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I-131 Avid Versus FDG avid Loco-Regional Recurrent Differentiated Thyroid Carcinoma; Clinic-Pathological, Diagnostic & Therapy Outcome DifferencesTalaat, O¹. Fathy H¹. Hussein M². Bahaa S³.

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ABSTRACT:

Purpose: To assess the clinic-pathological, diagnostic & therapy outcome differences between I-131 avid and FDG avid loco-regional recurrence in differentiated thyroid carcinoma (DTC) patients. **Materials and methods:** 125 patients with pathologically proved loco-regional recurrent DTC after initial remission with complete radio-surgical thyroid ablation were included. Clinico-pathological data, serum thyroglobulin levels, diagnostic radiology, I-131 & FDG PET/CT scanning, therapeutic approaches and follow up data were collected. **Results:** 125 patients with loco-regional recurrence were divided into: **(I) I-131 avid group:** 60 patients with 112 confirmed recurrent malignant lesions (8 thyroid bed, 104 nodal). **(II) FDG avid group:** 65 patients with 206 confirmed recurrent malignant lesions (14 thyroid bed, 192 nodal). Out of clinic-pathological data, significantly higher pathological grading was demonstrated in FDG

avid group (49 patients) compared to I-131 avid group (18 patients) $P < 0.05$. In I-131 avid group. The sensitivity, specificity and accuracy for loco-regional recurrence using I-131 WBS were 77%, 100% & 81% and 87.5%, 30% and 77% using ultrasound (US) respectively. In FDG avid group the sensitivity, specificity and accuracy for FDG PET/CT were 95.1%, 76.1% and 91.5%, for neck US were 78%, 37.5% and 72.2% and for CT were 83%, 47% and 79% respectively. The added value of post-operative RAI-131 therapy results in better outcome in I-131 avid group. **Conclusions:** FDG avid loco-regional recurrence seemed to be linked to higher pathological grading with less favorable prognosis compared to I-131 avid loco-regional recurrence. Specificity rather than sensitivity indices tend to be significantly higher with functional compared to anatomical based techniques in both groups.

Key words: Thyroid carcinoma FDG PET/CT versus I131**Corresponding Author:** Talaat ,O.**Email:** monytalaat@yahoo.com

INTRODUCTION:

Thyroid carcinoma is the most prevalent endocrine malignancy and accounts for 1% of all human cancers (1). Approximately 90% of thyroid malignancy is well differentiated thyroid carcinoma (DTC) which is classified as papillary or follicular based on histo-pathological criteria. DTC are usually curable or controllable disease by combination of surgery, radio-iodine and TSH suppression therapy. However, approximately 30% of patients may develop loco-regional recurrence after total thyroidectomy (2). These loco-regional DTC recurrences compromise a wide spectrum of behaviors, presentation and prognosis which reflected on selection of diagnostic imaging and therapy. The degree of similarity of the recurrent tumoral cell to the characteristics of the original thyroid cell is a major determinant for such broad behavioral variations. The most common is the well differentiated recurrent that retains with a variable degree the criteria of original thyroid cell located at one end of the spectrum. These recurrent DTC lesions are slowly growing and may still have the ability of RA I-131 handling via preservation of Na-Iodide Symporters. The less frequent de-differentiated and poorly differentiated ones located at the other end of the spectrum with aggressive behavior and may have criteria dissimilar to the original thyroid cells. These include more aggressive growth, enhanced invasive activity & angiogenesis, increased metastatic spread and

inability to concentrate radio-iodine. The clinical course therefore may diverse and well reflected on the diagnostic imaging work up particularly if surgery was purposed for a curative intent (3). RA I-131 may play important role in diagnosis and therapy of well differentiated recurrent thyroid carcinoma. Whereas in de-differentiated or poorly differentiated recurrent thyroid carcinoma, due to loss of power for I-131 concentration and increase glucose utilization, FDG may replace RA I-131 in diagnosis of such sub-type of recurrence (4).

