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Causes and Clinical Impact of Loss to Follow-Up in Patients with Differentiated Thyroid Cancer in Nuclear Medicine Department, Cairo University Hospital.

Kandeel, A,¹; Eltahlawy, E,²; Elhendy, A,¹ Anwar, H.¹

¹Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University, ²Department of Environmental and Occupational Medicine, National Research Centre, Giza, Egypt.

ABSTRACT:

Objective: to explore the causes and clinical impact of loss to follow-up (LTFU) in patients with differentiated thyroid cancer (DTC) in the nuclear medicine Unit, Faculty of medicine **Methods:** In this cross-sectional study, demographic and socio-economic characteristics of DTC patients who failed to show-up for their follow-up appointments as well as the causes of LTFU were assessed through survey questions. Clinical data were obtained from the patient's medical records. The clinical impact was assessed by comparing each patient's serum thyroglobulin (TG) level, anti-thyroglobulin (anti-TG) level, neck ultrasound (US) findings and thyroid stimulating hormone (TSH) level before and after LTFU. **Results:** 91 patients were identified during a period of six months. Regarding the demographic data; the mean age was 47.8 years, 84.6% were females and 38.5% had associated co-morbidities. Regarding the duration of LTFU; 29.6% of patients lost follow-up for less than one

year and 49% lost follow-up for one to two years, while 21.4% failed to show-up for more than two years. As regards the cause of LTFU; the predominant cause was financial (36.3%). Financial cause and the presence of other co-morbidities were significantly higher among patients who missed follow-up after the third year (P value = 0.037 and 0.016 respectively). Regarding the clinical impact of LTFU; 20.9% presented with inadequate TSH suppression or hypothyroidism. 18.7% presented with disease progression or recurrence. Disease progression or recurrence were significantly higher among those who did not achieve excellent response prior to LTFU and in high-risk patients (P value = 0.012).

Conclusion: Early identification and management of demographic and socioeconomic risk factors for LTFU in DTC patients are important for the prevention of adverse outcomes.

Keywords: Therapy monitoring, Thyroid malignancy, Quality in health care, Personalized medicine.

Correspondence to: Hoda Nagui Anwar

Email: hoda.nagui@gmail.com

INTRODUCTION:

Compared to other malignancies, differentiated thyroid cancer (DTC), especially the conventional papillary thyroid carcinoma (PTC) has good prognosis and longer survival rates ⁽¹⁾. Patient compliance plays a vital role to ensure adequate TSH suppression and for early detection of recurrent or metastatic disease ⁽²⁾. Many patient-related factors can contribute to no-shows, such as financial troubles, the presence of co-morbidities, remote residency, familial obligations and psychological issues among others ⁽³⁾. Failure to show-up for the follow-up

appointment can result in inadequate TSH monitoring or missing the chance for early detection of disease progression, resulting in reduced patient outcomes, which may warrant extensive interventions to control the patient's condition, potentially affecting the quality of life. In an era where the quality of healthcare and health economics are in focus, we conducted this study in order to gain a better understanding of the obstacles that hinder patients from adequate follow-up and the consequent immediate clinical outcome ⁽⁴⁾.

PATIENTS and METHODS:

This cross-sectional study was conducted at the department of Clinical Oncology and Nuclear Medicine, Cairo University from October 2021 to March 2022 after obtaining ethical approval from the institutional ethical committee (RECs code: MS-550-2021). All adult patients with DTC who have been following up in our clinic for at least three months and missed one or more follow-up appointments by a period of at least 3 months were included. We excluded patients with DTC whose follow-up was conducted in other thyroid clinics referred only for diagnostic imaging or therapeutic RAI doses and not intending to continue follow-up in our clinic. Causes of loss to follow-up (LTFU) were examined through survey questions about age, gender, marital status, educational level, occupation, associated co-

morbidities, residency (as per governorate), transportation cost as perceived by the patient (cheap, intermediate, expensive), financial issues (such as availability of laboratory investigations and neck ultrasonography in the hospital for free, affordability to do laboratory investigations and neck ultrasonography on own expenses as well as direct question about the cause of LTFU (financial troubles, remote residency, sickness/death of a family member, long waiting time at the clinic, mistreatment by working staff, waiting area is too hot or crowded, COVID-19 and other causes). Survey questions were proposed by the physician in the clinic for those who could not read the questions by themselves. Duration of LTFU was calculated from the date of the missed follow-up appointment to

the date of the patient show-up in the clinic. Clinical data were obtained from the patient's medical records including risk stratification, response to treatment prior to LTFU and after show-up (as measured by TG, anti-TG, neck US and TSH). Risk stratification and response to treatment were performed according to 2015 American Thyroid Association (ATA) guidelines ⁽⁵⁾. Condition after showing up was categorized as 1) Stationary course identified as stable level of TG, anti-TG and no newly developed suspicious lesions detected by ultrasonography. 2) Progressive course identified as rising TG, or rising anti-TG or the appearance of new lesions characteristic

