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Assessment of Treatment Response to 131-I Therapy for Patients with Differentiated Thyroid Carcinoma in the Past Three Years (Single Institutional Experience).

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ABSTRACT:

Background; The most frequent endocrine cancer is thyroid cancer. Differentiated thyroid carcinoma (DTC) is becoming more common lately. ***Aim of the work;*** The objective of this study is to assess the response to radioactive iodine 131 (RAI131) treatment outcome in the institution over the last three years. ***Methods;*** This retrospective analysis of 223 patients with differentiated thyroid carcinoma in the period between 2017-2019. Data collection included operative extent, pathology, ^{131}I dose, diagnostic and post-therapeutic radioactive iodine scan and neck ultrasound. ***Results;*** 223 patients, 61.9% were ≤45 years, most of them were females. Papillary thyroid carcinoma was the most frequent pathology with incidence 66.8%. There was statistically insignificant difference between low and high doses of iodine in achieving successful residual ablation in low as well as intermediate risk patients. Multivariate analysis of the different risk factors revealed that proper ablative dose, gender, serial serum thyroglobulin measurement, risk stratification were significant prognostic factors. ***Conclusion;*** Our data suggest that proper ablative dose, gender, serial serum thyroglobulin measurement, lack of metastatic lesions and risk stratification were significant prognostic predictors for excellent outcome in DTC patients.

Key words: DTC, RAI131, treatment, response.

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INTRODUCTION:

The prevalence of differentiated thyroid carcinoma (DTC), whose has been rising for several decades, is anticipated to rank as the fourth most common cancer diagnosis. Diagnoses of tiny, low risk malignancies account for a large portion of this increase in incidence. These low-risk malignancies have very good long-term survival rates [(1)].

Surgery is the mainstay of therapy for DTC. Recurrence is acknowledged as a significant contributor to increased morbidity and death despite the typically favorable prognosis of treated DTC, with a 10-year survival rate surpassing 90%. [(2)].

After initial surgery (total or nearly total thyroidectomy), the majority of DTC patients receive radioiodine (131I) therapy in an effort to destroy microscopic residual normal or tumoral thyroid cells and to aid in the early detection of tumor recurrence using serum thyroglobulin (TG) measurement and 131I whole-body scan (131I-WBS) [(3)]. A lack of visible radioactive iodine (RAI) absorption on a later diagnostic RAI scan or a stimulated serum TG that could not be found are often used as indicators of successful residual ablation [(4)].

Compared to DTC patients who developed distant metastases after first therapy, DTC patients who presented with initial distant metastases appear to have more favorable outcomes. The most crucial prognosis factor for all patients with distant metastases may be complete local control. In patients with distant metastases following first therapy, metastatic lesion iodine avidity had a substantial effect on both overall survival and disease-specific survival [(5)].

DTC aggressive histopathological subtypes are 18F-fluorodeoxyglucose (^{18}F-FDG)-rich tumors that are very susceptible to recurrent/persistent illness. In these individuals, when there is a suspicion of recurrence, thyroglobulin (TG) levels or thyroglobulin antibodies (TgAb)-based fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) are performed [(6)]. Additionally, recurring cancer patients with positive tumor markers and negative anatomic imaging may benefit from functional imaging using positron emission tomography (PET) or PET-CT [(7)].

AIM OF WORK

The aim of this retrospective study was to assess the adequacy of management of patients with differentiated thyroid carcinoma treated with ^{131}I therapy in the past 3-years with evaluation of frequency of different risk groups among cohort of patients with DTC.

PATIENTS AND METHODS:

The study was conducted at Nuclear Medicine and Radiation Oncology Department, Faculty of Medicine, Cairo University. Approval was obtained from the research ethics panels of Faculty of Medicine, Cairo University. All methods used in research involving human subjects were compliant with the 1964 Helsinki statement and its later revisions, as well as the ethical guidelines established by the institutional research committee. 223 adult patients' medical records were examined to gather data, of both genders above 18 years old with histologically proven well differentiated thyroid carcinoma. All cases were subjected to thyroid surgery (total, near total or subtotal thyroidectomy) then referred to our department for thyroid ablative or therapeutic doses of iodine-131 at least 4-6 weeks post-surgery from January 2017 to December 2019. Patients with incomplete data, patients who lost follow up or having co-existing other types of malignancy were excluded from the study.

