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Patterns of Relapse in Patients with Well Differentiated Thyroid Cancer (Single Institutional Experience).

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ABSTRACT:

Background: Recurrence of Well-differentiated thyroid cancer (WDTC) occurs in 6-30% of patients, commonly loco-regional recurrence. **Aim:** To explore recurrence patterns in WDTC patients, identifying variables linked to different relapse patterns. **Patients & Methods:** We retrospectively analyze data of 50 patients with WDTC who developed recurrence post successful complete ablation. **Results:** 58%, 38%, and 4% of patients developed loco-regional, mixed, and metastatic relapse respectively. Cervical lymph nodes and lungs are the commonest sites of loco-regional and metastatic relapse. 72% of recurrence occurred at 5-years post diagnosis. Recurrence was more encountered in old males and follicular carcinoma. All patients had two or more unfavorable pathological prognostic factors. Development of distant metastases is significantly more in males, high risk patients, follicular carcinoma, presence of capsular and vascular invasion, multi-focality together with failure of complete ablation post single radioactive iodine (131-I) ablation dose and higher serum thyroglobulin levels (sTg) at time of recurrence diagnosis. 11 patients lose ability to concentrate 131-I, solely, associated significantly with presence of higher sTg level on relapse diagnosis. FDG PET/CT localized recurrence site in 10 out of those 11 patients. **Conclusion:** Loco-regional recurrence is the commonest form of recurrence followed by mixed and metastatic relapse. 72% of relapse occurred 5-years post-initial diagnosis. Cervical lymph nodes and lungs are the commonest sites of loco-regional and metastatic relapse. Dedifferentiation of recurrence occurs in around one fifth of patients, FDG PET/CT sensitivity for localization of relapse site in patients with dedifferentiation is 90%.

Distant metastatic recurrence is significantly more encountered in males, follicular carcinoma, presence of capsular or vascular invasion and multi-focality, together with failure to achieve successful complete ablation post first 131-I ablative dose and in presence of higher sTg at time of diagnosis of recurrence. The latter is the sole factor that appears to be more significantly associated with occurrence of dedifferentiation.

Key Words: Well-differentiated thyroid cancer (WDTC) – Pattern of relapse – Radioactive iodine (131-I) – Dedifferentiation.

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INTRODUCTION:

Thyroid cancers account for around 1% of all malignancies. As a group, they make up the majority of malignant endocrine tumors and account for the vast majority of fatalities linked with these tumors. It is estimated that 90% of thyroid cancers are well-differentiated carcinomas (WDTC), develop from follicular epithelial cells, which can produce and release thyroid hormones. The 10-year survival rate of WDTCs is more than 90%, with most of them behaving like slow-growing neoplasms [(1)].

After total ablation of the thyroid gland with successful surgery and radioactive iodine (RAI) treatment, recurrence was recorded in 6-30% of patients despite this optimum management, most recurrences occur during the first five years after initial diagnosis and full ablation [(2)].

Patients' demographics (age and gender), have a significant impact on their prognosis. The WDTCs10-year survival rate was found to be lower in men and older patients, suggesting that these two factors are adverse prognostic indicators [(3)].

Among important prognostic variables: histo-pathological features as large tumors, multi-focality, vascular and muscle invasion, extra-thyroidal extension, and lymph node involvement, These also include follicular thyroid cancer (FTC), unfavorable pathological cell variants like tall cell carcinoma in papillary thyroid cancer (PTC) and Hurthle cell carcinoma in FTC, both local recurrence and distant metastasis have been proven to be linked to each of these variables [(4)]. The American thyroid association (ATA) revised recommendations said that the probability of recurrence ranged from <1% in low-risk patients to >50% in high-risk individuals, depending on the severity of the disease [(5)].

The most prevalent kind of recurrence was found to be local, followed by distant metastases, which mostly affect the lungs and bones [6].

131-I whole body scans (131-I WBS) with neck ultrasonography are preferable because they can better assess the location and pattern of recurrence, which may then be used to guide optimal patient therapy if recurrence is detected by an increase in serum stimulated thyroglobulin levels (sTg). Dedifferentiation of the recurrent lesions occurs in certain cases, when recurring lesions lose their capacity to concentrate 131-I, becoming more aggressive compared to the initial highly differentiated histology. Cases with high blood TG levels and negative 131-I WBS may be identified by FDGPET/CT, which is able to pin point the location of recurrence in most patients [7]. Recurrence is a frightening prospect, but the vast majority of recurrence patients may be saved with further treatment that involves surgery, radioactive iodine, and perhaps external beam radiation, as well as chemotherapy. Recurrence-free status or disease control is achieved in the majority of patients treated with several WDTC relapse therapy modalities. A small proportion of individuals do die from their recurrent condition [8].

