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Original Research Article

PROSPECTIVE PILOT ASSESSMENT OF COMPARATIVE AGREEMENT OF WHOLE BODY RADIO-IODINE (I-131), 2-(FLUORINE-18) FLUORO-2-DEOXY-D-GLUCOSE (FDG) POSITRON EMISSION TOMOGRAPHY (PET), AND SOMATOSTATIN RECEPTOR IMAGING USING Ga-68 DOTATATE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY SCANS IN ADVANCED FOLLICULAR CELL-DERIVED DIFFERENTIATED THYROID CANCERS

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ABSTRACT

Background: Somatostatin receptor (SSTR) expression has not been well-studied in non-medullary differentiated thyroid cancers (DTC) in advanced stages. The present study aimed to evaluate SSTR-expression in metastatic DTC and compare I-131, F-18 FDG PET and Ga-68 DOTATATE PET/CT scans in advanced follicular cell-derived DTC.

Materials and Methods: Twelve post-thyroidectomy patients of advanced DTC (age range:44-75years) attending our thyroid out-patient department underwent diagnostic I-131 whole body scan (WBS) and having at least one radio-iodine-avid metastatic lesion were included in this pilot study. All patients underwent FDG PET and Ga-68 DOTATATE PET/CT scans as per institutional protocol within 4 weeks of WBS. The number of lesions seen in all three scans in each patient was tabulated and comparatively analysed.

Results: Out of total 65 lesions analysed, 47(72.3%), 43(66.15%) and 44(67.69%) lesions were seen on I-131, FDG PET and Ga-68 DOTATATE PET/CT imaging respectively. 19/37(51.3%) concordant metastatic bone lesions detected by all three scans, but 4(10.8%) lesions only seen on Ga-68 DOTATATE PET/CT scan. And 27.77% metastatic bone lesions seen on both I-131 and Ga-68 DOTATATE PET/CT scans, were not detected on FDG PET scan. Notably, 12(18.46%) FDG-avid lesions and 11(16.9%) Ga-68 DOTATATE-avid lesions did not show significant radio-iodine uptake when each modalities was individually compared with I-13I imaging. Lin's concordance correlation coefficient (0.597) indicated good concordances between I-131 and Ga-68 DOTATATE PET/CT scans for detecting lesions.

Conclusions: FDG PET and SSTR-targeted imaging should be performed with routine radio-iodine scan in patients with advanced DTC. SSTR-expression in a substantial number of metastatic lesions probably reflects varying tumour biology of metastases and may be amenable to Peptide Receptor Radio-nuclide Therapy (PRRT), thereby providing an alternative therapeutic approach.

Key words: Somatostatin receptor imaging, Ga-68 DOTATATE Positron Emission Tomography/Computed Tomography, advanced follicular cell-derived differentiated thyroid cancers, Peptide Receptor Radio-nuclide Therapy, PRRT.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, and over 95% of the tumors arise from follicular cells.[1] Majority of differentiated thyroid cancers (DTC) comprises papillary thyroid carcinoma (PTC) and follicular thyroid cancers (FTC) and have an indolent course.[2] However, a small fraction of thyroid cancers are biologically aggressive namely Oncocytic (Hürthle cell), Insular, Tall cell and Columnar cell variants etc. There are other poorly-differentiated (1-3%) and anaplastic thyroid malignancies (1-3%) having a high malignant potential. These aggressive variants of thyroid malignancies can metastasize to the lung, bones etc., and are the main cause of thyroid cancer-related deaths. However rare brain, hepatic, renal, colon and adrenal metastases of thyroid cancers are also reported.[3-6]

Four criteria were established to classify advanced thyroid cancer in a recent consensus statement from the International Thyroid Oncology Group and the Endocrine Surgery Section of the American Head and Neck Society.[7] These criteria fall into the structural/surgical category: (a) large, inoperable, or invasive loco-regional disease; (b) recurrence; (c) distant metastases; (d) severe, persistent neck illness that fails to respond to reoperation; (e) rapid progression observed in imaging; (f) the imminent threat posed by the tumor burden. The biochemical category encompasses tumors that are resistant to radio-active iodine (RAI), do not show a response to thyroid stimulating hormone (TSH) suppression, and exhibit rapid doubling rates of serum calcitonin, carcinoembryonic antigen (CEA), or thyroglobulin (Tg) level. Findings include poorly-differentiated or other aggressive histological components, a high Ki67 index, a significant mitotic count, or tumor necrosis, with all types of anaplastic thyroid carcinoma included in the histologic/molecular category. The final decision by the treating physician in determining whether tumors can be categorized as advanced thyroid cancer based on their aggressive characteristics.