Clinical protocol:

Detailed clinical data were obtained from the patients' medical archive including age, gender, operative data, pathological report, serial serum thyroglobulin and anti-thyroglobulin anti-bodies, ablative dose of RAI131, the time interval between the first dose and the surgery as well as subsequent therapeutic doses of radioactive iodine 131 (RAI131) in addition to the time interval between each of them.

Collection of data regarding different diagnostic methods used during initial evaluation and regular follow up including; iodine-131 whole body scan, neck ultrasound, diagnostic neck and chest CT and ^{18}F-FDG PET/CT if performed.

The therapeutic doses of RAI131 in our department were given according to the Revised American Thyroid Association Guidelines, 2009 [(4)] which classify the patients into three main categories low, moderate, and high-risk patients are those who fall within the risk categorization.

Empirical ^{131}I dose selection criteria:

For low-risk patients, we aimed to propose an activity between 30 and 100 mCi; however, larger activities (between 100 and 200 mCi) may be required if residual microscopic disease has been suspected or proven, or if there is a more severe tumor histology (such as tall cell, insular, or columnar cell carcinoma). Patients who had evidence of microscopic invasion or cervical lymph node metastases received 125 mCi. If suspicious lymph nodes were detected and proved by histopathology, patient received 125-150 mCi. In case of high-risk patients proven to have lung metastases received 150 mCi if micro metastasis or 175 mCi macro metastases, differentiated by high resolution CT (HRCT).

Patients with bone metastasis received 200 mCi. Empirically administered doses of 131I more than 200 mCi, which frequently have the potential to surpass the maximum acceptable tissue dosage, were avoided in the treatment of patients with loco-regional or metastatic illness above the age of 70.

Patients with elevated (TG levels after T4 withdrawal of 10 ng/ml or higher) or rising serum TG levels were considered for RAI131 therapy (100-200 mCi) on an empirical basis if imaging failed to reveal a potential tumor source. If the post-therapy scan was negative, however, no additional RAI131 therapy was administered.

Before receiving their first dose of RAI131 treatment, all patients were required to stop taking their replacement L-thyroxine (T4) for 3 to 4 weeks and follow a low-iodine diet for at least 2 weeks. Serum thyroid stimulating hormone (TSH) levels were assessed to be greater than 30 IU/ml in all patients just before the 131I therapy. All patients had adequate CBC and renal function tests. Females in child-bearing periods or potentially reproductive were subjected to beta HCG test and must be negative just prior to ^{131}I therapy. All patients had nothing per oral (NPO) for 4-6 hours prior to ^{131}I therapy to ensure proper dose absorption from GIT.

^{131}I whole-body scan were obtained (between the fifth to seventh day post-therapy or second to third day for diagnostic imaging). Data acquisition was carried out by nuclear medicine team of physicists and technologists using a dual head SPECT-CT Gamma Camera.

Imaging protocol:

Planar imaging procedure; a large field-of-view dual-head gamma camera outfitted with a high energy general purpose parallel hole collimator was used to acquire a planar 131I whole boy scan. A scanning speed of 12 cm/s was employed in the continuous acquisition mode. The center of a 20% symmetric window was 364 Kev. Regional (spot) pictures were taken from the anterior neck region and the areas where the aberrant 131I uptake was visible on the whole-body images after the whole-body image was collected. The same technique was used for diagnostic and post-therapy imaging.

SPECT/CT imaging protocol: To provide better anatomic mapping and attenuation correction, SPECT/CT was performed by a hybrid system with an integrated X-ray transmission device and low dose CT at the same session when necessary on suspected areas of enhanced uptake seen in the planar whole-body scan.

