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Evaluation of Quality of Life of Well Differentiated Thyroid Carcinoma Patients at Baseline and Six Months after Low Dose versus High Dose Radioactive Iodine-131 Ablation

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Abstract: ***Background: Radioactive iodine RAI- 131 ablation of differentiated thyroid carcinoma DTC following total thyroidectomy can compromise the quality of life (QOL) of patients. We aimed to compare the effect of 30 versus 80 mCi RAI- 131 ablative doses on the quality of lifeof DTC patients. Methods: The validated Arabic version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30 version 3.0) was used to assess the QOLoflow risk DTC patients randomized to 80 or 30 mCiRAI post-thyroidectomy both pre-ablation, and 6 months post-ablation. Results: Fifty-sixDTC patients were randomized to 30mCi (30/56)and 80 mCi (26/56) RAI-13.At 6 months the global health status, functioning (p >0.000), and symptoms scores (p<0.05) improved compared to baseline. The effect of the two ablativedosesat baseline global health status and functioning scores was comparable (p >0.05), whereas the 30 mCi dose caused higher symptoms scores (p<0.05). 6 months later both doses had no significant impact on the global health, functioning, and symptoms scores except for insomnia (p 0.008). Female patients had more pre-ablation symptoms but better physical functioning role at 6 months (p <0.05)) than males. Conclusion: despite the limited number of our cohortwe demonstrated that both 30 and 80 mCi RAI-131 ablation doses had an overall comparable impact onQOL on the relatively short term. Baseline, short and long terms QOL of DTC patients need to be evaluated in larger studies given the increasing incidence and number of survivors of DTC.***

Keywords: Thyroid differentiated carcinoma; Quality of life;Follow-up, Radioactive iodine ablation

1. Introduction

The initial treatment of DTC is total or near-total thyroidectomy with or without cervical lymph node dissection, followed in some cases by RAI-131 ablation of the remnant thyroid tissue [1]. As Incidence of thyroid carcinoma especially low-risk DTC is increasing, lower doses of RAI-131 have been investigated to achieve risk-benefit ratio, namely low toxicity and minimal impact on quality of life[2], [3], [4],[5]. According to Husson et al [6] the QLQ of DTC patients may be influenced by the fear of cancer diagnosis, thyroidectomy, RAI-131 ablation, and the fluctuation in the thyroid hormone level. Although treatment of DTC is generally well tolerated, patients may experience short and long term complications. Some reported complications with thyroidectomy include recurrent laryngeal nerve injury and discomfort during swallowing [7]. Acute side effects associated with RAI-131 ablation include nausea, vomiting, and sialadenitis. Examples of late effects caused by RAI-131 include xerostomia, dental caries, recurrent sialadenitis, and pulmonary fibrosis [8].

Given the increasing incidence and number of survivors of DTC it is important to identify the factors affecting the QOL in DTC patients. The number of trials that studied the medium and long term QOL is limited and has disadvantages such as being cross-sectional [9], [10], small sample size [11], [12], limited number of QOL assessed functions[13], [12]and the absence of baseline QOL data. Measurement of QOL allow for detection of various problems such as emotional status, global health state, and social function. It also allows tailoring of appropriate supportive care programs which could minimize the factors negatively impacting QOL[14], [15]. Apple white et al [16] compared the QOL of thyroid cancer survivors to the QOL of survivors of other types of cancer using results from the North American Thyroid Cancer Survivorship Study (NATCSS) which is a large-scale survivorship study. The NATCSS assessed the overall QOL and four subcategories; physical, psychological, social and spiritual well-being. The authors found that the overall QOL of thyroid cancer patients was similar to that of patients with colon cancer (mean 5.20, p 0.13), glioma (mean 5.96, p0.23), and gynecologic cancer (mean 5.59, p 0.43). It was worse than studied breast cancer patients (mean 6.51, p<0.01).In view of these results the authors focused on the need for better care for the increasing number of thyroid carcinoma patients. Similarly, Ratki et al[17]recorded the QOL of 435 patients diagnosed with DTC using a validated EORTC QLQ-C30 version 3.0, in addition to a checklist which recorded information about the educational, marital and economic status of the patients The authors showed that the QOL scores were affected by socioeconomic, treatment and follow-up factors. They also emphasized the importance of maintaining the well-being of patients during treatment and follow-up.

Thus the goal of this study was to assess the quality of life of low risk DTC patients ablated with 30 versus 80 mCi RAI-131using the EORTC-QLQ C30.

2. Material and Methods

Study design and patients

This was part of a prospective randomized study of 56 patients diagnosed with DTC to compare the efficacy ofRAI-131 ablative dose 30 or 80 mCi. In addition the QOL was assessed at baseline before RAI-131 ablation, and 6 months post-ablation. Stages T1-T3 N0-N1 M0 (according to AJCC 7 th edition, 2010)was included. The Eastern Cooperative Oncology Group (ECOG) performance status of the patients was 0-2.