The fore mentioned considerations, encouraged us to perform the current retrospective study to assess the potential difference between I-131 avid and FDG avid loco-regional recurrence in DTC patients in respect to clinico-pathological prognostic indicators, disease extent, diagnostic imaging results, serum thyroglobulin levels & therapy outcome.

MATERIAL & METHODS:

This study was approved by the ethics committee of the board of nuclear medicine & radiology at the National cancer Institute, Cairo University. Informed consent was obtained from all patients or their relatives with a full description of the procedures. This work included 125 patients under follow up at the National Cancer Institute, Cairo University, between January 2004 & Feb 2015 (11 years and 2 months).

Inclusion criteria: Age above 18 year, documented histopathology of DTC, complete radio-surgical thyroid ablation, suspected loco-regional recurrence either clinically or by elevated thyroglobulin level > 10 ng/ml in hypothyroid state.

Exclusion criteria: Thyroid carcinoma other than DTC, elevated ant thyroglobulin Abs, pregnancy, presence of distant metastases. All patients were subjected to clinical assessment, neck U/S, 131I whole-body scan 4 weeks after eltroxin withdrawal with TSH level >30mU/L in the hypothyroid state. PET/CT was performed for 65 patients who had a negative I131 scan despite elevated thyroglobulin. The PET- CT result was compared with histopathology or clinical follow-up results.

Procedures: Thyroglobulin measurement:

Blood samples for measuring serum thyroglobulin levels were obtained from all patients in hypothyroid state (under high TSH stimulation). Serum TG levels were considered abnormal when their values were higher than 10ng/mL in the hypothyroid state.

Neck U/S and FNAC: Neck U/S was performed to all 125 patients to evaluate the thyroid bed as well as central and lateral cervical nodal compartments. Some of the sonographically suspicious lymph nodes were biopsied for cytology. Sonographic criteria to diagnose nodal metastases included size, configuration, hypo-echoic, calcification, hypervascularity and loss of

hilar architecture. Confirmation of malignancy of some suspicious LN was done by U/S guided FNAC.

CT was done for 65 patients only. CT criteria to diagnose nodal metastases include: Minimal axial diameter greater than 10 mm, longitudinal length/trans-axial width ratio < 2 (rounded shape vs. lima bean shape). Whereas areas of heterogeneous enhancement and central areas of low attenuation within a neck node are reliable signs of metastases.

Iodine -131 whole body scanning: Hormonal withdrawal [4 weeks] was instructed to all patients to elevate TSH Serum level >30mU/L at time of I-131 administration. Patients were also instructed to follow a low iodine diet 2 weeks prior to iodine intake. RAI-131 whole body scan was performed either 5 mCi [diagnostic scan] or empiric iodine therapy [Post-therapy scan]. Imaging was done with a dual-head gamma camera using high-energy collimators. The images were evaluated for iodine avid loco-regional recurrence. Images were interpreted accomplished by 2 experienced nuclear medicine physicians as any abnormal focal iodine activity in bed of thyroid gland or in anatomical sites of local lymph nodes. Accordingly, the patients were divided into two groups, iodine avid group (60 patients) and non-iodine avid group (65 patients).

FDG PET-CT: FDG PET –CT was done for the 65 non -iodine avid patients, using a dedicated PET-CT scanner .This camera allows the

acquisition of co-registered CT and PET images in one session. All patients fasted for 4 - 6 hours before the injection of 370-555 MBq 18 F-FDG. Scanning started 60-90min after tracer injection (5-7 bed positions; acquisition time, 2-3 min/bed position). Blood glucose levels did not exceed 150mg/dL. Intravenous contrast agent was administered in most patients. Initially, patients were examined in the supine position with arms elevated, and CT scanning was started at the level of skull base with the following parameters: 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5. The CT scans were acquired during breath holding within the normal expiration position and reached caudally to the mid thighs. PET over the same region was performed immediately after acquisition of the CT images (2-3 min/bed position). The CT-data were used for attenuation correction, and images were reconstructed as 3-mm slices applying a standard iterative algorithm (ordered-subset expectation maximization). Images were interpreted at a workstation equipped with fusion software that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images in any percentage relation. Image interpretation was accomplished by 2 experienced nuclear medicine physicians. The analysis was conducted on per patient basis and per lesion basis. Abnormal FDG uptake was defined as a focal increased uptake higher than that of surrounding tissue at certain anatomic localization with $SUV_{max} \geq 2$ or

more for nodal lesions. All recurrent lesions were documented by pathology, cytology or long term follow-up ranging 12 – 16 Months.