SPECT images were obtained over 360 degree (180 degree per head) at 364 KeV photo-peak and ±10 % energy window with patient supine. Body contouring system was used with an acquisition time of 30 sec per frame and with a 3 degree angular step then CT images were acquired within 4-5 min, multiple CT slices were obtained, 5 mm thick slice at 512x512 image matrix for 16 sec per slice and 10 min for total study duration.

Statistical Methods The information was entered and coded using SPSS version 26; this is statistical software designed specifically for the social sciences (IBM Corp., Armonk, NY, USA). Mean, standard deviation, median, minimum, and maximum were used for quantitative data, while frequency (count) and relative frequency (percent) were used for categorical data. Quantitative variables were compared using the non-parametric Kruskal-Wallis and Mann-Whitney tests [(8)]. In order to compare categorical information, the Chi-square (2) test was performed. A precise test was used instead of a statistical one when the expected frequency was less than 5. [(9)]. Logistic regression was used to identify factors that might independently predict a negative outcome [(10)]. P values lower than 0.05 were taken to indicate statistical significance.

RESULTS:

Descriptive and demographic data:

The overall studied population included 223 patients with histopathologically proven differentiated thyroid carcinoma; characteristics of the studied population are listed in ***Table (1)***. Based on our departmental protocol for management and iodine-131 treatment, patients in the study were divided into 3 main groups according to risk stratification; low, intermediate and high-risk groups. (***Table 1)*** also describes the patient's characteristics of the studied population in the 3 groups. Patients with age <45 years contributed for the majority of patients in low and high-risk groups representing 83.3% and 73.9%, respectively with significant difference between the 3 groups (p=0.001). Female patients prevailed in the 3 groups compared with male patients. Papillary type for thyroid carcinoma was predominant in the 3 groups. Most of patients had total thyroidectomy in more than half of patients in each group.

Post-operative, pre-ablative, ultrasonography was performed in almost all patients, there was statistically significant difference between post-operative neck ultrasound results and post-therapy findings (p<0.001), as post-therapy ^{131}I imaging detected thyroid bed residue in all 223 patients (100%) while post-operative neck ultrasound detected thyroid residue in only 94 patients (42.2%). On the other hand, neck ultrasonography showed higher detectability of suspicious cervical lymph nodes in 73 patients compared with 21 patients in post-therapy ^{131}I imaging. Cervical nodal metastases, lung and bone metastases were detected in intermediate and high-risk groups of patients in post-therapy scans, ***(Table 1)***.

In retrospective analysis for the final outcome after successful first iodine dose ablation, 30/42 patients (71.4%) had an excellent response after complete ablation in low risk group compared with 98/158 patients (62%) in intermediate risk group and only 3/23 patients (13%) in high-risk group, ***(Table 2)***.

Table (1): Patients characteristics of 223 patients with cancer thyroid in different risk groups.

(N, %)		All patients (223, 100%)	Low risk (42, 18.8%)	Intermediate risk (158,70.9%)	High risk (23, 10.3%)	p-value
Age (years)	**Less than 45**	138, 61.9	35, 83.3	86, 54.4	17, 73.9	**0.001**
	More than 45	85, 38.1	7, 16.7	72, 45.6	6, 26.1	**0.001**
Gender	**Female**	154, 69.1	39, 92.9	101, 63.9	14, 60.9	**0.001**
	Male	69, 30.9	3, 7.1	57, 36.1	9, 39.1	
Type of Surgery	**Total thyroidectomy**	125, 56.1	24, 57.2	89, 56.3	12, 52.2	**0.900**
	Near total thyroidectomy	41, 18.4	9, 21.4	27, 17.1	5, 21.7	
	Subtotal thyroidectomy	57, 25.6	9, 21.4	42, 26.6	6, 26.1	
Pathology	**Papillary carcinoma**	149, 66.8	35, 83.3	103, 65.3	11, 47.8	**0.006**
	Follicular carcinoma	50, 22.4	2, 4.8	39, 24.7	9, 39.1	
	Follicular Variant of papillary carcinoma	22, 9.9	5, 11.9	14, 8.8	3, 13	
	Hurthle cell carcinoma	2, 0.9	-	2, 1.2	-	
Neck dissection	**No**	122, 54.7	33, 78.6	81, 51.3	8, 34.8	
	Yes	101, 45.3	9, 21.4	77, 48.7	15, 65.2	
Post-operative neck ultrasound	**Free**		21, 50	42, 26.6	9, 39.1	**<0.001**
	Thyroid bed residue		11, 26.2	69, 43.7	14, 60.8	
	Suspicious cervical LNS		10, 23.8	47, 29.7	16, 69.5	
First post-therapy ^{131}I whole body scan	**Thyroid bed residue**		42, 100	158, 100	23, 100	
	Local cervical LNs uptake		-	10, 6.3	11, 47.8	
	Lung metastases avid lesions		-	3, 1.8	10, 43.5	
	Bone metastases avid lesions		-	3, 1.8	9, 39.9	

