.94%)
Not done	
Positive	7 (8.64%)
Negative	70 (86.42%)
Post op Tg (ng/ml)	0.01-300 [25.66±54.29]
Not done	4(4.94%)
<1	16 (19.75%)
1-10	32 (39.51%)
>10-30	15 (18.52%)
>30	14 (17.28%)
Imaging methods	
WBS in 6-12Ms post op	11(13.85%)
Not done	
Positive	23 (28.40%)
Negative	47 (58.02%)
U/S in 6 month Post op	
Not done	5(6.17%)
Positive	22 (27.16%)
Negative	54 (66.67%)
Pet-CT	2 (2.47%)

The Progression free survival (PFS) was (23.67±12.26) ms in range of (8-48) ms. no death was recorded in study population until the end point of study so overall survival (OS) was not analysed. Figure 10 below show treatment response distribution in the study group. 4 patients had a local relapse (4.94%), 7 patients (8.64%) with only regional relapse, 5 patients (6.17%) with loco regional disease, 2 patients (2.47%) had a distal metastasis in addition to loco regional foci,2 patients(2.47%)found to have regional + distal foci, and 1 patient(1.23%)with only distal foci the distal metastasis foci occurred in lung and bone. Figure 11 below showing type of relapse distribution of the study group.

Table 4. Treatment outcomes of the study group

	Total No. (81)
Type of Relapse	Total 21 (25.93%)
Local	4 (4.94%)
Locoregional + distal mets.	2 (2.47%)
Locoregional	5 (6.17%)
Distal mets.	1 (1.23%)
Regional + distal mets.	2 (2.47%)
Regional	7 (8.64%)
Relapse status	
Positive	21 (25.93%)
Negative	60 (74.07%)
PFS (months)	8-48 [23.67±12.26]
Response to treatment	
Relapsed	21 (25.9%)
Partial response	6 (7.4%)
Complete resolution	54 (66.7%)

Statistical Univariateanalysis of possible prognostic factors and correlation with risk of relapse:

Demographic data analysis: There was high statistically significant difference according to age at diagnosis p-value<0.001, where the risk of relapse was significantly higher in those patients with ages≥45 years in comparison with younger patients who were<45 years, while there wasn't statistically significant difference between male and female gender in relation to risk of relapse as shown below in Table 16.

Table 5. Comparison between relapsed and not relapsed patients according to demographic data

Demographic Data	Type of Relapse		Chi-square test		
	Relapsed	Not relapsed	ℜ²	p-value	Sig.
Age (years)					
<45	7 (33.3%)	46 (76.7%)	12.914	<0.001	HS
≥45	14 (66.7%)	14 (23.3%)			
Sex					
Female	15 (71.4%)	49 (81.7%)	0.983	0.321	NS
Male	6 (28.6%)	11 (18.3%)			

HS=Highly significant, NS=Non significant

Histopathological data analysis: In regarding to histology there was no statistical significant difference between papillary and follicular histology in relation to relapse risk, while significant difference was found according to tumor size and lymph node metastasis, where there was higher risk for relapse in those patients with larger tumors and N1 feature, and thus both act as independent poor prognostic factors. Higher stage tumors carried a higher risk for relapses, where statistically significant difference was found, also this could be said about grade and capsular invasion, where patients with higher grade and those with capsular invasive tumors have more risk to relapse. There wasn't significant statistical difference according to lympho-vascular invasion or tumor multi-focality in relation to relapse risk between patients in the study group as shown in table 17 below.

RAI^{131} uptake: Results in the current study showed no significant statistically difference in relapsed and not relapsed patients who received different doses of RAI^{131} ablation therapy as clarified in Table 18.

Investigations and imaging methods data analysis: Post operativeTg levels showed significant statistically difference between patients in relation to cancer relapse, where those patients withbasal Tg levels >10(ng/ml) had more cancer relapses than those with lower levels, also patients who had a rise in their Tg levels during follow up had a much more cancer relapses in compare to those patients without Tg rise. This table shows highly statistically significant difference between relapsed and not relapsed according to TG rise on follow up. High significant statistically difference was present (p-value <0.001) between relapsed and not relapsed patients according to both DxWBS and U/S positive and negative findings, where noticeably more cancer relapses was found in patients with positive findings in 6months period of followup in comparison with patients with negative findings as shown in Table 20.