Aim of Work: The aim of the current study is to explore relapse patterns in patients with WDTC, and to identify poor prognosis variables linked to recurrence patterns.

PATIENTS AND METHODS:

A single institutional cross-sectional analysis of data from patients with WDTC presented in the period from 2010-2013 for post-operative RAI131 ablation therapy and frequent follow-up thereafter.

The current study included 160 patients who developed recurrence in the period from 2010-2013. However, we only analyzed 50 patients whom the full clinical & pathological data and follow up to 2020 were available.

- **Inclusion criteria:**

✓ Both males and females.

✓ Ages≥16 years old,

✓ Thyroidectomy (Total/near total) with WDTC confirmed histo-pathologically (either PTC or FTC).

✓ Patient with recurrence after biochemical and structural full ablation after RAI 131 treatment for a variable period of time.

✓ Patient with at least one follow up visit in the year 2020.

Any patient with one of the following criteria was excluded from the current study:

- ✓ Metastatic lesions at first diagnosis.
- ✓ Increased anti Tg anti bodies (anti Tg Abs) levels (at first diagnosis or during follow-up).
- ✓ Loco-regional progression or distant metastases before biochemical and structural successful complete ablation.

- Data from chosen patients' medical records was gathered and analyzed using statistical methods.

Statistical Analysis: Statistical calculations were done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 25. Data were statistically described in terms of mean and standard deviation, median and interquartile range, number and percentages when appropriate. For comparing categorical data, Chi square (χ^2) test was performed. Fisher's exact test was used instead when the expected frequency was less than 5.

Continuous normally distributed variables were tested by student "t" test to compare between two independent means while non-normally distributed variables were compared by Mann Whitney U-test. Correlation between various variables was done using Pearson moment correlation equation for linear correlation in normally distributed variables and Spearman rank correlation equation for non-normal variables. All tests were two tailed and probability (p-value) ≤ 0.05 is considered significant.

RESULTS:

The current study includes 50 patients with recurrent WDTC post successful complete ablation. The mean age of the patients was 41.62 ± 15.12 years, ranging from 16 to 72 years; around half of them (46%) were between 30 and 50 years. About two thirds of the study participants (68%) were females ***(Table 1)***, with a female to male ratio of 2.13:1. There is gradual decrease in female: male ratio as patients get older, being 5.5:1, 2.8:1and 0.75:1 for those from 16 to ≤ 30 years, from > 30 to ≤ 50 years and > 50 years respectively, with more male patients with recurrent WDTC in the last group. Total thyroidectomy was performed in 36 patients (72%) and the remaining 14 patients (28%) underwent near total thyroidectomy. This was associated with central and lateral neck dissection in 21 patients (42%) due to cervical lymph nodal involvement either clinically and/or sonographically.

According to risk stratification system, patients were divided into those with low, intermediate and high risk, more than 50% of patients were in the intermediate risk group. Also, according to TNM staging system 84% of patients were stage I, aged < 55 years ***(Table1)***.

Histopathological reports showed that 36 patients (72%) have PTC, including two patients with follicular variant of papillary carcinoma. The remaining 14 (28%) patients had FTC, including two patients with Hurthle cell carcinoma. The mean size of the primary lesions was 2.34 ± 1.10 cm, ranging from 0.7 up to 5.3 cm. Multi-focality, capsular invasion and vascular invasion were reported in more than 50% of patients while lymph nodal involvement was reported in 42% of patients ***(Table 1)***.

According to department policy, no initial diagnostic I-131 WBS was performed; yet, all patients have elevated initial post-operative serum sTg level, with positive neck ultrasound for variable sized residual thyroid tissue in the thyroid bed in only 19 patients (38%). So, all patients received post-operative ablative/adjuvant RAI dose. According to risk stratification the given dose range was from 30-120 mCi (1110-4440 Mbq) with a mean dose figure of 87.8 ± 31.7mCi. The median duration between the surgery and receiving the ablative dose was 3.7 months (range: 1.1-7.2). Post therapeutic WBS was performed for all patients from 5-10 days post iodine dose ***(Table 2)***.

The results of post I-131 therapy WBS revealed presence of variable sized residual functioning thyroid tissue in the anterior neck in the thyroid bed, either at both thyroid lobe beds or on one side. No other I-131 avid lesions depicted neither in the neck nor elsewhere. Estimation of sTg level and diagnostic I-131 WBS were done 6-9 months post RAI therapy for all patients. Results of the two studies revealed biochemical and structural successful complete ablation in 29 patients (58%). For the remaining 21 patients, there was reduction of serum sTg level, but still elevated (>2ng/ml) in all patients. This is associated with diminution in size and activity of residual thyroid tissue in the neck in WBS, with no new I-131 avid lesions all over the rest of the body.