EORTC QLQ-C30 version 3.0[18]

56patients participated in the questionnaire and were compliant with its completion. EORTC QLQ-C30 is a cancer-specific 30 item questionnaire. It contains five functional domains (physical, social, role, cognitive and emotional), nine symptom scales (fatigue, nausea & vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) and a global health and QOL scale. All responses in this questionnaire are categorized in four levels, from "not at all" to "very much" except for two items of global health and quality of life which are classified with seven points from "very poor" to "excellent". The summative scores, which range from 0 to 100 points, were calculated according to the EORTC QLQ-C30 manual. A high score on the functional scales, global health status indicate better QOL, while high scores on the symptoms domain mean poorer QOL [17]. The validated Arabic account of EORTC QLQ-C30 (version 3.0)was used in this study [19]. This study was approved by the Research and Ethical Committee of Faculty of Medicine, Ain-Shams University. Informed consent was obtained from the patients.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric while non-parametric data were presented as median with interquartile range (IQR). The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent t-test while non- parametric data were compared with Mann-Whitney test. The comparison between pre and post was done using Wilcoxon Rank test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: $P > 0.05$: Non significant, $P < 0.05$: Significant, and $P < 0.01$: Highly significant.

3. Results

Patients

Fifty-six patients diagnosed with DTC responded to the questionnaire.(Table 1) summarizes the patients and clinical characteristics. 42/56 (75%) patients were female and 14/56 (25%) were males. The mean age was 37.36 years. Papillary carcinoma was the most common histologic type (46/56, 82.1%). All the patients had low risk disease and stage I disease predominated (48/56, 85.7%). Total or near total thyroidectomy was performed in all patients. The patients were randomized to RAI-131 ablative dose where30/56 (53.6%) and 26/56 (46.4%) patients received 30 and 80 mCi respectively. By 6 months post-ablation few patients developed failure of ablation at the thyroid bed (4/56, 7.1%) and locoregional lymph nodes (4/56, 7.1%), while none of the patients had distant metastases. QLQ-C30 was performed in 30/56, and 26/56 of the patients ablated with 30 mCi 80 mCi RAI respectively. Four patients who received 80 mCi RAI- 131 refused to participate.

QOLoutcomes

(Table 2, Figure 1) show comparison of the QOL of the cohort (56 patients) at baseline versus 6 months after iodine ablation. The three domains scored better at 6 months than at baseline (p 0.000). ***Baseline QOL*** recorded better global health status score in the 30 mCi group,while all of the functioning scale sub domains scored better in the 80 mCi RAI-131ablated group ($p \geq 0.05$).The 30 mCi RAI- 131 ablated patients significantly experienced more fatigue, pain, dyspnea and financial difficulties (Table 3).***6 months post-ablation*** the global health status improved as opposed to baseline in both ablation groups but at non-significant levels($p \geq 0.05$) (Figure 2).The participants continued to report improved functioning levels particularly the in the 30 mCi group ($p \geq 0.05$). The symptoms scale scores became better at 6 months than at baseline in both groups ($p \geq 0.05$)except for more insomnia in the 30 mCi ablated patients (p 0.008)(Table 4).

The relationship between the QOL-C30 domains and some of the clinical and treatment variables was evaluated at baseline and 6 months namely; sex, side effects during ablation, and the result of the follow-up whole body scan (WBS) performed at 6 months post-ablation. There was no link detected between these factors and the baseline and 6 months global health status score ($p \geq 0.05$), except for males had better score at 6 months (p 0.047), (Table 5).

The functioning scale at baseline (Table 6):female patients and patients who developed side effects during admission tended to have better functioning scores ($p \geq 0.05$).Patients who had free follow-up WBS scored high on the physical functioning role, emotional, and social functioning scales (p 0.001, 0.002, 0.044 respectively). On the other hand, at 6 months post-ablation males and females had comparable non-significant functioning scale, except for the physical functioning role which was better in females than in males (p 0.041), (Table 7).

The symptoms scale at baseline: female patients experienced more fatigue (p 0.033), and constipation (p 0.005) than males. Interestingly, patients who had more pre-ablation symptoms as; fatigue (p 0.012), nausea and vomiting (p 0.026), dyspnea (p 0.041) and diarrhea (p 0.006)developed no side effects during ablation, in contrast to patients who had side effects during ablation who experienced fewer symptoms before ablation($p \geq 0.05$), (Table 8). 6 months later, patients who developed no side effects during ablation experienced only insomnia (p 0.034). Participants who developed lymph nodes and thyroid bed recurrences as detected by the WBS at 6 months had nausea, vomiting (p 0.009) and constipation (p 0.003),(Table 9).