DTCs are generally managed in the nuclear medicine department after a patient undergoes total or completion thyroidectomy and have to be planned for radio-active iodine (remnant ablation, adjuvant therapy or therapy with palliative intent). The patient is then followed-up with clinical evaluation, measurement of serum TSH, serum thyroglobulin (Tg) as a tumor marker, anti-thyroglobulin antibody (ATG), neck ultrasound and whole-body radio-iodine scintigraphy (WBS). Advanced DTC demonstrates a reduced ability to retain radio-iodine either at the onset of disease or over some time.

Over the last two decade, Positron Emission Tomography (PET) using 2-(Fluorine-18) Fluoro-2-deoxy-D-glucose (FDG) has been established as an essential radio-nuclide imaging tool in clinical oncology by combining the metabolic activity information from FDG PET scan with the morphologic resolution of Computed Tomography (CT).[8] Conventionally, FDG PET/CT scan used to detect local recurrence or metastases with a high degree of sensitivity in advanced DTC. As per the 2015 American Thyroid Association (ATA) guidelines, F-18 FDG PET/CT is not recommended for the routine preoperative evaluation of thyroid nodules.[9] However, in the follow-up of high risk individual with elevated serum Tg and negative radio-iodine WBS, F-18 FDG PET/CT is strongly recommended.[10]

Further indications for F-18 FDG PET/CT include assessing treatment response, detecting lesions in patients with metastases, and predict outcomes in high-risk patients and FDG PET/CT scan result may change the further management.[11] The uptake and retention of F-18 FDG in metastatic lesions may indicate a poor histological prognosis for the tumor; the level of the FDG uptake shows the degree of dedifferentiation process and gives information about the timing and aggressiveness of therapeutic interventions.[12-13]

Somatostatin (SST) is a small, cyclic neuropeptide present in neurons and endocrine cells.

There are five different subtypes of the seven-subunit trans-membrane G protein-coupled receptors known as SSTRs in humans namely SSTR 1, 2, 3, 4, and 5.[14] A high density of SSTR is found in the brain, peripheral neurons, endocrine pancreas, and gastrointestinal tract. SSTRs are significantly overexpressed, especially in neuroendocrine tumors (NETs), which originate from neuroendocrine cells and/or neural crest cells. Gastroenteropancreatic tumors (both functioning and non-functioning), pheochromocytoma, paraganglioma, neuroblastoma, ganglioneuroma, medullary thyroid carcinoma (MTC), pituitary adenoma, Merkel cell carcinoma, small-cell lung cancer usually show high SSTR expression.[15] Breast cancer, melanoma, lymphomas, prostate cancer, non-small cell lung cancer, sarcomas, renal cell carcinoma, DTC, astrocytoma, and meningioma are showing low-grade SSTR expression.[16-17]

Ga-68–1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA)-peptides are having a very high affinity for Somatostatin receptors (SSTR) and specifically bind to these receptors.[18] The majority of NETs express SSTR, so they can be effectively targeted and visualized with radio-labeled SST analogues in-vivo to localize primary tumors, staging, restaging, recurrence detection and monitoring the response to therapy, to determine SSTR status to select the patients for SSTR-targeted radionuclide therapy.[19]

One of the most important therapeutic approaches for NETs is Peptide Receptor Radionuclide Therapy (PRRT). As a type of targeted treatment, PRRT uses a radio-labelled peptide as a vector to deliver lethal radiation doses to cancer cells that have high levels of receptors for that specific peptide.[20] Based on the data from the NETTER-1 trial, the United States

Food and Drug Administration (FDA) approved Lu-177-DOTATATE in January 2018 for the treatment of SSTR-expressing Gastro-entero-pancreatic NETs (GEP-NETs).[21]

Among the thyroid cancers, SSTR imaging has been primarily used for MTC. SSTR expressing metastatic lesions of MTCs are treated with PRRT mostly in palliative settings. Maghsoomi Z et.al demonstrated efficacy of Lu-177 DOTATATE in SSTR-avid metastatic MTC patients.[22] However, SSTR expression in advanced non-medullary thyroid malignancy has not been well-studied.

Therapeutic alternatives for metastatic advanced thyroid cancers including Oncocytic (Hürthle cell) thyroid cancers (OTC) are limited (chemotherapy is not effective, radiation therapy is of little help and radio-iodine uptake is minimal). Several studies revealed that normal thyroid tissue expresses SSTR 2, 3 & 5 and several metastases of DTCs and the majority of OTC metastases express SSTR expression.[23] Hence, these could be amenable to PRRT in the absence of other definitive therapies. The main objective of the study was to evaluate SSTR expression in advanced follicular cell-derived DTCs and to compare I-131 WBS, F-18 FDG PET and Ga-68 DOTATATE PET/CT scans in those patients.