The incomplete ablation post first RAI dose calls for a re-ablative dose of RAI, which was given with the same follow up post 6-9months. The second dose achieved complete biochemical and structural ablation in 15 patients. Six months later this was achieved for the remaining 6 patients with a third dose of I-131.

The ablation outcome of first, second and third RAI doses were found to be 58% (29/50), 71.4% (15/21) and 100% (6/6) with the final result of complete ablation of the whole patient population (50 patients). The median total iodine dose received by the patients to achieve successful complete ablation is 150 mCi, ranging from 30 to 280 mCi ***(Table 3)***. Recurrence was diagnosed in all patients by elevated sTg level during follow-up. Subsequently, I-131 WBS was performed, and it was positive for I-131 avid recurrence (either loco-regional, metastatic or both) in 39 patients, and proved negative in the remaining 11 patients.

Relapse was diagnosed after a variable period of time post thyroidectomy, ranging from 11 months to 9.5 years, with a median time of 3.3 years. Recurrence occurs within three years after initial treatment in 23 patients (46%), increasing to 36 patients (72%) within the first five year. Recurrence in the remaining 14 patients occurred after 5 years of initial diagnosis.

Table (1): Different characteristics of patients with recurrent WDTC.

Characteristics		Number	Percent (%)
Gender	Female	34	68.0
	Male	16	32.0
Type of Surgery	Total thyroidectomy	36	72.0
	Near total thyroidectomy	14	28.0
	Lymph node dissection	21	42.0
Risk Stratification	Low risk	7	14.0
	Intermediate risk	26	52.0
	High risk	17	34.0
Initial Staging	Stage I	42	84.0
	Stage II	5	10.0
	Stage III	3	6.0
Histopathological data	Papillary Carcinoma	36	72.0
	Follicular Carcinoma	14	28.0
	Positive Capsular Invasion	27	54.0
	Positive Lymph Node Metastases	21	42.0
	Positive Muscle Invasion	8	16.0
	Presence of Multi-focality	29	58.0
	Positive Vascular Invasion	31	62.0
	Presence of Extra-thyroidal Extension	13	26.0

Table (2): Timing of first RAI dose and its amount for patients with different risk stratification.

First RAI Dose for the Fifty Patients (mCi)	Mean	87.8 ± 31.7
	Range	30-120
	Low risk patients (7patients)	All patients-30 mCi
	Intermediate risk patients (26 patients)	17 patients-80mCi 9 patients-100mCi
	High risk patients (17 patients)	6 patients-100mCi 11 patients -120mCi
Time between Initial Surgery and first RAI Dose	Median	3.7 months
	Q1-Q3*	1.9-4.7
	IQR(Q3-Q1)**	2.8
	Range	1.1-7.2

*Q1: First quartile-*Q3: Third quartile-**IQR: Interquartile rangeQ3-Q1.

Table (3): Number of doses and total amount of RAI given to achieve successful complete ablation.

		Number of patients	**Number of patients with Successful Complete Ablation Outcome**	**%**
Number of RAI doses	1 dose	50	29	58.0
	2 doses	21	15	71.4
	3 doses	6	6	100
Total Iodine dose given to Achieve Successful Compete Ablation Outcome (mCi)	Median	150		
	Q1-Q3*	130-180		
	IQR**	50		
	Range	30-280		

*Q1: First quartile-*Q3: Third quartile-**IQR: I nterquartile rangeQ3-Q1.

As regards the pattern of recurrence, 29 patients (58%) had loco-regional recurrence ***(Figure1),*** 19 patients (38%) had combined loco-regional and metastatic recurrence ***(Figure 2)*** and only two patients (4%) had relapse in the form of distant metastatic disease. Out of the 29 patients with loco-regional recurrence (the former group) cervical lymph nodal relapse (regional recurrence) was the commonest site of relapse found alone in 41% (12/29) versus 21% (6/29) for patients with thyroid bed relapse only (local recurrence). Both local and regional recurrences were found together in the remaining 11 patients (38%). Lung metastasis was the commonest distant metastatic recurrence, found in 26% of the whole group, representing 62% of distant metastatic relapse site with or without loco-regional recurrence ***(Table 4)***.