Table 1: Patients characteristics

Patients number = 56		
Age	Mean±SD	37.36 ± 9.25
	Range	21 – 55
Sex	Females	42 (75.0%)
	Males	14 (25.0%)
Histologic type	Papillary	46 (82.1%)
	Follicular	2 (3.6%)
	Papillary follicular pattern	8 (14.3%)
Tumor grade	1	30 (53.6%)
	2	22 (39.3%)
	3	4 (7.1%)
Tumor size T	1	14 (25.0%)
	2	32 (57.1%)
	3	10 (17.9%)
Lymph Nodes N	0	54 (96.4%)
	1	2 (3.6%)
Metastases M	0	56 (100.0%)
Stage	I	48 (85.7%)
	II	4 (7.1%)
	III	4 (7.1%)
Surgery	Yes	56 (100.0%)
Type of surgery	Total thyroidectomy	34 (60.7%)
	Completion thyroidectomy	22 (39.3%)
I-131 dose	30 mCi	30 (53.6%)
	80 mCi	26 (46.4%)
Admission	No	18 (32.1%)
	Yes	38 (67.9%)
Number of admission days	0	18 (32.1%)
	2	2 (3.6%)
	3	24 (42.9%)
	4	8 (14.3%)
	5	4 (7.1%)
Side effects during admission	No	26 (46.4%)
	Yes	30 (53.6%)
Neck pain	No	40 (71.4%)
	Yes	16 (28.6%)
Fatigue	No	46 (82.1%)
	Yes	10 (17.9%)
Sialadenitis	No	44 (78.6%)
	Yes	12 (21.4%)
Headache	No	48 (85.7%)
	Yes	8 (14.3%)
WBS post iodine	residual functioning thyroid tissue	56 (100.0%)
Thyroid U/S at 6 months	Not done	4 (7.1%)
	Done	52 (92.9%)
Result	Free	46 (88.5%)
	Thyroid bed recurrence	2 (3.8%)
	Malignant looking lymph nodes	2 (3.8%)
	Both	2 (3.8%)
WBS at 6 months	locoregional lymph node recurrence	4 (7.1%)
	non-significant faint uptake	46 (82.1%)
	not done	2 (3.6%)
	thyroid bed recurrence	4 (7.1%)
Thyroglobulin level	Median (IQR)	0.95 (0.1 – 8.95)
	Range	0.04 - 107
second ablative dose at 6 months	No	44 (78.6%)
	Yes	10 (17.9%)
	Lost follow up	2 (3.6%)
Distant recurrence at 6 months	No	54 (96.4%)
	Lost follow up	2 (3.6%)

Table 2: Comparison of QOL at baseline and 6 months

Global health status score		Baseline	6 months	Paired t-test	
		No.=56	No.=56	t	P-value
Mean±SD		63.75 ± 21.37	72.50 ± 18.13	3.762	**0.000**
Range		20 – 100	40 – 100		
Functional score					
Physical functioning score	Mean±SD	69.54 ± 23.27	75.96 ± 23.95	1.902	0.062
	Range	10 – 100	30 – 100		
Role functioning score	Mean±SD	62.96 ± 31.08	76.79 ± 28.29	3.839	0.000
	Range	0 – 100	0 – 100		
Emotional functioning score	Mean±SD	70.25 ± 22.57	71.96 ± 22.13	0.565	0.575
	Range	10 – 100	20 – 100		
Cognitive functioning score	Mean±SD	64.04 ± 30.05	71.79 ± 28.29	3.573	**0.001**
	Range	0 – 100	20 – 100		
Social functioning score	Mean±SD	67.96 ± 32.29	75.00 ± 28.87	2.041	0.046
	Range	20 – 100	30 – 100		
Symptoms score				**Wilcoxon Ranks test**	
				Z	**P-value**
Fatigue	Median (IQR)	30 (20–60)	20 (0–60)	-2.524	**0.012**
	Range	0 – 100	0 – 90		
Nausea and Vomiting	Median (IQR)	0 (0–25)	0 (0–20)	-1.206	0.228
	Range	0 – 100	0 –50		
Pain	Median (IQR)	25 (10–60)	20 (0–50)	-1.734	0.083
	Range	0 – 100	0 – 100		
Dyspnea	Median (IQR)	0 (0–30)	0 (0–30)	-0.838	0.402
	Range	0 – 100	0 – 100		
Insomnia	Median (IQR)	15 (0–70)	0 (0–50)	-1.976	**0.048**
	Range	0 – 100	0 –100		
Appetite loss	Median (IQR)	30 (0–70)	0 (0–30)	-3.551	**0.000**
	Range	0 – 100	0 – 100		
Constipation	Median (IQR)	0 (0–30)	0 (0–0)	-0.585	0.558
	Range	0 – 100	0 – 100		
Diarrhea	Median (IQR)	0 (0–30)	0 (0–15)	-0.330	0.741
	Range	0 – 100	0 – 100		
Financial difficulties	Median (IQR)	30 (30–70)	30 (30–70)	-0.993	0.321
	Range	0 – 100	0 – 100		