Evaluation of therapeutic efficacy: Serum thyroglobulin level, clinico-radiological, nuclear imaging, FU and/or histopathology were used to assess therapy outcome in I-131 avid and FDG avid loco-regional recurrent DTC patients. Patients were divided into:

Group (1) (complete response): Patients with negative imaging studies who had no abnormalities in US or no persistent uptake either in 131-I WBS (in iodine avid patients) and markedly reduced thyroglobulin level less than 2ng/ml.

Group (2) (partial response): Patients who had only mild improvement of the recurrence in neck US with mild decrease in TG level from (15%-25%) or remaining uptake either in 131I WBS (in iodine avid patients).

Group (3) (stationary Disease): Patients who show almost stationary state of recurrence on neck US or either in 131I WBS (in iodine avid patients) with no change or change less than 15% in TG level.

Group (4) (progression): Patients who had progressive state on Neck US or either in 131I WBS in iodine avid patients with increasing thyroglobulin level more than 25% (5).

Statistical Analysis: Data was analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). Numerical data were

expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For not normally distributed quantitative data, comparison between two groups was done using Mann-Whitney test (non-parametric t-test). The sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of iodine ,neck US , CT alone and PET/CT were calculated on the basis of the true-positive and true-negative findings as described in the same anatomic region with a lesion-based and a patient-based analysis. Spearman's rho test was also used hoping to analyze the correlation between TG level & maximum SUV.

RESULTS:

Based on the preferential avidity of loco-regional recurrence to I-131, the patients were divided into two main groups:

RAI-131 avid group (60 patients): - Diagnostic or post therapy I-131 WBS to detect one or more of the locally recurrent DTC lesions.

FDG avid (Non I-131 avid) group(65 patients): -Locally recurrent DTC lesion(s) were negative for I-131 in diagnostic or post therapy scans & positive for FDG in F-18 FDG PET/CT scans. The main clinico-pathological characteristics are compared between both groups in **Table1:** there is significantly high frequency of papillary thyroid carcinoma in both groups as well as significantly higher frequency of moderate and high grade were noticed in FDG avid group compared to I-131 avid group.

Table (1): Clinical-pathological characteristics of I-131 avid and FDG avid groups (n= 125).

		<i>RAI-131 avid</i>		<i>FDG avid</i>		<i>P-value</i>
		<i>No</i>	<i>%</i>	<i>No</i>	<i>%</i>	
Number (%)		60	48%	65	52%	
MedianAge:		39		43		0.148
Sex:	Female(n=66)	26	43%	33	50.8%	0.181
	Male (n=59)	34	57%	32	49.2%	
<u>Histopathology:</u>						
Papillary (n=101)		52	86.7%	49	75.4%	0.781
Follicular (n=24)		8	13.3 %	16	24.6%	
<u>Path- Grading :</u>						
Low grade		42		16		0.023
Moderate		18		26		0.034
High grade		0		23		0.001

Table (2): Thyroglobulin levels in I-131 avid & FDG avid groups (n=125).

	Iodine avid group	FDG avid Group	P-value
<u>Thyroglobulin level</u>			
-Range (ng/L)	10.3-112	12 -148	0.034
-Median (ng/L)	55.2	82.1	

Receiver operating characteristic (ROC) curve analysis was used to determine the difference in the values of cut off point for serum thyroglobulin levels between I-131 and FDG that result in the best cost effective yield in term of accuracy in both groups. A significantly higher serum thyroglobulin Cut off value was marked for I-131 (36.8 ng/ ml) compared to FDG (14.1ng/ml). P value (less than 0.05) **Figure 1, Figure.**