Table (4): Patterns and sites of occurrence of recurrence**.**

Characteristic	Number	% to total group (50 patients)	% to Subgroup
Pattern of recurrence			
-Loco-regional (thyroid bed and/or local lymph nodes)	29	58.0	
- Combined (loco-regional + distant metastases)	19	38.0	
- Distant metastases	2	4.0	
Site of recurrence			
Loco-regional recurrence only (29 patients/ 58%)	6	12.0	21.0
- Thyroid bed alone (local recurrence)	12	24.0	41.0
- Cervical lymph nodes alone (regional recurrence)	11	22.0	38.0
- Combined (loco-regional recurrence)			

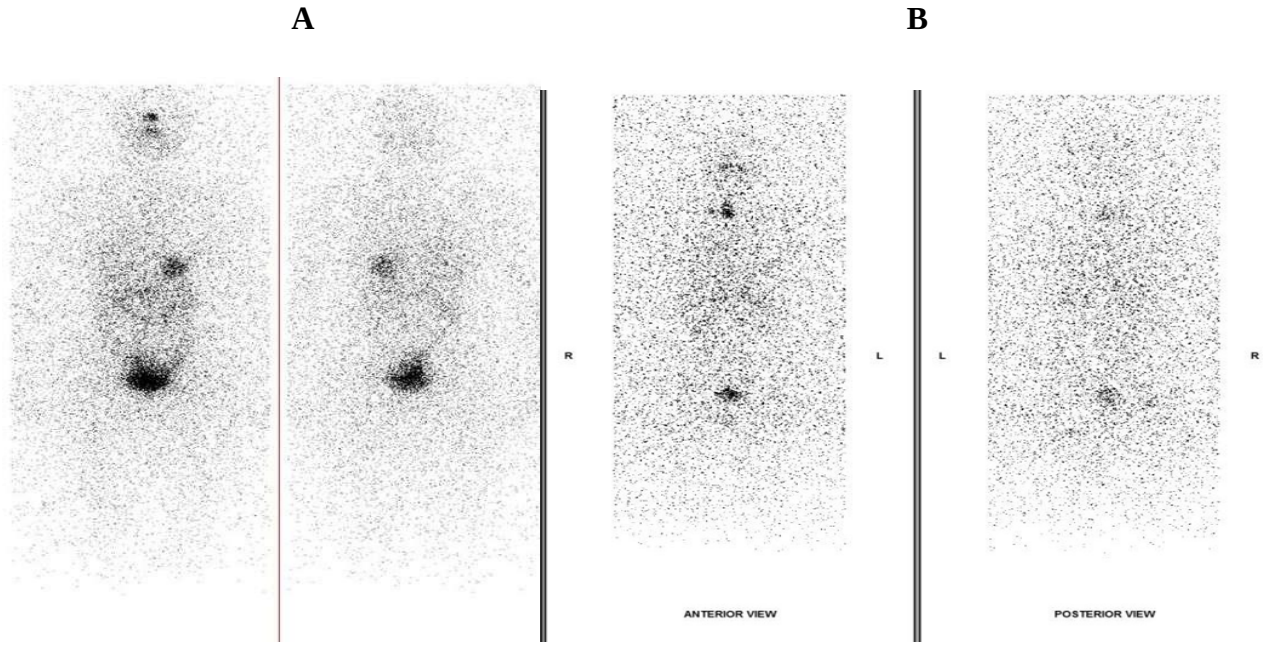

Figure (1): A- Normal diagnostic I-131 WBS post successful complete ablation.

B- I-131 WBS showing loco-regional recurrence developed 3 years post complete ablation.