Statistical multivariate regressionanalysis of possible prognostic factors and correlation with risk of relapse: Table 22 shows that age, tumor size, lymph node metastasis, Stage, Grade, Capsular invasion and basal. Tg level have a significant effect on the DTC relapses in multivariate analysis for the prognostic factors.

DISCUSSION

Management of thyroid cancer is guided by clinico-pathological risk stratification of the disease, which has proven to be effective for many decades and is currently the mainstream of the practice of thyroid cancer medicine [(9)]. Our findings in the present study confirming the importance of clinical data, that are strongly concordant with the modern approaches to risk stratification, considering not only an initial DTC stage but also clinical features and the response to treatment administered. Age at diagnosis is considered to be one of the established risk factors for stratification in DTC patients [(10)]. In the present study age was a strong independent poor prognostic factor with a high significant statistically difference between patients <45 and those with age ≥45 years in relation to cancer relapse in univarite analysis, where patients older than 45 years formed (66.7%) of relapsed cases while patients younger than 45 years were (33.3%), moreover age was also a potent poor prognostic factor in multivariate analysis when put with the other prognostic factors as shown previously in table 21 at results. So findings in this study about the age as important prognostic factor could be confirmed by noting that many stratification systems considered DTC patients under 45 years age cutoff as less risk than those who were older. as in Memorial Sloan Kettering, (GAMES), and AJCC/UICC systems [(11)], however recently Shi *et al*., in their study supposed that DTC with aging generally showed more aggressive features after the age of 60 instead of 45 years [(12)]. Although gender is present in some currently employed prognostic systems, the effect of gender on the course of treatment in DTC patients seems to be a somewhat controversial prognostic factor. The current study there was no significant statistical difference between papillary and follicular types to affect the PFS of the patients, in both univariate and multivariate analysis, and so histological type wasn't an independent prognostic factor according to our results. D'Avanso*et al*., concluded that,there is a correlation between invasiveness and prognosis rather than the specific histology type when reviewed 132 patients with FTC who were stratified into three groups: minimally invasive (only capsular invasion), moderately invasive (blood vessel invasion with or without capsular invasion), or widely invasive, The 5-year survival rates were 98%, 80%, and 38%, respectively [(13)]. From another hand In an analysis of prognostic factors in 1,227 patients with DTC,Lang *et al*., found that having FTC was a poor prognostic factor for cancer specific survival (relative risk = 3.1) along with older age, presence of bone metastases, and lack of avidity for radioiodine [(14)].

Tumor size commonly considered as an important prognostic factor in DTC patients and has long been associated with outcome, with less favorable outcomes with large tumors in comparison to those with small ones [(15)]. In the present study our results confirmed the important role of the tumor size as a potent independent prognostic factor in univariate and multivariate analysis, and there was a significant statistically difference with P value (0.016) between patients outcomes in relation to their tumor sizes. We observed that during follow up, patients with T1 tumors (≤1cm) didn't record any case of relapse, while patients with larger tumors, showed more relapse rates. Our findings about effect of tumor size on DTC outcomes was similar to many authors, where Mazzaferri concluded that PTMC recurrence or persistence disease rate can be reduce to zero when total thyroidectomy RAI^{131} therapy had given [(16)], while Roti *et al*., in a descriptive and meta-analysis study reported that the risk of recurrence in papillary micro carcinomas ranges from 1% to 2% in unifocal papillary microcarcimomas, and from 4% to 6% in multifocal papillary microcarcinomas [(17)]. Lymphnode involvement at diagnosis is a common finding in DTC patients in proportion 35–40%[(18)],in our study 23.25% of the DTC patients had a lymph node metastasis at diagnosis. According to the 2017 National Comprehensive Cancer Network (NCCN) guideline of thyroid carcinoma, the prognostic value of regional lymph node metastases is still controversial [(19)].However an analysis of more than 9900 patients