Table 3: Comparison of baseline QOL in 30 and 80 mCi RAI-131ablation groups

Global health status score		30 mCi	80 mCi	Independent t-test	
		No.=30	No.=26	t	P-value
Mean±SD		66.00 ± 16.82	61.15 ± 26.15	0.852	0.398
Range		30 – 100	20 – 100		
Functional score					
Physical functioning score	Mean±SD	67.80 ± 24.43	71.54 ± 22.67	0.602	0.550
	Range	10 – 100	30 – 100		

Role functioning score	Mean±SD	63.33 ± 29.68	62.54 ± 33.84	0.095	0.924
	Range	0 – 100	20 – 100		
Emotional functioning score	Mean±SD	66.00 ± 20.72	75.15 ± 24.43	1.547	0.128
	Range	25 – 100	10 – 100		
Cognitive functioning score	Mean±SD	57.33 ± 26.58	71.77 ± 32.95	1.849	0.070
	Range	20 – 100	0 – 100		
Social functioning score	Mean±SD	66.67 ± 32.22	69.46 ± 33.62	0.323	0.748
	Range	20– 100	30 – 100		
Symptoms scale				**Mann Whitney test**	
				Z	**P-value**
Fatigue	Median (IQR)	40 (30.0 – 70.0)	20 (10.0 – 30.0)	3.645	**0.000**
	Range	10 – 100	0 – 70		
Nausea and Vomiting	Median (IQR)	10 (0.0 – 30.0)	0 (0.0 – 25.0)	1.533	0.125
	Range	0 – 100	0 – 30		
Pain	Median (IQR)	30 (0.0 – 80.0)	20 (20.0 – 25.0)	2.303	0.021
	Range	0 – 100	0 – 70		
Dyspnea	Median (IQR)	30 (0.0 – 30.0)	0 (0.0 – 0.0)	3.013	**0.003**
	Range	0 – 100	0 – 30		
Insomnia	Median (IQR)	30 (0.0 – 70.0)	0 (0.0 – 70.0)	1.488	0.137
	Range	0 – 100	0 – 100		
Appetite loss	Median (IQR)	30 (0.0 – 70.0)	30 (0. 0 – 30.0)	1.351	0.177
	Range	0 –100	0 – 70		
Constipation	Median (IQR)	0 (0.0 – 30.0)	0 (0.0 – 0.0)	1.437	0.151
	Range	0 – 100	0 – 30		
Diarrhea	Median (IQR)	0 (0.0 – 30.0)	0 (0.0 – 30.0)	0.167	0.867
	Range	0 – 100	0 – 30		
Financial difficulties	Median (IQR)	70 (30.0– 70.0)	30 (0.0– 30.0)	3.267	**0.001**
	Range	0 – 100	0 – 100		

Table 4: Comparison of QOL 6months post-ablation with30 and 80 mCi RAI-131

Global health status score	30 mCi	80 mCi	Independent t-test	
	No.=30	No.=26	t	P-value
Mean±SD	75.67 ± 14.98	68.85 ±21.23	1.430	0.158
Range	50 – 100	40 – 100		

Functional score					
Physical functioning score	Mean± SD	79.13 ± 22.64	72.31 ± 25.80	1.075	0.287
	Range	30 – 100	30 – 100		
Role functioning score	Mean± SD	74.00 ± 31.58	80.00 ± 24.83	0.796	0.429
	Range	0 – 100	20 – 100		
Emotional functioning score	Mean± SD	72.67 ± 20.52	71.15 ± 24.68	0.255	0.799
	Range	20 – 100	30 – 100		
Cognitive functioning score	Mean± SD	68.00 ± 28.59	76.15 ± 28.44	1.087	0.282
	Range	20 –100	20 – 100		
Social functioning score	Mean± SD	77.33 ± 28.40	72.31 ± 30.32	0.652	0.517
	Range	30 – 100	30 – 100		
Symptoms score				Mann Whitney test	
				Z	P-value
Fatigue	Median (IQR)	30 (0.0– 60.0)	20 (0.0 – 60.0)	-0.068	0.946
	Range	0 – 90	0 – 80		
Nausea and Vomiting	Median (IQR)	0 (0.0 – 20.0)	0 (0.0 – 20.0)	-0.119	0.905
	Range	0 – 50	0 – 50		
Pain	Median (IQR)	10 (0.0 – 70.0)	20 (0.0 – 30.0)	-0.345	0.730
	Range	0 – 100	0 – 70		
Dyspnea	Median (IQR)	30 (0.0 – 70.0)	0 (0.0 – 30.0)	-1.515	0.130
	Range	0 – 100	0 – 100		
Insomnia	Median (IQR)	30 (0.0 – 70.0)	0 (0.0 – 0.0)	-2.655	0.008
	Range	0 – 100	0 – 100		
Appetite loss	Median (IQR)	0 (0.0 – 30.0)	0 (0.0 – 10.0)	-1.206	0.228
	Range	0 – 100	0 – 100		
Constipation	Median (IQR)	0 (0.0 – 0.0)	0 (0.0 – 0.0)	0.000	1.000
	Range	0 – 100	0 – 30		
Diarrhea	Median (IQR)	0 (0.0 – 0.0)	0 (0.0 – 30.0)	-0.741	0.459
	Range	0 – 100	0 – 30		
Financial difficulties	Median (IQR)	30 (30.0 – 70.0)	30 (0.0 – 70.0)	-1.342	0.179
	Range	0 – 100	0 – 100		