of loco-regional recurrence or distant metastases on neck ultrasound or other radiological investigations. TSH suppression was classified as 1) Adequate suppression: TSH level below 0.1 mIU/mL in high risk patients, 0.1 to 0.5 mIU/mL in intermediate risk patients or 0.5 – 2 mIU/mL in low risk patients who have undergone remnant ablation with undetectable TG level ⁽⁵⁾. 2) Inadequate suppression: serum TSH above the afore-mentioned levels. 3) Hypothyroidism including TSH level above 5 mIU/mL. The clinical condition of the patients who were not able to submit the requested investigations was described as “not assessed”.

Statistical analysis:

The data were coded and transferred into an excel sheet then exported to SPSS version 22 to calculate the needed statistics. For continuous data mean, maximum, minimum

and standard deviation were used and for qualitative data percentage and chi square test were used. The test for significance was less than 0.05 and power of 80%.

RESULTS:

During six months, 91 patients met the selection criteria, with a mean age of 47.8 years + SD 11.4. Patient demographic and socio-economic characteristics are summarized in **Table 1**. Among the studied patients, 84.6% were females, 40.7% were illiterate, 76.9% were housewives, 44% lived in Governorates other than Greater Cairo mostly in rural areas and 38.5% had

associated co-morbidities. Transportation cost, insurance status, availability and affordability of the requested investigations are summarized in the **Table 2**. 23% reported transportation cost to be expensive, 73.6% could not afford doing the requested laboratory investigations on their own expenses. Duration of follow-up, duration and causes of LTFU are summarized in **Table 3**.

Table 1: Patient demographic and socio-economic characteristics.

		Count	%
Gender	Female	77	84.6%
	Male	14	15.4%
Marital Status	Married	77	84.6%
	Not married	14	15.4%
Educational level	Illiterate	37	40.7%
	Below secondary level of education	15	16.5%
	Secondary level of education	25	27.4%
	Beyond secondary level	14	15.4%
Residency	Greater Cairo	51	56%
	Lower Egypt governorates	25	27.5%
	Upper Egypt Governorates	12	13.2%
	Other Urban Governorates	3	3.3%
Occupation	Housewife	70	76.9
	Other jobs	21	23.1%
Smoker	No	89	97.8%
	Yes	2	2.2%
Other co-morbidities	No	56	61.5%
	Yes	35	38.5%

Table 2: Transportation cost, insurance status, availability and affordability of the requested investigations.

		Count	%
Transportation cost (as perceived by the patient)	Expensive	21	23%
	Intermediate	38	41.8%
	Cheap	32	35.2%
Healthcare insurance	No	82	90.1%
	Yes	9	9.9%
Availability of laboratory investigations in the hospital	Not always	91	100%
Affordability of laboratory investigations outside hospital	Not affordable	67	73.6%
	Affordable	24	26.4%
Availability of neck ultrasound in the hospital	No	91	100%
Affordability of neck ultrasound outside hospital	Not affordable	31	34.1%
	Affordable	60	65.9%

Table 3: Follow up duration, duration and cause of loss to follow and previous periods of loss to follow up.

		Count	%
Follow up duration	< 3 years	23	25%
	≥ 3 years	68	75%
Duration of loss to follow up	Less than one year	27	29.6%
	One to two years	45	49%
	More than two years	19	21.4%
Cause of loss to follow-up	Financial	33	36.3%
	Family health problems	17	18.7%
	COVID 19 infection or fear of infection	13	14.3%
	Remote Residency	7	7.7%
	Feeling tired	6	6.6%
	Miscellaneous causes	15	16.3%
Previous periods of loss to follow up	No	65	71.4%
	Yes	26	28.6%

Regarding the onset of LTFU, 75% of patients lost follow-up at or beyond the third year of follow-up. Regarding the duration of LTFU, 49% lost follow-up for one to two years, while 29.6% lost follow-up for less than one year and 21.4% failed to show-up for more than two years. The predominant cause of LTFU was financial (36.3%),

followed by pre-occupation with family health problems (18.7%), COVID-19 infection or fear of getting infected (14.3%) and remote residency (7.7%) among others. 28.6% of patients had previous history of missing one or more follow-up appointments. Patients' clinical data are summarized in **Table 4.**

Table 4: Patients' clinical data.