Table 6. Comparison between relapsed and not relapsed patients according to histopathology

Histopathology	Type of Relapse		Chi-square test		
	Relapsed	Not relapsed	x2	p-value	Sig.
Histology			0.185	0.667	NS
Follicular	2 (9.5%)	4 (6.7%)			
Papillary	19 (90.5%)	56 (93.3%)			
T			12.164	0.016	S
T1a	0 (0.0%)	13 (21.7%)			
T1b	2 (9.5%)	10 (16.7%)			
T2	8 (38.1%)	26 (43.3%)			
T3	8 (38.1%)	9 (15.0%)			
T4a	3 (14.3%)	2 (3.3%)			
N				0.011	S
N0	13 (61.9%)	49 (81.7%)	3.384		
N1	8 (38.1%)	11 (18.3%)			
M			0.089	0.765	NS
M0	20 (95.2%)	58 (96.7%)			
M1	1 (4.8%)	2 (3.3%)			
Stage			37.581	<0.001	HS
I	6 (28.6%)	55 (91.7%)			
II	5 (23.8%)	2 (3.3%)			
III	6 (28.6%)	2 (3.3%)			
IV	4 (19.0%)	0 (0.0%)			
Iva	0 (0.0%)	1 (1.7%)			
Grade			9.757	0.002	S
I	5 (23.8%)	38 (63.3%)			
II	16 (76.2%)	22 (36.7%)			
Capsular invasion				<0.001	HS
Positive	13 (61.9%)	12 (20.0%)	12.801		
Negative	8 (38.1%)	48 (80.0%)			
Lym. Vas Inv.			1.177	0.278	NS
Positive	4 (19.0%)	6 (10.0%)			
Negative	17 (81.0%)	54 (90.0%)			
Multi-focality					NS
Positive	9 (42.9%)	14 (23.3%)	2.916	0.088	
Negative	12 (57.1%)	46 (76.7%)			

S=significant, NS= non-significant, HS= highly significant

Table 7.Comparison between relapsed and not relapsed according to RAI ablation dose mCi

RAI ablation Dose mCi	Type of Relapsed				Chi-square test	
	Relapsed		Not relapsed			
	No.	%	No.	%	ℜ	p-value
High dose (≥80mCi)	19	90.5%	42	70.0%	4.549	0.103
Low dose(30mCi)	2	9.5%	8	13.3%		
Non	0	0.0%	10	16.7%		
Total	21	100.0%	60	100.0%		

Table 7. Different doses of RAI^{131} received by patients and their relapse status

RAI^{131} ablation Dose mCi	Type of Relapsed			
	Relapsed		Not relapsed	
	No.	%	No.	%
30	3	14.4%	8	13.3%
80	7	33.3%	16	26.7%
90	0	0.0%	1	1.7%
100	5	23.8%	14	23.3%
120	4	19.0%	8	13.3%
150	2	9.5%	2	3.3%
180	0	0.0%	1	1.7%
Non	0	0.0%	10	16.7%
Total	21	100.0%	60	100.0%

Table 8.Comparison between relapsed and not relapsed according to investigations

Investigations	Type of Relapse		Chi-square test		
	Relapsed	Not relapsed	ℜ	p-value	Sig.
TG rise on Follow up					HS
Positive	15 (71.4%)	4 (6.7%)	41.436	<0.001	
Negative	3 (14.3%)	52 (86.7%)			
TG-ab					NS
Positive	3 (14.3%)	4 (6.7%)	1.141	0.285	
Negative	17 (81.0%)	53 (88.3%)			
Post op Tg (ng/ml)			17.348	0.002	S
<1	1 (5.6%)	15 (25.4%)			
1-10	3 (16.7%)	29 (49.2%)			
>10-30	6 (33.3%)	9 (15.3%)			
>30	8 (44.4%)	6 (10.2%)			

HS = Highly significant, S = Significant, NS= Non significant

Table 9. Comparison between relapsed and not relapsed patients according to imaging methods