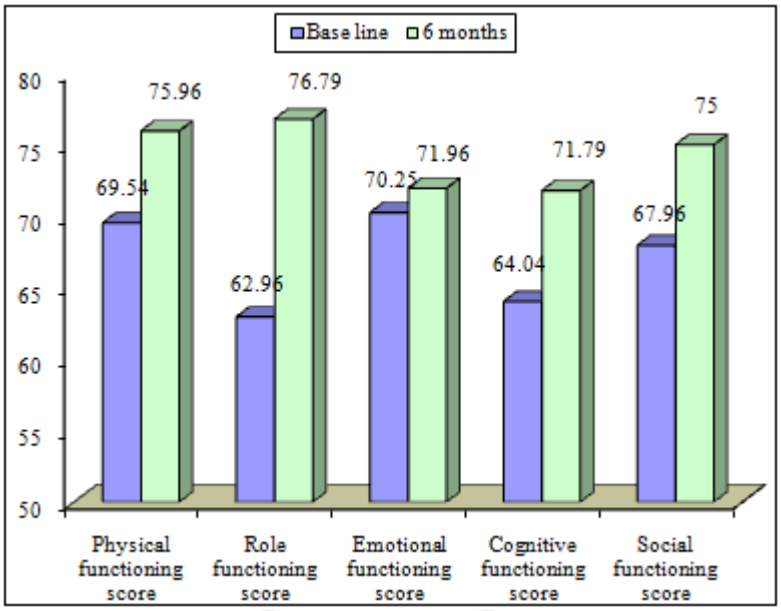

Figure 1: Comparison of functional score at baseline and 6 months post-RAI-131ablation

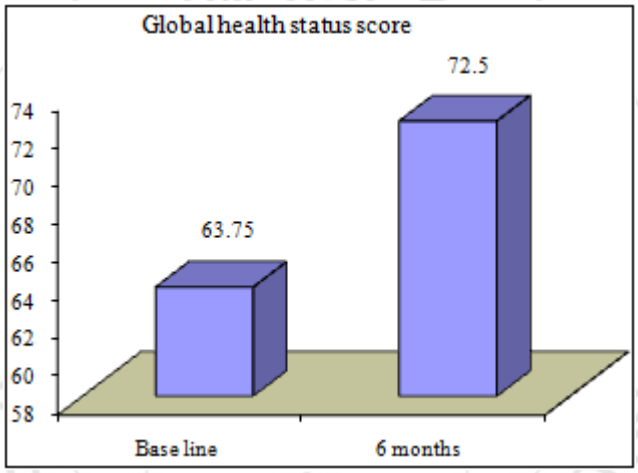

Figure 2: Comparison of global health score at baseline and 6 months post-RAI- 131 ablation

Table 5: Association of global health status with clinical variables at baseline and 6 months

		Global health status score at baseline	P-value	Global health status score at 6 months	P-value
		Mean±SD		Mean±SD	
Sex	Females	62.14±22.12	0.33	69.76±18.64	0.047
	Males	68.57±17.91		80.71±13.13	
Side effects during admission	No	62.31±18.4	0.639	72.31±14.51	0.941
	Yes	65±23.56		72.67±20.75	
WBS at 6 months	Locoregional lymph node recurrence	65±17.32	0.642	77.5±2.89	0.473
	Non-significant faint uptake	62.39±22.6		71.09±19.32	
	Not done	80±0		90±0	
	Thyroid bed recurrence	70±0		75±5.77	

Table 6: Association of functional subdomains at baseline with some clinical variables

baseline		Physical functioning score	P-value	Role functioning score	P-value	Emotional functioning score	P-value	Cognitive functioning score	P-value	Social functioning score	P-value
		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD	
Sex	Females	68.71 ± 24.79	0.648	64.43 ± 29.97	0.543	68.67 ± 21.75	0.364	63.95 ± 31.39	0.971	69.19 ± 31.12	0.624
	Males	72.00 ± 17.40		58.57 ± 33.94		75.00 ± 24.34		64.29 ± 25.33		64.29 ± 35.46	
Side effects during admission	No	65.92 ± 29.13	0.279	60.77 ± 32.36	0.624	67.69 ± 23.46	0.431	60.77 ± 27.56	0.450	62.31 ± 33.74	0.221
	Yes	72.67 ± 15.96		64.87 ± 29.80		72.47 ± 21.52		66.87 ± 31.76		72.87 ± 30.11	
WBS at 6	locoregional	67.00 ± 19.63	0.001	45.00 ± 28.87	0.079	90.00 ± 11.55	0.002	65.00 ± 17.32	0.698	65.00 ± 40.41	**0.044**