MATERIALS AND METHODS

Study population: Twelve post-operative subjects of histologically proven advanced well-differentiated follicular cell-derived thyroid tumors referred to our center for evaluation and treatment of metastatic thyroid cancer in 1 year study duration were included after taking informed consent forms.

Inclusion criteria: Subjects with at least one radio-iodine-avid metastatic lesion (uptake in neck or metastatic sites on diagnostic or post-radioactive iodine treatment scan) were included in the study.

Exclusion criteria: Subjects with a negative whole-body radio-iodine scan were excluded. Pregnant and breastfeeding females and individuals unwilling to provide written informed consent were excluded.

Data collection and screening: A patient information sheet was developed to collect data from 12 patients through clinical history including age, sex, time of total thyroidectomy, histopathology of thyroid cancer, clinical examinations, laboratory findings including stimulated serum Thyroglobulin (Tg), anti-thyroglobulin antibody levels, serum TSH and scan findings with number of lesions counts of all 3 scans (I-131 WBS, FDG PET and Ga-68 DOTATATE PET/CT scans) in each patient.

All patients had undergone a whole-body diagnostic scans with I-131 (WBS) after 3-4 weeks withdrawal of Thyroid hormone suppressant therapy (THW) and following iodine restriction as per the institutional protocol. Neck uptake and WBS were done after 48-72 hours of 2-3 mCi radio-iodine administration as per the institute protocol. Serum Tg was estimated by using Immunoradiometric Assay (IRMA) technique.

All 12 patients underwent FDG PET scan within 7 days of radio-iodine scan (range from 2 to 7 days, median 3 days). Seven patients underwent F-18 FDG PET scan 60 minute after intravenous administration of 7-10 mCi FDG on Time of flight PET/CT scanner as per institutional protocol (after a fasting period of 6 hours and blood glucose levels less than 150 mg/dL as measured just before FDG injection). All 12 patients underwent a Ga-68 DOTATATE PET/CT scan after intravenous administration of 2-3 mCi of radio-tracer Ga-68 DOTATATE within 3 weeks (range from 3 to 21 days, median 11 days) of the FDG PET scan.

Statistical Analysis

All the collected data were entered and analyzed in MS Excel version 10 using Excel commands. Continuous variables were presented as Mean + SD, and categorical variables were presented as proportions. The positive lesions were measured as numerical data (count), hence, Lin's concordance correlation coefficient was determined. The Bland-Altman diagram was plotted for the difference between the number of lesions against the mean value of the number of lesions by the two tests. The results and pertinent illustrations (figures and tables) were tabulated.

RESULTS

Twelve consecutive patients (age group: 44–75 years; median age: 57 years) including 4 males and 8 females harbouring 65 lesions of advanced DTC were included in the study. Six (50%) out of 12 cases were metastatic PTC whereas the remaining 6 (50%) cases were metastatic FTC. Out of six PTCs, 5 (83.33%) were a metastatic follicular variant of PTC and remaining 1 case (16.66%) with Columnar cell variant.

A total of 65 lesions were evaluated in 12 advanced DTC patients, each of whom was subjected to I-131 whole body scan, F-18 FDG PET scan and Ga-68 DOTATATE PET/CT scan (a total of 36 scans) and presented in Table 1.

The number of positive lesions detected by I-131, F-18 FDG PET, and Ga-68 DOTATATE PET/CT scans were 47 of 65 (72.3%), 43 of 65 (66.15%), and 44 of 65 (67.69%) respectively.

During analysis, it was found that out of a total of 65 lesions, 41.5% (27/65) concordant lesions were detected by all 3 scans. Notably, 18.46% (12/65) lesions seen on F-18 FDG PET scan and 16.9% (11/65) lesions on Ga-68 DOTATATE PET/CT scan did not show any significant radio-iodine uptake when each of these modalities was individually compared with radio-iodine (I-13I) imaging.

Out of a total of 37 bone lesions, 51.3% (19/37) concordant skeletal lesions were detected by all 3 scans [Table 2]. And 27.77% (5/18) out of the

remaining 18 bone lesions were seen on both I-131 and Ga-68 DOTATATE PET/CT scan but not detected on FDG PET scan. Out of 37 metastatic bone lesions, 10.8% (4/37) lesions were detected only on the Ga-68 DOTATATE PET/CT scan.