Imaging methods	Type of Relapse		Chi-square test		
	Relapsed	Not relapsed	x2	p-value	Sig.
DxWBS in (6-12 months)					
Positive	12 (57.1%)	11 (18.3%)	12.555	<0.001	HS
Negative	6 (28.6%)	41 (68.3%)			
U/S in 6 months Post op					
Positive	11 (52.4%)	11 (18.3%)	10.310	<0.001	HS
Negative	8 (38.1%)	46 (76.7%)			

HS = Highly significant

Table 10. Logistic regression of factors affecting relapsed and not relapsed

	B	Sig.	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Age (years)	-1.792	0.014	1.067	0.155	5.792
Sex	-0.336	0.685	0.715	0.141	3.620
Histology	1.328	0.447	2.774	0.123	11.747
T	-0.399	0.039	0.766	0.350	1.672
N	0.833	0.043	2.345	0.407	8.014
M	-0.498	0.811	0.608	0.010	3.377
Stage	-2.092	0.039	0.912	0.281	4.967
Grade	1.365	0.012	2.707	0.844	17.172
Capsular invasion	1.241	0.011	2.461	0.767	15.611
Lym. Vas Inv.	-0.114	0.924	0.892	0.086	9.283
Multi-focality	0.610	0.417	1.841	0.422	8.028
RAI ablat. Dose mCi	-0.004	0.732	0.996	0.972	1.020
Post op Tg (ng/ml)	-0.439	0.043	0.843	0.385	1.839

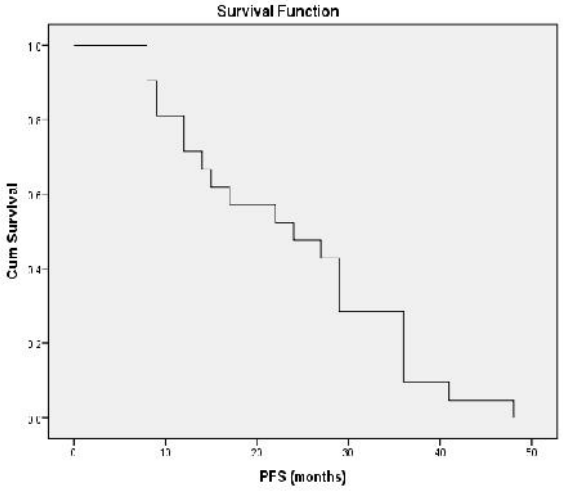

Figure 1. Progression free survival using Kaplan-Meier Survival analysis of the study group

Median		95% Confidence Interval	
Estimate	Std. Error	Lower	Upper
24.00	7.63	9.05	38.95

PFS= 47.6%

in the seer database found a significant difference in survival at 14 years for those with and without lymph node involvement (79% vs 82%)respectively [(20)]. In the present study our findings were also compatible with those who support the prognostic role of lymph node involvement, where (38.1%) of relapsed patients where nodal affected at diagnoses, and there was a significant statistical difference with P value (0.011) between relapsed patients with nodal involvement at patient without. From another hand some authors contra verse this opinion through their studies, Schneider *et al* indicated that indicate that nodal metastases do not impact survival [(21)]. In this work, other histopathological prognostic factors as thyroid capsule invasion, tumormultifocality and lymph vascular invasion also evaluated, the proportions was (30.86)%, (12.35%) and (28.40%) respectively. Obviously significant statistically difference found between relapsed patients with capsular invasion and those without it, while both tumor multifoculity and vascular invasion didn't prove themselves as an independent prognostic factors in both univarite and multivariate analysis. Indeed the importance of thyroid capsule infiltration, angioinvasion, and multifocality as prognostic factors was emphasised by numerous retrospective analyses that showed their negative impact on both OS [(22)] and DFS [(13,23)] but other papers questioned these data [(24)]. In regarding to the Range of prescribed activity for post-operative RAI^{131} remnant ablation has also been very controversial with many publications [(25)]. In the present study, we didn't find a significant statistically difference in relapse rates between patients who received low or high doses of ablative RAI^{131}.