months	lymph node recurrence										
	non-significant faint uptake	72.17 ± 20.43		64.91 ± 28.65		71.39 ± 21.28		64.48 ± 31.60		70.13 ± 31.03	
	not done	93.00 ± 0.00		100.00 ± 0.00		75.00 ± 0.00		80.00 ± 0.00		100.00 ± 0.00	
	thyroid bed recurrence	30.00 ± 23.09		40.00 ± 46.19		35.00 ± 5.77		50.00 ± 23.09		30.00 ± 0.00	

Table 7: Association of functional subdomains with clinical variables at 6 months

6 months		Physical functioning score	P-value	Role functioning score	P-value	Emotional functioning score	P-value	Cognitive functioning score	P-value	Social functioning score	P-value
		Mean±SD		Mean±SD		Mean±SD		Mean±SD		Mean±SD	
Sex	Females	72.24±25.59	0.041	75.24±29.57	0.479	73.10±22.11	0.509	71.43±29.35	0.871	72.38±30.43	0.239
	Males	87.14±11.77		81.43±23.16		68.57±21.79		72.86±24.63		82.86±21.28	
Side effects during admission	No	69.77±28.61	0.069	69.23±31.36	0.060	68.46±21.48	0.270	69.23±25.44	0.530	70.77±30.84	0.307
	Yes	81.33±17.28		83.33±23.39		75.00±22.21		74.00±30.35		78.67±26.49	
WBS at 6 months	locoregional lymph node recurrence	80.00±11.55	0.395	85.00±17.32	0.610	50.00±23.09	0.103	55.00±28.87	0.467	100.00±0.00	0.144
	non-significant faint uptake	75.52±23.08		75.22±29.19		74.57±18.55		73.04±27.40		72.61±28.16	
	not done	100.00±0.00		100.00±0.00		80.00±0.00		90.00±0.00		100.00±0.00	
	thyroid bed recurrence	65.00±40.41		75.00±28.87		60.00±46.19		65.00±40.41		65.00±40.41	

Table 8: Association of symptoms scale with clinical variables at baseline

baseline		Fatigue	P-value	Nausea and Vomiting	P-value	Pain	P-value	Dyspnea	P-value	Insomnia	P-value	Appetite loss	P-value	Constipation	P-value	Diarrhea	P-value	Financial difficulties	P-value
		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)	
Sex	Females	40 (20 – 70)	**0.03**	0 (0 – 30)	0.6	20 (0 – 70)	0.7	0 (0 – 30)	0.7	30 (0 – 70)	0.1	30 (0 – 70)	0.6	0 (0 – 0)	**0.005**	0 (0 – 30)	0.7	30 (30 – 70)	0.05
	Males	20 (10 – 40)		0 (0 – 25)		25 (20 – 50)		0 (0 – 30)		0 (0 – 30)		30 (0 – 70)		30 (0 – 70)		0 (0 – 30)		70 (30 – 100)	
Side effects during admission	No	40 (30 – 70)	0.01	20 (0 – 30)	**0.02**	30 (0 – 80)	0.5	30 (0 – 30)	**0.04**	30 (0 – 70)	0.6	30 (0 – 70)	0.06	0 (0 – 30)	0.06	0 (0 – 30)	**0.006**	70 (30 – 70)	0.3
	Yes	20 (10 – 40)		0 (0 – 25)		25 (20 – 50)		0 (0 – 30)		0 (0 – 70)		30 (0 – 30)		0 (0 – 0)		0 (0 – 0)		30 (30 – 70)	
WBS at 6 months	locoregional lymph node recurrence	35 (20 –50)	**0.002**	12.5 (0 – 25)	0.09	27.5 (25 – 30)	0.6	0 (0 – 0)	0.05	0 (0 – 0)	**0.006**	50 (30 – 70)	**0.003**	15 (0 – 30)	0.6	15 (0 – 30)	0.6	85 (70 – 100)	**0.006**
	non-significant faint uptake	30 (20 – 60)		0 (0 – 25)		25 (0 – 70)		0 (0 – 30)		30 (0 – 70)		30 (0 – 30)		0 (0 – 30)		0 (0 – 30)		30 (30 – 70)	
	not done	10 (10 – 10)		0 (0 – 0)		20 (20 – 20)		0 (0 – 0)		0 (0 – 0)		0 (0 – 0)		0 (0 - 0)		0 (0 – 0)		30 (30 – 30)	
	thyroid bed recurrence	85 (70 – 100)		45 (20 – 70)		50 (0 – 100)		50 (0 – 100)		85 (70 – 100)		85 (70 – 100)		25 (20 – 30)		0 (0 – 0)		85 (70 – 100)	