		Count	%
Risk stratification	Low	6	6.6%
	Intermediate	83	90.1%
	High	2	3.3%
Response to treatment	Excellent response	73	80.2%
	Other than excellent response	18	19.8%
Condition after show up	Stationary	59	64.8%
	Progression	11	12.1%
	Recurrence	6	6.6%
	Not assessed	15	16.5%
TSH suppression prior to loss to follow up	Adequate	69	78.8%
	Inadequate	12	13.2%
	Hypothyroidism	10	11%
TSH suppression after patient show up	Adequate	54	59.3%
	Inadequate	10	11.0%
	Hypothyroidism	9	9.9%
	Not assessed	18	19.8%

Based on follow-up duration, patients were divided into 2 groups: patients whose follow-up duration lasted 3 years or more (68

patients) and those whose follow-up duration lasted less than 3 years (23 patients), as summarized in **Table 5**.

Table 5: Relation between cause of loss to follow up, and other clinical parameters with the follow up duration.

		Follow up duration				Chi square	P value
		< 3 years N = 23		≥ 3 years N = 68			
		No	%	No	%		
Causes of loss to follow up	Financial	4	17.4%	29	42.6%	14.924	0.037
	Family health problems	6	26.1%	11	16.2%		
	COVID 19 infection or fear of infection	1	4.3%	12	17.6%		
	Remote Residency	3	13.0%	4	5.9%		
	Feeling tired	2	8.7%	4	5.9%		
	Travel abroad	0	0.0%	2	2.9%		
	Mother caring for her children	1	4.3%	0	0.0%		
	Miscellaneous causes	6	26.1%	6	8.8%		
Other co-morbidities	No	19	82.6%	37	54.4%	5.773	0.016
	Yes	4	17.4%	31	45.6%		
Treatment response	Excellent response	14	60.9%	59	86.8%	7.263	.007
	Other than excellent response	9	39.1%	9	13.2%		
Condition after patient show up*	Stationary	12	60%	47	72%	3.5789	0.058
	Progression or recurrence	8	40%	9	28%		
TSH suppression prior loss to follow up	Adequate	12	52.2%	57	83.8%	9.3917	<.001
	Inadequate or hypothyroidism	11	47.8%	11	16.2%		
TSH suppression after patient show up*	Adequate	14	60.9%	40	58.8%	1.74	0.186
	Inadequate	3	13.0%	7	10.3%		
	Hypothyroidism	5	21.7%	4	5.9%		

The financial cause was found to be significantly higher in the former group, representing 42.6% of all causes, compared to 17.4% for the latter (P value = 0.037),

while there was no statistically significant difference for the other causes among the two groups. Similarly, the presence of other co-morbidities was found to be significantly

higher in the former group (45.6%), compared to the latter (17.4%) (P value = 0.016). There was no statistically significant difference between duration of LTFU and condition after show-up.

90.1% of our patient cohorts were categorized as intermediate risk, 19.8% did not achieve excellent response, 13.2% did not achieve adequate TSH suppression prior to LTFU and 11% had hypothyroidism prior to LTFU. 18.7% of patients presented with disease progression or recurrence and 20.9% presented with inadequate TSH suppression or hypothyroidism. 16.5% and 19.8% of

patients could not be assessed for recurrence or TSH suppression, respectively, as they could not provide the requested investigations.

Progression and recurrence were significantly higher among those who did not achieve excellent response prior to LTFU (P value = 0.012), as summarized in **Table 6**. The group of patients who achieved excellent response prior to LTFU included 2 patients in the high-risk category, one of them presented with distant metastasis and the other had stationary course.

Table 6 Relation between condition after patient show up and response to treatment. *

		Response to treatment				Chi square	P value
		Excellent response		Other than excellent response			
		No	%	No	%		
Condition after patient show up	Stationary	51	85%	8	50%	9.962	<0.001
	Progression	5	8.3%	6	37.5%		
	Recurrence	4	6.7%	2	12.5%		

* Patients who were not assessed are not included.

DISCUSSION:

According the ATA guidelines, some patients with low-risk thyroid cancer do not require RAI remnant ablation. However, these patients should adhere to a close follow-up schedule, and the treating physician should be certain about the patient’s compliance to avoid the risk of undetected recurrence ⁽⁵⁾. This highlights the importance of close follow-up for DTC patients and the fact that,

although DTC is mostly an indolent disease with a rather less aggressive course, leaving it without adequate follow-up can result in numerous adverse outcomes and consequences.

For this reason, many authors investigated the quality and effectiveness of follow-up in DTC patients. Lam et al. conducted a cross-

sectional study of 91 patients with DTC in a Canadian tertiary referral center aiming to evaluate the quality of follow-up. They found that 29.7% of patients had no serum Tg measurement within one year and 17.6% had no available data regarding TG measurement⁽⁶⁾. From a complementary perspective, we found that the variation in the quality of care and the deviation from the current standardized practice guidelines are attributed in part to patient-related factors.