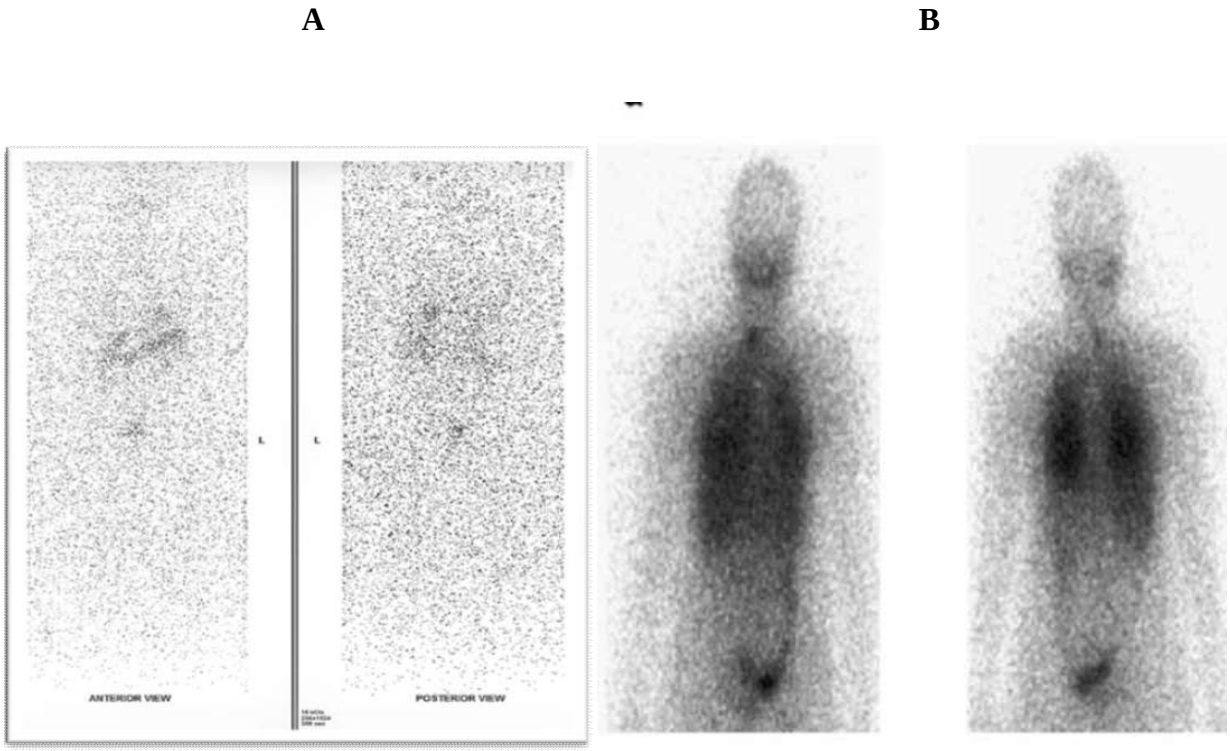

Figure (2): A- Normal diagnostic I-131 WBS post successful complete ablation.

B- I-131 WBS showing combined recurrence in neck and lungs developed 4.5 years post complete ablation.

Variable demographic, pathological and clinical post-operative factors were studied in relation to the development of recurrence. As regards demographic factors, female patients showed significantly higher prevalence of loco-regional recurrence (67.6%) compared to 37.5% for male patients, on the contrary distant metastatic relapse was encountered more significantly in male patients (p: 0.026). While age was not significantly different between patients with local recurrence alone and those who developed combined/ distant metastatic recurrence ***(Table 5)***.

Also, type of surgery and neck dissection was not significantly associated with the pattern of recurrence. As regards risk stratification, patients with high risk showed significantly higher distant recurrence compared to those with intermediate or low risk with a p-value of 0.002 ***(Table 5)***.

Patients with PTC were associated with significantly lower distant recurrence compared to those with FTC ($p< 0.001$). Patients with distant recurrence had significantly larger primary tumor size (mean 3.2cm) compared to the mean primary tumors size in patients with local recurrence (mean 1.8 cm) ($p< 0.001$).

Patients with capsular invasion, vascular invasion and multi-focality were significantly associated with higher distant metastatic recurrence compared to patients with absence of those pathological features with significant p-values ***(Table 5)***.

Serum sTg level at time of diagnosis of recurrence was significantly higher in patients with distant metastases compared to patients with local recurrence ($P < 0.001$).

Similarly, patients who required more than one ablative dose to achieve successful complete ablation developed significantly more distant metastatic recurrence compared to those who achieved successful complete ablation from the first dose of RAI ($P :< 0.05$) ***(Table 6)***.

Eleven patients had elevated serum sTg level and negative I131 WBS, meaning that recurrent tissue had lost its ability to concentrate I-131.

The incidence of dedifferentiation of recurrent thyroid tissues is 22%. For those 11 patients FDG PET/CT was performed. The latter was positive in 10 patients showing hyper metabolic active foci. Six patients had positive tracer uptake in cervical lymph nodes, one patient had thyroid bed uptake, another one had loco-regional hyper metabolic foci (thyroid bed & neck nodes), and two with bone metastases.

Table (5): Correlation between pattern of relapse with various demographic, clinical and pathological data.