IQR interquartile range

Table 9: Association of symptoms scale with clinical variables at 6 months

		Fatigue	P-value	Nausea and Vomiting	P-value	Pain	P-value	Dyspnea	P-value	Insomnia	P-value	Appetite loss	P-value	Constipation	P-value	Diarrhea	P-value	Financial difficulties	P-value
		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)	
Sex	Females	30 (0 – 60)	0.2	0 (0 – 20)	0.8	30 (0 – 70)	0.05	0 (0 – 30)	0.7	0 (0 – 30)	0.6	0 (0 – 30)	0.6	0 (0 – 0)	0.4	0 (0 – 30)	0.2	30 (30 – 70)	0.2
	Males	10 (0 – 60)		0 (0 – 50)		0 (0 – 20)		0 (0 – 30)		0 (0 – 70)		0 (0 – 30)		0 (0 – 30)		0 (0 – 0)		70 (30 – 70)	
Side effects during admission	No	30 (0 – 60)	0.7	0 (0 – 20)	0.4	30 (0 – 70)	0.1	30 (0 – 70)	0.07	30 (0 – 70)	**0.03**	0 (0 – 30)	0.9	0 (0 – 0)	0.3	0 (0 – 0)	0.8	30 (30 – 70)	0.9
	Yes	20 (0 – 70)		0 (0 – 20)		0 (0 – 30)		0 (0 – 30)		0 (0 – 0)		0 (0 – 30)		0 (0 – 30)		0 (0 – 30)		30 (0 – 70)	
WBS at 6 months	Locoregional lymph	35 (0 – 70)	0.3	0 (0 – 0)	**0.009**	10 (0 – 20)	0.3	35 (0 – 70)	0.5	35 (0 – 70)	0.4	50 (0 – 100)	0.05	0 (0 – 0)	**0.003**	0 (0 – 0)	0.6	65 (30 – 100)	0.2

	node recurrence																		
	Non-significant faint uptake	20 (0 – 60)		0 (0 – 20)		30 (0 – 70)		0 (0 – 30)		0 (0 – 30)		0 (0 – 30)		0 (0 – 0)		0 (0 – 30)		30 (0 – 70)	
	Not done	0 (0 – 0)		0 (0 – 0)		0 (0 – 0)		0 (0 – 0)		0 (0 – 0)		0 (0 – 0)		0 (0 – 0)		0 (0 – 0)		30 (30 – 30)	
	Thyroid bed recurrence	45 (0 – 90)		35 (20 – 50)		40 (0 – 80)		15 (0 – 30)		50 (0 – 100)		15 (0 – 30)		50 (0 - 100)		15 (0 – 30)		65 (30 – 100)	

IQR interquartile range

4. Discussion

The role and efficacy of RAI-131 in increasing survival is well documented [20], however it has been associated with a decrease in QOL of DTC patients. So, in this study we enrolled 56patients who underwent total thyroidectomy then they were randomizedto receive 30 or 80 mCi RAI-131 ablation. QOL assessment was performed at baseline before ablation, and 6 months post-ablation using the EORTC-QLQ C30 (version 3.0). We evaluated the impact of low and high ablative doses of RAI-131 on the QOL of the patients. To the best of our knowledge this is one of the few studies that evaluated the baseline QOL of DTC patients. We were able to show that the both low and high doses RAI-131 ablation had comparable effect on the quality of life of DTC on relativelyshort term follow-up.

The EORTC QLQ-C30 was able to detect changes in QOL overtime. Most of the scales showed a decline of QOL during RAI-131 ablation, followed by increase in post-ablation QOL. There is lack of evaluation of baseline status, where other QOL studies have not accounted for the potential impact of baseline QOL. We demonstrated worse baseline global health status, role, cognitive, and social functioning scores in the 56 patients at highly significant levels. Similarly, the patients experienced statistically significant more fatigue, insomnia, and appetite loss at baseline.Taieb et al 2011[21] conducted a longitudinal study which included 83 patients, with similar inclusion criteria to the current study, newly diagnosed well-differentiated thyroid carcinoma stages pT1-T3, N0-NxN1, M0. The patients had total thyroidectomy followed by RAI-131 100 mCi. The patients were assessed at the time of inclusion and at 9 months post- ablation. The authors evaluated anxiety and depression using self-administered Beck Depression inventory BDI and QOL using functional assessment of chronic illness therapy FACIT scores. This study was integrated in a previous prospective randomized study [22]. The authors concluded that medium-term QOL in thyroid DTC was mainly determined by pre-ablation QOL. According to the authors low baseline QOL is a predictor of poor subjective outcomes. So they suggested that such patients would benefit from cancer support groups for patients and their families, more targeted cancer-related patient information, nurse and psychologist's aides, and participation in treatment decision-making. Ratki et al [17] evaluated the influence of baseline and treatment –related factors on QOL of 435 cured DTC patients who received RAI. The authors used a validated EORTC QLQ-C30 version 3.0. The number of RAI therapies was one of the factors that affected the total QOL score because it significantly influenced the physical, emotional and social subdomains of functioning in DTC patients.