Table (2): Number of iodine doses required to obtain successful thyroid ablation in different risk groups.

Number of ^{131}I doses	Successful ablation N (%)						Overall successful ablation	
	Low risk (N=42)		Intermediate risk (N=158)		High risk (N=23)			
	No.	%	No.	%	No.	%	No.	%
1	30	71.4%	98	62.0%	3	13.0%	131	58.7%
2	11	26.1%	45	28.4%	7	30.4%	63	28.2%
3	-	-	4	2.5%	7	30.4%	11	4.9%
Total No	41		147		17		205	

Additionally, there was statistically significant difference between mean value of serial serum thyroglobulin measurements among the three groups (p<0.001), **(Table 3)**.

Table (3): Serial serum thyroglobulin measurements over regular follow up in the studied in different risk groups.

		Low risk	Intermediate risk	High risk	p-value
Serial follow-up of serum thyroglobulin level (ng/dl)	TG0	27.9	51.7	142.1	<0.001
	TG1	14.7	37.3	106.3	
	TG2	6.5	26.4	113.3	
	TG3	3.2	17.5	83.0	
	TG4	1.4	16.5	60.8	
	TG5	0.6	9.2	37.7	

Impact of the risk factors with the final outcome in the studied groups

A univariate analysis was used to study the impact of different risk factors on complete overall response including age, gender, pathology, type of surgery, risk stratification and initial thyroglobulin level. Incomplete response was higher among patients with high risk stratification (p<0.001) and among male gender (p=0.01), ***(Table 4)***.

Table (4): The final outcome of 223 patients with cancer thyroid in correlation with different risk groups.

		Excellent response		Incomplete response		p-value
		No	%	No	%	
Age	<45	85	61.5	53	38.5	0.621
	>45	46	54.1	39	45.9	
Gender	Female	100	65.0	54	35.0	**0.01**
	Male	31	45.0	38	55.0	
Pathology	Papillary carcinoma	90	60.5	59	39.5	0.381
	Follicular	26	52.0	24	48.0	
	Follicular variant of papillary	13	59.0	8	41.0	
	Hurthle cell carcinoma	2	100	-	-	
Surgery	Total thyroidectomy	68	54.5	57	45.5	0.381
	Subtotal thyroidectomy	34	59.5	23	40.5	
	Near total thyroidectomy	29	70.7	12	29.3	
Risk stratification	Low risk	36	85.7	6	14.3	**<0.001**
	Intermediate	88	55.6	70	44.4	
	High risk	7	30.5	16	69.5	
Initial Thyroglobulin	Mean (ng/dl)	41.33		62.5		0.135

Multivariate analysis showed that risk stratification was the most significant factor that influenced the outcome. However, the higher mean value of first ablative iodine-131 dose was seen in patients with incomplete response as most of these patients were in the intermediate and high-risk groups with higher mean first dose value (p=0.002), ***(Table 5)***.