Patients' characteristic		Loco-regional recurrence		Distant recurrence		p-value
Demographic data		**No.**	**%**	**No.**	**%**	
Gender: **-Female** **-Male**		 23 6	 67.6 37.5	 11 10	 32.4 62.5	0.026
Age (years), (mean ± S.D)		39.6±13.9	---	44.7±16.7	---	0.251
Clinical Data:						
Surgery	Total thyroidectomy	21	58.3	15	41.6	0.797
	Near total thyroidectomy	8	57.1	6	42.9	
Neck Dissection	Yes	10	47.5	11	52.5	0.077
	No	19	65.5	10	34.5	
Risk Stratification	Low Risk	7	100	0	0.0	0.002
	Intermediate Risk	17	65.3	9	34.6	
	High Risk	5	29.4	12	70.6	
Histopathological data						
Pathological type						
-Papillary carcinoma		28	77.7	8	22.3	< 0.001
-Follicular carcinoma		1	7.1	13	92.9	
Lymph node involvement:						
-Present		10	47.6	11	52.4	0.093
-Absent		19	65.5	10	34.5	
Size of primary tumor (cm), Mean ± SD		1.8±0.7		3.2±1.0		< 0.001
Muscle invasion:						
-Present		5	62.5	3	37.5	0.599
-Absent		24	57.1	18	42.9	
Capsular invasion:						
-Present		11	40.7	16	59.3	0.023
-Absent		18	78.0	5	22.0	
Vascular invasion:						
-Present		13	42.0	18	58.0	0.019
-Absent		16	84.0	3	16.0	
Multi-focality:						
-Present		12	41.4	17	58.6	0.021
-Absent		17	81.0	4	19.0	
Extra-thyroidal extension(ETE) -Present -Absent		 8 21	 27.6 72.4	 5 16	 23.8 76.2	0.479

Table (6): Correlation between pattern of relapse with serum levels of sTg at time of diagnosis of recurrence and ablation outcome post first dose of RAI.

Risk Factors	Local Recurrence	Distant Recurrence	P value
sTg (ng/ ml) at diagnosis of recurrence **- Median** **- Range**	63.7 (19.1–116.3)	346.5 (66.8–498.3)	0.001
Complete ablation after first RAI dose			
- Successful complete ablation (%). - Negative successful complete ablation (%).	24 (83) 7 (33)	5 (17) 14 (67)	0.009

One patient with negative FDGPET/CT was diagnosed positive for recurrence in small cervical lymph node by high resolution US and biopsy ***(Table 7)***.

The level of sTg at time of diagnosis of recurrence was the only factor that owes a significant association with occurrence of dedifferentiation in recurrent lesions (p: 0.020) ***(Table 8)***.

Table (7): Results of FDG–PET/CT in11 patients with elevated sTg and negative I-131WBS.

Characteristic	Number	Percent (%)
PET/CT		
Done	11	22.0
Not done	39	78.0
PET/CT results		
Positive	10/11	91.0
Negative	1/11	9.0
Site of hyper metabolic Foci in PET/CT		
Cervical lymph nodes	6	55.0
Thyroid bed	1	9.0
Loco-regional (thyroid bed & cervical lymph nodes)	1	9.0
Bone	2	18.0
No hyper metabolic foci (false negative)	1	9.0

Table (8): Association between sTg level and dedifferentiation.

Tumor marker at time Of diagnosis of recurrence	Dedifferentiation Median (Range)	No Dedifferentiation Median (Range)	P value
TG (ng/ ml)	169.7 (63.4 –498.3)	76.4 (19.1 – 172.5)	**0.020**

DISCUSSION:

The current study includes 50 patients with already diagnosed and confirmed recurrent WDTC post biochemical and structural successful complete ablation. The mean age of the patients was 41.62 ± 15.12 years, ranging from 16 to 72 years. Comparable age groups were reported by ***Palme et al*** and ***Aboelnaga and Ahmed***, for patients with recurrent WDTC and newly diagnosed patients respectively [3, 9 and 10]. About two thirds of the study participants (68%) were females with a female to male ratio equals 2.13:1. According to ***Ito et al,.*** male gender was shown to be an independent predictive factor for both PTC and FTC [11].

Moreover, the reports of ***Rosler et al,.*** claiming that men patients over the age of 50 are more likely to relapse than their female counter parts [12]. Recurrence rates for WDTC rise in older men (> 50 years of age) even though female patients are more than twice as likely to be impacted by the disease. In the current study we observed that older male patients have higher rate of recurrence compared to females, with female to male ratio of 0.75:1. This is in agreement with the previously documented data that gender and age are independent prognostic variable. Besides, reports stated that older patients have tumors that owe less favorable characteristics together with others reported that men have tumors with greater aggressiveness [13]. According to risk stratification, patients were divided into those with low, intermediate and high risk, representing 7 patients (14%), 26 patients (52%) and 17 patients (34%) respectively. This denotes that, patients with low-risk disease represent a minority compared to those with intermediate and high-risk group; the latter together represent 86% of patients with recurrent WDTC.

According to ATA Initial Risk Stratification System, purposed in 2009, each risk category has range for recurrence, lowest for the low-risk group, with an upper limit of recurrence rate of 5%, 30% and 55% for low, intermediate and high-risk WDTC patients respectively. This system was enhanced in 2015, presenting a continuum of risk of recurrence, ranging from < 1% in very low risk patients to > 50% in high-risk patients [(5)]. When using the ATA risk classification system, it was reported that 86% of patients defined as low risk remained with no evidence of disease post complete ablation, whereas 57% and 14% in the intermediate-risk and in the high-risk groups with no evidence of disease [(5)].