Florenzano et al [23] evaluated the frequency and intensity of early and late effects of RAI-131 in DTC patients who underwent thyroidectomy. The patients answered 2 surveys from 0-6 months and between 6-18 months. The authors created the surveys based on published literature information on RAI related symptoms [24], [25], [26], [27]. The authors analyzed data using four categories of intensity:0 (inexistent), 1-2 (mild), 3-4 (moderate), and 5 (severe).The authors defined low and high RAI doses as 50 versus ≥100 mCi.80% of the patients received RAI ablation. The late post-RAI related symptoms were surveyed at a median of 11 months (6-18.6 months). The following symptoms were statistically more frequent and intense as compared to patients who did not receive RAI; periorbital edema (p 0.012), salivary gland pain (p 0.001), and dry mouth (p 0.014). The authors did not detect significant differences in the intensity and frequency of the late symptoms between low and high RAI doses. By six months follow up these symptoms were less intense when compared to the first survey of the early RAI related symptoms done at a median of 2.5 months (0.5-5.8) months after ablation. These findings agree with our observations of the symptoms domains of the QLQ-C30, in terms of less symptoms at 6 months post-ablation than at baseline such as fatigue (p 0.012), insomnia (p 0.048), and appetite loss (p 0.000).Also, we demonstrated no effect of low and high doses RAI on symptoms ($p \geq 0.05$) except for fatigue, pain, and dyspnea which statistically scored higher in the 30 mCi RAI- 131 dose.

Literature is controversial regarding the relationship between RAI dose and RAI related symptoms frequency[23].We demonstrated that the overall QOL-C30 score was comparable at baseline between the two ablative doses, and also wasalmost equally affected at 6 months after RAI-131 ablation of DTC patients. Similarly, Vega-Vazquez et al [28]assessed the QOL of 75 DTC patients using the Spanish version of the University Of Washington Quality Of Life Questionnaire (UW-QOL) which included multiple aspects of physical and social functioning. They found that the overall QOL score was minimally affected after the diagnosis and treatment of DTC patients. Vega-Vazquez et al [28] divided the RAI- 131 ablative doses into low dose (≤ 150 mCi, n=40), and high dose (> 150 mCi, n= 14) in 66/75 patients who received RAI ablation after total thyroidectomy. The authors classified the period of time since RAI ablation into recent exposure (≥ 12 months, n= 15) and long-time exposure (more than 12 months, n= 51). Patients who received a cumulative therapeutic RAI dose > 150 mCi had a tendency toward high pain score. On the other hand, Almedia et al [9]reported on the impact of higher cumulative RAI doses on the worse scores of the domains of swallowing, chewing, speech, taste, and anxiety. Similarly, Dingle et al [29] showed significant reduction in

QOL in the recreation domain in DTC patients who received higher cumulative doses of RAI.

According to recent publications by Applewhite et al [30], and Ascherbrook et al [31],DTC causes important effects on QOL. Applewhite et al [30]demonstrated that QOL scored the lowest at initial diagnosis, after surgery, thyroid hormone withdrawal, and after RAI ablation. The authors have shown that thyroid cancer survivors can have similar or worse QOL scores when compared to other types of cancer as colon cancer, gynecologic cancer, and breast cancer. Thus, given the increasing incidence of DTC, the prolonged survival of patients, and the side effects of DTC diagnosis and treatment which negatively affect the long term QOL, physicians should cautiously decide treatment approaches including RAI doses, taking in consideration the physical and psychological side effects.

Vega-Vázquez et al [28] did not find any association between gender, tumor size, type of surgery, or time since RAI-131 therapy with the twelve domain scores included in the UW-QOL questionnaires.On the other hand, age < 45 years old scored worse on the pain domain (p 0.02). Ratki et al [17]demonstrated that global health status and functional domains were better in females, single and higher educated patients. The female patients scored better in four functional subdomains; physical, emotional, role and cognitive, but not for social functioning. Increased number of radio-iodine therapies, radio-iodine cumulative doses and number of surgeries had negative impact on QOL.

5. Conclusion

When deciding the treatment strategies of the growing population of DTC patients with increasing life span, physicians should consider the QOL assessment. Periodic quality of life evaluations are necessary, at baseline, medium-term, and long-term in order to tailor therapy and potentially improve outcome. Larger studies are required using thyroid specific QOL questionnaires to improve the long term-care and QOL for this group of patients.

Conflict of interest none to declare

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