Our observation agree with Castagna *et al* [26], who reported that their study provides the first evidence thatin patients who are at intermediate risk, high RAI activities (e.g., 3.7 GBq (100 mCi)) at ablation has no major advantage over low activities (e.g., 1.11 GBq (30 mCi)). At 6–18-month follow-up, they reported rates for 100 mCi vs. 30 mCiof 60% vs. 60% for remission, 18.8% vs. 14.3% for biochemical (Tg) disease, and 21.2% vs. 25.7% for metastatic disease, respectively. At the last follow-up of their patients, they reported recurrent disease 2.4% vs. 2.1%, persistent disease 18.8% vs. 23.6%, and death 2.4% and 2.1%. Indeed this may mean there is no advantage to these different prescribed activity. also we found similar findings in publications of Mallick *et al* [27], and Schlumberger *et al* [28], in their prospective studies with low and intermediate risk of disease. On another hand, in contrast to our findings, in an Egyptian study in Cairo university, Amin *et al*., reported that magnitude of the ablation dose is an influential factor on the full ablation [29]. High stimulated Tg level above 30 ng/mL, evaluated before RAI ablation (baslaTg), was the most potent, independent prognostic factor in many analysed group studies regarding the risk of DTC relapse in recent years. Similarly, the prognostic value of Tg measurements in follow up was demonstrated in numerous studies as well [30,31].

In 2012 Webb *et al*., published the results of meta-analysis involving nearly 4000 DTC patients and evaluating the utility of serum Tg measurement performed at the time of RAI remnant ablation [32], the authors clearly demonstrated that postoperative pre-ablation Tg concentration was a negative predictor of persistent or recurrent disease. Subjects with a postoperative, pre-ablation Tg value < 10 ng/mL showed a 6% likelihood of persistent DTC In contrast to the high negative predictive value the positive predictive value of preablationTg> 10 ng/mL was rather poor, at only 47% [33].Also according to the study by Hussain *et al.* both preablation-stimulated Tg (sTg) level was significantly associated with ablation outcome [34]. These studies agree with our findings in the present study, where (33.3%) of relapsed cases were with basal Tg between10-30 ng/mL and (44.4%).

With >30ng/mL, while only (5.6%) with patients with basal Tg<1ng/mL, and a significant statistical difference was present between basal Tg values and thus in our study the basal Tg represented as a potent prognostic factor.Also some controversy exists regarding the clinical significance of TgAb in DTC patients. Some investigations have presented higher frequencies of recurrent or persistent disease related to persistent TgAb**[35]**,however, no complete statement exists on the clinical significance of basal TgAb levels in DTC patients. In a study in 2014 byNeshandar *et al* **[36]**,the study showed that basal serum Tg levels and postablation. basalTgAblevels did not demonstrate a significant correlated with patient outcomes Neck U/S is thus becoming the mainstay of the postoperative follow-up of DTCs, especially during the early months, when, in the increasingly large proportion of patients with low- or very-low-risk tumors who have not undergone RRA, Tg assay results are difficult to interpret. When the initial postoperative scan is negative, the probability of a favorable long-term outcome is quite high, regardless of serum Tg levels **[37]**. In the current study the prognostic rule of ultrasound in the short term follow up postoperatively was analyzed to predict the survival outcomes, there was a high significant statistical difference between patients with negative and positive findings in relation to relapse rate with P value(<0.001).Our findings was almost compatible with a large, long-term study by, Durante *et al*., on 312 patients with low risk DTC, they reported that, those with negative findings on the first postoperative U/S study (3–12 months after surgery) were all disease free at the end of the follow-up **[38]**.On another hand other authors think that, metastatic disease can still be discovered with negative ultrasound findings, sometimes several years after the initial treatment so surveillance must be continued and the value of serum Tg assays increases with time, as consecutive measurements accumulate and allow increasingly reliable assessments of production trends. In the later phases of the follow-up, greater reliance might be placed on basal Tg assays than on neck U/S **[39]**.