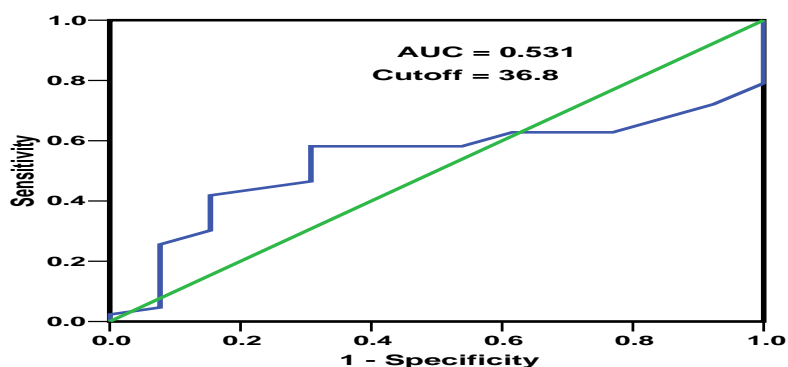


Fig. 1: ROC curve for thyroglobulin cut-off value between false negative and true positive lesions in iodine avid patients.

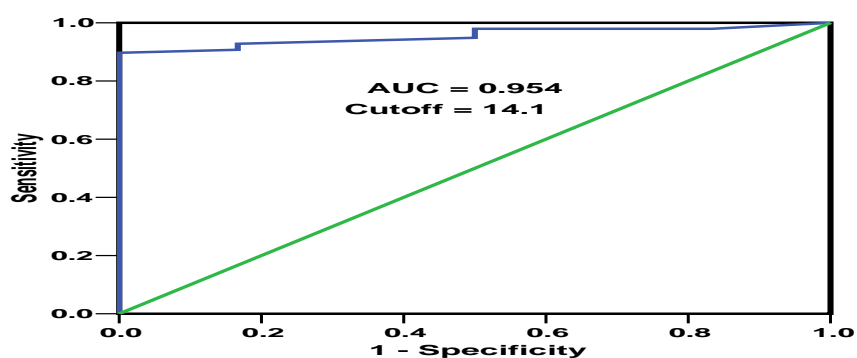


Fig. 2: ROC curve for thyroglobulin cut-off value between false negative and true positive lesions in FDG avid patients.

The histo-pathological data and follow up data of a 318 loco-regional recurrent lesions were documented in both groups: 112 in I-131 Avid group and 206 in FDG avid group. 222 lesions were confirmed pathologically of which 127 via post-operative histopathology while 95 lesions were confirmed by FNAC. The remaining 96 lesions were confirmed by monitoring their progressive course during follow up period for at least 12 – 18 months. **Iodine avid group: Table**

3 showed a trend of relatively better sensitivity for ultrasound compared to I-131;. Regarding accuracy, comparable results for I-131 (81%) and neck ultrasound (77%) were detected with no statistically significant difference ($P > 0.05$). The absence of false positive results for I-131 and the relatively high false positive results for ultrasound resulted in higher specificity & PPV for I-131 (100% for both) compared to 30% & 84% for ultrasound respectively.

Table 3: Neck ultrasound per site in I-131 avid group in comparison to clinic-pathological and FU data in 60 recurrent DTC Patients.

<i>Loco-regional Site</i>	<i>RA I-131</i>		<i>Neck Ultrasound</i>	
		<i>No %</i>		<i>No %</i>
Thyroid bed (n= 8)	8/ 8	100 %	8/8	100%
Nodes (n=104)	78/104	75 %	90/104	86.5%
Sensitively	86/112	77%	98/112	87.5%
specificity		100%		30 %
accuracy		81%		77%
NPV		50%		36.3%
PPV		100%		84%

FDG avid (Non I-131 avid) group: The overall results showed higher sensitivity for FDG PET/CT compared to Neck Ultrasound; FDG PET/CT showed higher accuracy (91%), with comparable results for neck Ultrasound (72.2%) & no statistically significant difference was found ($P>0.05$). On the other hand, the relatively low false positive results for FDG PET/CT and the relatively high false positive results for ultrasound, higher specificity & PPV (76.1% and 95%) respectively were achieved for FDG PET/CT compared to (37.5% & 80%) for ultrasound as **Table 4**.