This confirms that low risk group has significantly less liability to relapse than the other two categories, which is shown in our study as patients with low risk had the lowest share in patients with recurrent disease with significant difference compared to the other two groups. Patients with stage I disease represents 84% of patients with recurrence compared to stage II and III patients, these results seem to overestimate recurrence in stage I disease. Actually, this is considered a drawback for systems that use age to stratify stage of the disease making them tend to be inaccurate in predicting recurrence-free survival.

It was reported that most staging systems have been derived from multivariate analyses that do not consider other factors as response to initial therapy or post-operative factors of increase liability of disease for recurrence, and all rely on information that is often available only before and after surgery, including patients' age.

Disease-free status and survival cannot be assured by low stage in most systems, inclusion of age is an important accused factor, thus providing imperfect guidance in selecting therapy and many clinicians do not use age to influence their decision about therapy [(13)].

As regards histopathology, 36 patients had PTC (72%) and the remaining 14 patients had FTC (28%). This is relatively higher than in patients at initial presentation where PTC represents around 85% to 90% of patients with WDTC.

This can be explained by the relatively higher recurrence rate in patients with FTC, increasing its incidence in patients in the current study with already diagnosed recurrence. This is deduced from the reported relatively lower disease free survival (DFS) for FTC in many studies, as in that done in Egypt by ***Aboelnaga and Ahmed*** reporting that the 10 years DFS was 77.2% and 65% for PTC and FTC respectively [(10)].

Besides, for PTC in a study done by ***Zhuet al.*** recurrence was reported in 11% and ranging from 5% to 21% in another study [14, 15].

This range is wider for FTC according to degree of invasiveness ranging from 4-43% [16]. This goes with more percentage of FTC patients with recurrence in this study. Every patient in the current study has at least two of the reported significant unfavorable prognostic pathological factors for occurrence of tumor relapse. As regards primary tumor size, 90% of patients in the current study with recurrence showed a primary lesion more than 1 cm in diameter Tumor size was described as a determinant for outcome in patients with WDTC being an independent risk factor for occurrence recurrence [17].

Larger primary tumor size together with multi-focality as well as capsular and vascular invasion are more significantly associated with occurrence of distant metastatic relapse with or without loco-regional recurrence. Besides, distant metastatic recurrence appears to be more significantly associated with higher level of serum sTg level at time of relapse diagnosis and with failure of achievement of successful complete ablation after first dose of RAI as well. Other unfavorable pathological factors encountered in our patient group, as lymph nodal involvement, muscle invasion, extra-thyroidal extension has no significant correlation with the pattern of relapse.

Mazzaferri and Sissy stated that 57% of recurrences were diagnosed in the first 5 years of follow-up, whereas 43% of the recurrences were detected 5-35 years after initial treatment [2]. Also, in ***Tsai et al***, study, over around 30 years of follow-up, more than half (59%) of recurrences were detected within the first 5 years following the initial therapy with a mean time to tumor recurrence of 5.6 ± 0.4 years [18].

All patients in the current study developed recurrence after a variable period of time. The median time to develop recurrence is 3.3 years with a range from 11 months - 9.5 years. 23 patients (46%) developed recurrence within the first three years, increasing up to 36 patients (72%) in the first 5 years. It was reported that recurrence occurred, on average, after 3.65 years with 50% occurring within three years after first operation, and 75% within 5 years [19]. This is more or less similar to our results. It is worth to mention that early recurrence in patients with WDTC was reported to be associated with high mortalities with a reported 10-year disease-specific survival rates of 52.5% and 85.1% for early and late recurrence respectively [20].

We emphasize that patients with well-differentiated thyroid carcinoma who are not post operatively diagnosed with persistent/recurrent disease within the first 6 months should be closely monitored for 5 years since among the cases of recurrence nearly 60% - 70% of recurrences occur within this time period.

The pattern of recurrence was loco-regional recurrence, seen in 29 patients (58%), combined loco-regional and metastatic recurrence in 19 patients (38%) and in remote metastatic site in only 2 patients (4%).

Out of the 29 patients with loco-regional recurrence, 12 patients (41%) have lymph nodal recurrence only, 6 (21%) thyroid bed recurrence and 11 (38%) both lymph nodal and thyroid bed recurrence.

Lungs were the commonest site of distant metastases, found in 13 patients (26%) followed by bone metastases in 6 patients (12%), representing 62% and 29% out of the 21 patients with distant metastases. Concordant to our study, many reports stated that the most common type of recurrence is the loco-regional recurrence. ***Shokoohi et al,.*** reported that the most common pattern of failure for DTC patients is regional or cervical nodal recurrence [(8)].