Table (5): Multivariate analysis of the different risk factors of 223 patients with cancer thyroid in correlation with different risk groups.

		p-value	OR	95% C.I.	
				Lower	Upper
Incomplete response	Dose one in mCi	**0.002**	1.007	0.998	1.017
	Gender	**0.010**	1.736	0.917	3.289
	Risk stratification	**0.001**	2.879	1.056	7.850

DISCUSSION:

Thyroid carcinoma is the most frequent endocrine malignancy, accounting for 1% of all malignant illnesses [11]. However, the prognosis for malignant thyroid tumors is often favorable. Despite this, some patients experience chronic, metastatic, and/or recurring illness, necessitating a thorough diagnostic assessment to identify additional therapeutic choices that ultimately enhance outcomes and survival [12,13].

Most of the results in cancer thyroid are actually based on large number of retrospective studies with multivariate analysis to detect risk factors. It is noted as well that the available studies are affected by selection of patients, staging systems in addition to the different management strategies of cancer thyroid patients [12,14].

An astonishing shift in the clinical strategy has been observed with the ongoing review of diagnostic modalities, along with a dramatic alteration in the disease's natural history due to the globally growing frequency of thyroid cancer [15,16]. Meanwhile, the standard of care for differentiated thyroid cancer follow-up has gradually modified to strike a balance between curing patients and avoiding overtreatment [12,17].

In the present study, data from 223 patients with differentiated thyroid carcinoma, which were treated and managed at our institution in the last three years. They were classified into three groups according to risk stratification; low, intermediate and high-risk groups; were retrospectively analyzed.

To investigate the clinical efficacy of thyroidectomy followed by radioactive iodine treatment in patients with thyroid cancer, as well as serial follow-up to find the final response and the prognostic role of examined variables in relation to the outcome, the study's end points focused on the pattern of DTC referred to our department in the previous three years.

The relative distribution of papillary and follicular cancer in the current research was markedly skewed in favour of the former (169 patients; 76.4%) over the latter (52 patients; 23.6%). According to a comparable finding made in the United States in the same years, this result most likely indicates a growing peak of papillary carcinoma in the most recent time in Europe [12,18-20].

The management of these patients have been advocated on risk stratification. This approach was implemented with the initial cohort and has served as the basis for our care standard ever since, albeit with some adjustments over the years." total or near total thyroidectomy was the traditional trend in management of well differentiated thyroid carcinoma that was encountered in all patients [21].

Pre-operative neck ultrasonography, as recently performed or intra-operative evaluation can also be used to evaluate the contralateral lobe. Groups at high risk should undergo a whole thyroidectomy or a more thorough resection, followed by radioactive iodine therapy. Surgical excision of all clinically apparent illness is the most vital aspect of therapy. To prevent extracapsular invasion, a complete thyroidectomy is performed in conjunction with excision of strap muscles, laryngo-tracheal and even recurrent nerve or esophageal structures, if necessary, to guarantee macroscopic surgical clearance. An individual treatment decision is made for cases with intermediate risk based on the advice of the multidisciplinary team (MDT), which is mostly based on tumor characteristics [21]. However, they noted in their final report that "trends in therapy demonstrated that patients were less likely to receive thyroid lobectomy with a commensurate rise in rates of complete thyroidectomy with its influence on the 10-year survival being about 96%."

However, in the current retrospective research, the absence of operative information for patients was a significant obstacle to correct assessment of the impact of surgical extent on the cohort's final result.

Certain observations are considered regarding lymph nodes dissection as non-uniform methodology was used regarding node dissection decision by different surgeons. Complementary neck ultrasound examination may be used prior to radioactive iodine therapy ablation to assess node status. Recently, required for papillary thyroid cancer central lymph node dissection ± lateral compartmental dissection and the latter is usually carried out as a routine procedure in follicular carcinoma in some reported series [20,22].

Regarding age and gender distribution, the majority of our patients with DTC were less than 45 years representing 61.9% with predominance of females with a female to male ratio of 2.23:1, this coincides with other studies in the literature [21,23], Predominance of intermediate risk group in 158 patients (70.9%) postulating that with the rising age of patients there is an increasing percentage of intermediate risk cases as stated in **Nixon et al**. study [21].