Response to therapy: In both I-131 avid and FDG groups, only 83 patients were evaluated by TG, neck U-S and 131-I WBS

after treatment; five groups of patients were identified: complete response, partial response, stationary disease, disease progression & relapse. Treatment response of the remaining 16 patients who were admitted during 2012 could not be assessed. The overall response rate shows significantly higher frequency of complete remission in I-131 avid group (66.6%) compared to FDG avid group (43.7%) respectively. Moreover both disease progression and/or re-recurrence were not seen in I-131 avid group. On the other hand disease progression and second recurrence (relapse) were presented in FDG avid group in 15.6% and 9.3% respectively. Finally comparable frequencies of partial remission were obtained among both groups as seen in **Table 5**.

Table 4: Neck Ultrasound in FDG avid group in comparison to Clinico-pathological and FU data in recurrent DTC Patients.

<i>Loco-regional Site</i>	<i>FDG PET/CT</i>		<i>Neck Ultrasound</i>	
	<i>No</i>	<i>%</i>	<i>No</i>	<i>%</i>
Thyroid bed (n= 14)	14/14	100 %	14/14	100%
Nodes (n=192)	180/192	94 %	146/192	76%
Sensitivity		94.1%		78%
specificity		76.1%		37.5 %
accuracy		91%		72.2%
NPV		94.1%		21%
PPV		95%		80%

Table (5): Therapy response in I-131 Avid & FDG avid groups in loco-regional recurrent 83 DTC patients.

	I-131 Avid Group		FDG Avid Group	
	(N=30)	No %	(N=53)	No %
Complete remission	20	66.6 %	23	43.7 %
Partial remission	6	20 %	12	21.8 %
Stationary disease	4	13.3 %	5	9.3 %
Progression disease	0	-----	8	15.6%
Second recurrence	0	-----	5	9.3 %

DISCUSSION:

Cancer thyroid represents the most common malignancies of endocrine system (1,6). After initial treatment of DTC, loco regional recurrence may occur in 30-40% of patients, (local thyroid recurrence or most commonly involves lymph nodes in neck(2,7). Follow up for detection of recurrence usually done by measurement of serum thyroglobulin concentrations, combined with physical examination, ultrasonography, or other imaging strategies (6). Based on the preferential avidity of loco-regional recurrence to I-131, it was possible in this study to assess the difference between iodine avid and non I-131 avid (FDG avid) recurrence. Out of clinic-pathological prognostic variables grading was the main predictor for preferential avidity of recurrent DTC to either I-131 or FDG. This finding points to the importance of pathological grading in rolling future tumour behaviour via modification of the biological and functional criteria of the recurrent tumoral cells in DTC. The low grade recurrent DTC lesion reflects to a variable degree the biological and functional status of the original thyroid cells. Measurement of serum thyroglobulin, which is produced exclusively by thyroid follicular cells, is a very sensitive and specific marker for persistent or recurrent disease in the absence of anti-thyroglobulin antibodies (9,10).

In the current study serum thyroglobulin level was estimated as indicator for disease recurrence

during off thyroxin therapy in both I-131 avid and FDG avid group. A statistically significant difference was demonstrated between the median value of serum thyroglobulin among I-131 avid (55.2 IU/L) and FDG avid (82 IU/L) group ($P < 0.05$). This significant higher thyroglobulin level in FDG group can be postulated to de-differentiated nature of such type of recurrence that had more aggressive characteristics compared to the well differentiated I-131 avid group (11,12). To reach a complete consensus to define the optimal diagnostic utility of both I-131 and F-18-FDG PET/CT in differentiated thyroid cancer the level of serum TG cut off point that provides the utmost sensitivity & specificity for its use is clinically desired. Receiver operating characteristic curve was used to mark a TG cut off value that point to the best yield in term of accuracy for both I-131 and FDG in diagnosis of recurrent DTC. A lower cut off point for thyroglobulin level was marked for FDG avid group (14.1 ng/ml) compared to iodine avid group (36.8 ng/ml). This relatively lower TG cut-off point that correspond to the higher accuracy of F-18 FDG-PET/CT could be attributed to better physical characteristic of F-18 FDG and higher resolving power of PET/CT system compared to I-131 and conventional gamma camera respectively in term of lesion detection. In the current study, comparison has been made between different imaging tools in

diagnoses of loco-regional recurrence in DTC according to their use in the study protocols using histo-pathological and follow up data as a reference.