Coburn et al,. reported that more than 50% of patients with recurrent WDTC had regional recurrence (53%), followed by local (28%), distant (13%) and combined (6%) recurrence [(21)]. In a cohort study done by ***Mazzaferri and Kloos***, they reported local recurrence in 68% of the recurrences while distant metastases, mostly to the lungs, represented 32% [(22)].

The combined recurrence in our study is more common compared to others, found in 38% compared to only 6% in ***Mazzaferri and Kloos study***. In a trial to find an explanation for this discordance, it was found that combined recurrence in our study was reported in 75% of patients in the high-risk group, in 31% of the intermediate risk group with no single patient had combined recurrence in the low-risk group with statistically significant difference (P:0.002). This may be due to longer follow-up intervals (usually about 6-9 months) given to all patients in our study after successful complete ablation, irrespective of risk stratification, with possible some delay from the patient, mounting this period to one year. This gives chance for the high or intermediate risk patients, especially if dedifferentiation occurs, for recurrence and to metastasize during this period [(22)].

This raises the importance of the development of individualized surveillance plan for thyroid cancer patients that should adopt a more risk-stratified approach for better patient care and early diagnosis of distant metastatic relapse if occurred.

Distant metastases either alone or combined with loco-regional recurrence were found to be significantly also associated with multiple unfavorable prognostic factors as male gender, FTC, larger primary tumor size, vascular and capsular invasion, multi-focality and high risk patients.

Besides, metastatic recurrence was significantly associated with higher serum Tg level at time of recurrence and unsuccessful complete ablation after first RAI ablation dose. This emphasizes the stricter and personalized surveillance plan with short interval follow up for those patients, keeping in mind the probability of more occurrences of distant metastases. Previous studies reported that elevated Tg levels and negative radioiodine scans had been found in10–15 % of the patients with PTC [(23)].

In the current study, this was noted in 22% of patients. In literatures, ^{18}F-FDG PET/CT was shown to be a potentially useful imaging modality to localize recurrent or metastatic lesions in patients with elevated Tg and negative I-131WBS.

FDG PET/CT becomes a strongly recommended diagnostic modality in the follow-up of those patients [(7)]. 11 patients in this study showed biochemical recurrence with negative I-131 WBS.

The indication of FDG PET/CT in those patients is not only for detection of non I131 avid new lesions, but also for prediction of outcome as well as modification and individualization of further management plans, obviating the need of I-131 therapy and saving the patient from radiation overexposure. Ten patients had positive FDG uptake as deduced from presence of hyper metabolic foci. These were found in 6 patients in cervical lymph nodes, one thyroid bed uptake, one loco-regional relapse and two with bone metastases. One patient has false negative result, proved by high resolution neck US and biopsy to be positive for small lymph nodal recurrence.

The sensitivity of FDG in this small number of patients is 91%, which is higher than the patient-based pooled sensitivity of ^{18}F-FDG for the detection of recurrent WDTC reported to be 80% [(24)].

Other studies have shown a sensitivity of 70–95% [25]. These differences may be related to small number of patients in our study and also may be due to different Tg level in different patient population included in different studies, as sensitivity of FDGPET/CT increases with more elevation in serum Tg level [25]. On the contrary of presence of multiple factors associated significantly with development of distant metastases, yet no single one of the studied demographic and histopathological factors had significant correlation with the occurrence of dedifferentiation. The level of sTg level at time of diagnosis of recurrence was found to be the sole factor associated significantly with dedifferentiation of recurrent lesions of WDTC.

Though few studies are there studying this correlation, our results are concordant with the report of ***Talaat et al,.*** in an Egyptian study, they found a statistically significant difference in the median value of sTg level between I-131 avid and FDG avid group of patients with recurrent WDTC [26]. They stated that this significant higher thyroglobulin level in FDG positive group can be postulated to be due to de-differentiated recurrence had more aggressive characteristics compared to the well differentiated I-131 avid group, this was emphasized by presence of a more significant correlation of de-differentiation with the tumor grade in their study, with significantly more occurrence of dedifferentiation in high grade tumors [26].

CONCLUSIONS:

Loco-regional recurrence is the commonest form of relapse of WDTC followed by combined and distant metastatic relapse, occurring mainly within five years of successful complete ablation. Relapse is significantly more associated with male gender, FTC, vascular and capsular invasion, multi-focality, failure of successful complete ablation post first dose of RAI, high risk and higher sTg level at time of diagnosis of recurrence. The latter may be the sole factor significantly associated with occurrence of dedifferentiation diagnosed with PET/CT with high sensitivity.

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