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Concerning the effectiveness of RAI-131 therapy, it is well-known that successful RAI-131 thyroid remnant ablation is associated with an enhanced prognosis in terms of recurrence-free survival and overall survival, decreased rates of distant metastases, and decreased cancer mortality rates, compared to surgery with combined L-thyroxin therapy alone [24]. Additionally, it allows the long-term monitoring of patients with differentiated thyroid cancer. Verburg et al. [25] revealed that a successful ablation appears to be an important indicator of a patient's prognosis in the long run. After 10 years, 87% of those who had a successful ablation were still disease-free, but only 50% of those who had a failed ablation remained disease-free. The survival rate for thyroid cancer was 93% versus 78% (p less than 0.001). Similarly in the current retrospective analysis for the final outcome after successful first iodine dose ablation.

We noticed that 30/42 patients (71.4%) had an excellent response after complete ablation in low risk group compared with 98/185 patients (62%) in intermediate risk group and only 3 patients (13%) in high-risk group. Successful ablation was achieved in higher percentages of patients after second RAI131 dose in low risk group being 11/12 patients (91%) of the remaining patients after first successful ablation compared with 45/60 patients (75%) in intermediate risk group and 7/20 patients (35%) in high-risk group.

There was statistically insignificant difference in the outcomes for low-risk and intermediate-risk patients who received low or high dosages of iodine, with p values of 0.374 and 0.485, respectively.

Multiple multicenter studies [24,26–29] compared the effectiveness of RAI131 ablation with low or high RAI131 activities (greater than 100 mCi) and found that lower RAI131 activities are equally efficient as high RAI131 activities. According to ATA and ETA standards [4,17], high RAI131 activities should be administered to high-risk patients. There is still much dispute over the activities that should be performed with intermediate-risk individuals. At the same time, no data is provided on how much RAI-131 should be administered, and the present guidelines, which favour administering high doses of RAI-131, are mostly based on expert opinion as opposed to clinical evidence [4,17].Not all research demonstrate that low and high RAI-131 dosages are equally beneficial. ***Prpic et al***. conducted a trial on 259 individuals with histopathologically confirmed differentiated thyroid cancer restricted to the thyroid and found that 100 mCi of RAI131 was significantly more successful at killing the thyroid than 30–50 mCi and also superior to 75 mCi. But after a second dose of RAI131, the ablation rates were almost the same. This second dose was somewhere between 30 and 100 mCi. Unfortunately, the authors didn't explain why they chose the second dose of ablation, and the results of the first dose were different from those of the second dose [30]. In the current study, higher percentages of patients in the low-risk group had successful ablation after the second RAI-131 dose, with 11 of 12 patients (91%) of the remaining patients after the first successful ablation, compared to 45 of 60 patients (75%) in the intermediate-risk group and seven of twenty patients (35 percent) in the high-risk group.

Another retrospective study in our institution concluded data of 390 patients with histopathologically proven differentiated thyroid carcinoma who were managed and treated during the period from 2006 till 2013, our results concur with it in the age spectrum of the patient with majority of patients belonging to age group less than 45 years, additionally female predominance in both studies could be noted with female to male ratio 2.9:1 versus 2.23:1 in our study. Papillary thyroid carcinoma was the most common pathology in both studied 86.1% versus 67.4% in our study [31]. Serum thyroglobulin level was an important landmark in the current study to follow the final response of patients treated with RAI-131. We considered final excellent response when there was no clinical, biochemical or structural evidence of disease. Serum TG levels below one ng/dl was considered biochemical free of disease. Serial TG measurements are an important indicator for monitoring response with significant lower values among patients in lower risk group.

CONCLUSIONS:

Our data suggest that proper ablative dose, absence of remote metastasis gender, serial serum thyroglobulin measurement, risk stratification were the powerful predictors for excellent outcome in DTC patients. Proper radioactive iodine ablation is a highly significant prognostic factor. Regular and continuous follow up of patients specifically with serum thyroglobulin level is highly recommended for proper management and to detect early recurrence or metastatic disease. The need of multidisciplinary team is highly appreciated for earlier and proper management of patients with differentiated thyroid carcinoma aiming at achieving excellent response in higher percentage of patient with better long-term outcome.

Declaration of competing interest: Authors declares that there is no conflict of Interest.

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