In the present study, the findings indicated DxWBS after 6 months of RRA as a potent independent prognostic factor in predicting the morbidity in univariate analysis with a high significant statistical difference between patients with positive and negative DxWBS, where it was positive in (28.40%) and negative in (58.02%). These results agree with cohort of 164 patients study in 2015 done by Amin *et al*., who reported significant prognostic rule of DxWBS in 6 months postop in predicting morbidity in patients with high risk of recurrence **[40]**. Also before many years Robbins *et al*.,in his study reported the prognostic significance of DxWBS and compare it with that of serum Tg and strongly advocated the routine performance of DxWBS in almost all patients with DTC during follow-up. When he found that 13% of those patients with serum Tg less than 2 ng/ml had evidence for metastatic disease **[41]**. However major Guidelines and many authors in last few years no longer recommend the use of DxWBS in low risk patients with an undetectable Tg on thyroid hormone with negative antithyroglobulin antibodies and a negative U/S **[19]**

Regarding relapse rate, it was found in 21/81 [25.93%] based on the guidelines tools [Dx-WBS, U/S and Tg]. In fact, a 15%–30% recurrence rate over 30-year period is generally reported with just most of all recurrence occurring within 5 years from the initial diagnosis [42]. The current study concurs in a more or less manner with the former reports, however Amin *et al* [40], on his study carried up on 164 patients. reported a relapse rate of 13.4% [22/164 patients] and the explanation for this difference is that in the current study, the study population groupis much less compared to Amin *et al*. group. Lastly, it is important and fair to mention the limitations of this study, first to say, this study is of a retrospective one and the exclusion of some cases was inevitable. Also, the interval or duration of follow-up was not strictly controlled. Also we were unable to correlate the current results with a relative specific molecular & immune-histochemical markers that determine either the predisposing gene mutation e.g. $BRAF^{V600E}$&/or sub-cellular molecular changes related to differentiation which are not done routinely in our institute. Secondly, the accuracy of this diagnostic imaging was partially but not fully established on bases of clinical follow up by histo-pathological examination and Tg value. Thirdly, this study was carried out on relatively small number of patients with variation in duration of disease and on relatively short-term bases. Lastly, lack of standardisation of the treatment.

Conclusion

Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer, with increasing incidence in last years, especially in female with three to four times in female comparing to male, also the relative increasing incidence of DTC in the mulitnodular goiter which was clearly observed in this study.

The clinical course of DTC is relatively favorable, where It have a very low mortality rates, and survival rates have been increased in the past years due to modern diagnostic and therapeutic protocols. Determining and applying the prognostic factors of survival, give a big chance to design an individualized proper risk assessment concerning the treatment plan and follow up. The optimal management for most patients diagnosed with thyroid cancer, either by fine needle aspiration or at the time of surgery, is total or near total thyroidectomy with or without neck dissection followed by radioiodine ablation of remnant thyroid tissue.

The objective of our study was to analyze the clinical and pathological features and their impacts on the prognosis of patients with DTC. Data collected, included patient demographics, surgical details, histopathological reports, radioactive iodine therapy doses. Also level of baseline and series of Tg measurements, finding in neck U/s, and WBS during follow up visits. The mean period of follow up was 39.85±18.28 ms. Relapse rate in this study was found in 21/81 patients (25.9%), which is relatively high in comparing to other studies, no death was recorded, and the PFS was PFS was (23.67±12.26) ms. Age was the most potent demographic prognostic factor that have a significance in related to relapse risk in DTC, whereas gender was insignificant. Rise in Tg level during follow up, basal Tg level, positive U/S findings in 6 months postoperative, positive DxWBS,were independent poor prognostic factors that increase risk of relapse in DTC patients, while TgAb level was insignificant. The tumor size, lymph node metastases, capsular invasion, stage and grade were mostimportant histopathological prognostic factors in relation to relapse risk, while the rule of tumor multifocality and LVI were Insignificant. The role of different ablative doses of RAI^{131} was not significant in relation to risk of relapse in DTC patients.

Recommendation

- The use of proper risk stratification system by reassessing of relapse risk using the level of serum Tg and results of follow-up diagnostic images as markers of the response to initial surgery and radioactive iodine (RAI) remnant ablation.
- Further studies with larger number populations are needed to confirm the results obtained by the current work and to evaluate the role of gene mutations and other molecular markers which may affect the prognosis of DTC.

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