I-131 Avid groups (I-131 WBS vs. Neck US) A notable difference was demonstrated in the overall and regional results of neck ultrasound when compared to iodine 131 in iodine avid group. In agreement with (13) they reported that neck US was more sensitive than I-131 WBS in the detection of DTC neck recurrence with sensitivity ranging from 70 to 100%. Similarly (14) and (15) reported that iodine WBS confirmed to be a low sensitivity tool in detecting loco-regional recurrences with sensitivity ranging from 43% to 55%. Also, in this study relatively better sensitivity for ultrasound compared to I-131; (87.5% vs. 77%) respectively. Moreover, in respect to accuracy comparable results for I-131 (81%) and neck ultrasound (77%) were noticed with no statistically significant difference ($P > 0.05$). There is higher specificity and PPV (100%) for I-131 compared to 30% and 84% for US respectively. In respect to neck US, it is still the main method of routine follow up of DTC patients, the main reasons for false results in U/S, are lateral inflammatory nodes, posterior structural & superior mediastinal nodal lesions as well as post therapy granulation or fibrotic tissue at thyroid bed (16).

FDG (non I-131) avid patients (PET/CT vs. Neck U/S) Significantly higher sensitivity and accuracy for

FDG PET/CT (94%, 91%) compared to neck ultrasound (78%, 72.2%) respectively ($P < 0.05$) is noted. Moreover, the significantly better specificity for F-18 FDG PET/CT (76.1%) compared to US (37.5%) respectively that was attributed to higher capability of F-18 FDG in exclusion of false positive lesions (17) or those small nodal lesions that are similar in density and adherent to neck muscle (18). Similarly to estimate the diagnostic accuracy of 18F-FDG PET, *Cabrera Martin* et al (19) studied 58 patients were suspected to have neck recurrence of DTC with high thyroglobulin levels and negative 131I whole-body scan. Sensitivity, specificity, diagnostic accuracy, positive and negative predictive values were calculated for all patients. Sensitivity was 71%, Specificity 96%, PPV 96.4%, NPV 69.4%.

I-131 avid loco-regional DTC recurrence group usually have a better response to therapy compared to FDG avid group. Biological behaviour, tumour load as well as the added value of I-131 therapy are contributing. (20). **Maxonet al** reported that surgery followed by 131I treatment of regional nodal metastases yielded a complete response in 80% of patients if at least 8000 to 10000 cGy were given. Patients with iodine-negative tumor tissue had a less favorable prognosis. These tumors cannot be detected or treated with radio-iodine. Consequently, tumor cells will continue to grow undetected and the chance of cure decreases significantly (20).

The limitations of this retrospective study may include inability to correlate our results with a relative specific molecular & immune-histochemical markers that determine either the predisposing gene mutation e.g. BRAF-V600E &/or sub-cellular molecular changes related to differentiation which

are not done routinely in our institute . Also, The accuracy of this diagnostic imaging was partial as FDG imaging was not done in both groups ,absence of final histo-pathological examination for all patients with relatively short-term follow up assessment.

CONCLUSION:

Grading seems to be the main predictor for preferential tracer avidity of recurrent DTC. I-

131 remain a corner stone in management of iodophylic avid recurrence due to its utmost specificity.FDG PET/CT is the most effective imaging tool in assessment of Non-I-131 avid recurrent De-DTC. Surgery is additional valuable tool in both I-131 avid and FDG avid recurrencesDTC especially in regional cervical lymph nodes.

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