In another interesting study, **Aizer et al.** reported that, generally, cancer patients who are married have better outcomes, irrespective of disease stage and other socio-economic factors⁽⁷⁾. In another study on thyroid cancer patients, Wenaas et al. also reported that married patients and those aged between 45 and 64 years are more likely to receive medical care compliant with the ATA guidelines for advanced PTC compared to non-married patients and those above the age of 65⁽⁸⁾. In our study, the mean age of the patients was 47.8 years, 84% of whom were married. This discrepancy could be attributed to the concurrent increased financial and familial obligations that were found to be among the leading causes of LTFU.

The influence of educational level on therapeutic compliance of patients with various disease conditions remains controversial. Nasrollahzadeh and Yavuz et al. reported increased compliance with higher educational level in patients with renal transplantation^(9,10), Stille et al. and Wai et al. reported no effect in patients with high cholesterol levels and with Hepatitis B respectively^(11,12), while **Kyngas et al.** and Senior et al. reported decreased compliance with higher educational level^(13,14). In our

study, 40.7% of patients could not read or write, which shows that the educational status does not necessarily correlate with the compliance of the patients.

Rurality is associated with increased no-show rates as reported by Fiorillo et al.⁽¹⁵⁾. In compliance to this finding, 44% of our patient cohort lived outside Greater Cairo mostly in rural areas, more than the half of them reported transportation cost to be expensive and 7.7% of patients reported remote residency as a standalone cause for LTFU.

According to the 2014 Egypt demographic and health survey⁽¹⁶⁾, problems reported by females in accessing healthcare included getting permission to go for treatment, getting money for treatment, distance to health facility, having to take transport, not wanting to go alone, concern no female provider available, concern no health provider available and concern no drugs available. Apart from the financial cause and remote residency, none of the above-mentioned causes were reported.

Healthcare coverage is a crucial determinant of patients' compliance, especially for those suffering from chronic diseases⁽¹⁷⁻²⁰⁾. Patients with no healthcare insurance and low income are at risk of being not compliant to treatment as per **Choi-Kwon and Mishra et al.**^(21,22). In the same context, Paul et al. reported that occupational status and income among other socio-economic factors significantly contribute to LTFU⁽²³⁾. In our study, most of the identified patients were housewives (76.9%), had no healthcare coverage (90.1%) and the financial cause was the leading cause of LTFU (36.3%).

Previous periods of LTFU can be used as predictors for future no-shows⁽³⁾. Kim et al. added history of no-show to a model aiming at improving profits for healthcare providers⁽²⁴⁾. In our study, 26 patients (28.6%) had a previous history of LTFU, which can potentially serve as a predictor for future LTFU.

In our study, 13 patients (14.3%) reported COVID-19 and fear of infection as a standalone cause for LTFU. Smulever et al. reported their experience of following up of patients with DTC during the COVID-19 outbreak. In such circumstances, postponing appointments, evaluation through telemedicine and office visits for selected patients can be adopted.

Hypothyroidism has a great impact on the physical and psychological status of the patient. Rasha et al. reported levothyroxin withdrawal reduced the quality of life in DTC patients, especially among those who have been following up for less than three years⁽²⁵⁾. In our study, the number of patients with inadequate TSH suppression and hypothyroidism prior to LTFU was significantly higher in the early course of follow-up representing 47.8% compared to 16.2% in the late course of follow-up, highlighting the importance of regular TSH monitoring in such period.

The presence of co-morbidities can lead patients to therapeutic non-compliance, as reported by **Jin et al.**⁽²⁶⁾. In this study, some patients reported to have other co-morbidities especially among those whose follow-up duration lasted for more than 3 years. This emphasizes the importance of comprehensive medical care for patients with DTC. A suitable solution for this problem would be

the internal arrangement of follow-up visits on the same day at different departments of the hospital, to facilitate the hospital visit and minimize the number of commutes for patients who are being treated from several disease conditions.

Krajewska et al. demonstrated in numerous retrospective analyses that dynamic risk stratification allows for better prediction and individualized risk of recurrence in DTC⁽²⁷⁾. Our results showed that progression and recurrence were significantly higher among patients who lost follow-up before achieving excellent response and in high risk patients as well.

Conclusions: physicians treating patients with DTC should be aware of factors that are associated with LTFU in order to enable more personalized care according to each patient's condition. Suggested solutions that could minimize LTFU and improve patients' outcomes include: patient education, monitoring patients' early identification of patients that are prone to LTFU, active reengagement of LTFU patients, improving access to affordable quality healthcare services in rural areas, establishing and adapting clinical guidelines that take into account the availability of resources and providing personalized alternative ways for follow-up such as telemedicine. Special attention should be made to patients with financial difficulties and associated co-morbidities especially after the third year of follow-up, patients with inadequate TSH suppression or hypothyroidism especially in the early course of follow-up, high risk patients and those who did not achieve an excellent response.

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