Comparisons of I-131 whole body scan and F-18 FDG PET scan findings:

When the FDG PET scan in each patient was compared with the I-131 WBS, 56.92% (37/65) concordant lesions were found. The mean (standard deviation) number of positive lesions detected by I-131 WBS was found to be 3.92 (2.36), and for the F-18 FDG PET, it was 3.58(2.02). Lin's concordance correlation coefficient between I-131 and F-18 FDG PET was 0.317 with a 95% confidence interval (-0.27 – 0.73) indicating a poor concordance between the two methods for detecting lesions. The Pearson's correlation coefficient between I-131 and F-18 FDG PET was r=0.31 indicating a poor agreement. The value of the coefficient of determination r-square was estimated to be 0.10 indicating that just under 10% of the variation of F-18 FDG PET is explained by I-131, indicating a poor measure of goodness of fit [Figure 2]

Comparison of I-131 whole body scan and Ga-68 DOTATATE PET/CT scan:

When the Ga-68 DOTATATE PET/CT scan in each patient was compared with the I-131 WBS, 60% (39/65) concordant lesions were found. The mean (standard deviation) number of positive lesions detected by I-131 WBS was found to be 3.92(2.36), and for the Ga-68 DOTATATE PET/CT scan, it was 3.67(3.14). Lin's concordance correlation coefficient between I-131 WBS and Ga-68 DOTATATE PET/CT scan was 0.597 with a 95% confidence interval (0.11 – 0.85) indicating a good concordance between the two methods for detecting lesions. The Pearson's correlation coefficient between the I-13I WBS and Ga-68 DOTATATE PET/CT scan was r=0.624 indicating a good agreement. The value of the coefficient of determination r-square was estimated to be 0.40 indicating that just under 40% of the variation of Ga-68 DOTATATE PET/CT scan is explained by I-131 WBS, indicating a good measure of goodness of fit [Figure 1]

Comparisons of F-18 FDG PET scan findings and Ga-68 DOTATATE PET/CT scan:

When the FDG PET scan in each patient was compared with the Ga-68 DOTATATE PET/CT scan, 66.15% (43/65) concordant lesions were found. The mean (standard deviation) number of positive lesions detected by the F-18 FDG PET scan was found to be 3.58(2.09), and for the Ga-68 DOTATATE PET/CT scan, it was 3.67(3.14). Lin's concordance correlation coefficient between F-18 FDG PET and Ga-68 DOTATATE PET/CT scan was 0.743 with a 95% confidence interval (0.44 – 0.89) indicating an excellent concordance between the two methods for detecting lesions. Pearson's correlation coefficient between the F-18 FDG PET and Ga-68 DOTATATE PET/CT scans was r=0.818 indicating an excellent agreement. The value of the coefficient of determination r-square was estimated to be 0.69 indicating that just under 69% of the variation of Ga-68 DOTATATE PET/CT scan is explained by F-18 FDG PET scan, indicating a good measure of goodness of fit [Figure 3]

The overall result showed that the Ga-68 DOTATATE PET/CT scan had a good agreement with the I-131 WBS but the F-18 FDG PET scan did not show a good agreement with I-131. However, the F-18 FDG PET scan showed an excellent agreement with the Ga-68 DOTATATE PET/CT scan [Figure 4,5]

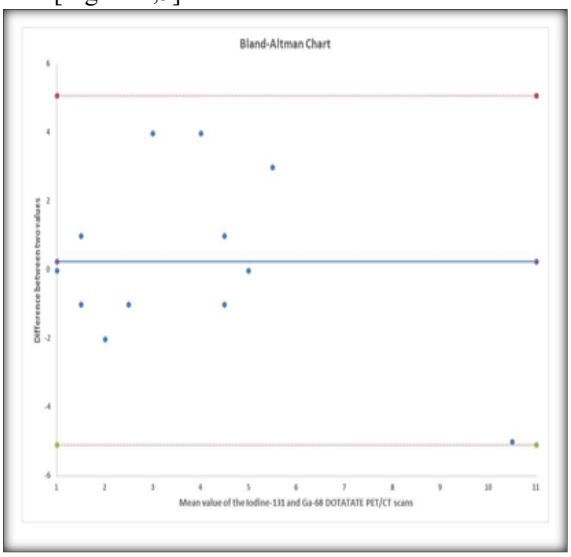

Figure 1: Presents the Bland-Altman diagram showing the plot of the difference between the number of positive lesions between I-131 and Ga-68 DOTATATE PET/CT scan against the mean value of the pair (n=12). The diagram shows that the standard deviation of the difference is estimated as 2.598 and the 95% limits of the agreement by -5.01 and 5.01. Most of the coordinates are close to the mean difference indicating a good agreement between the two tests.

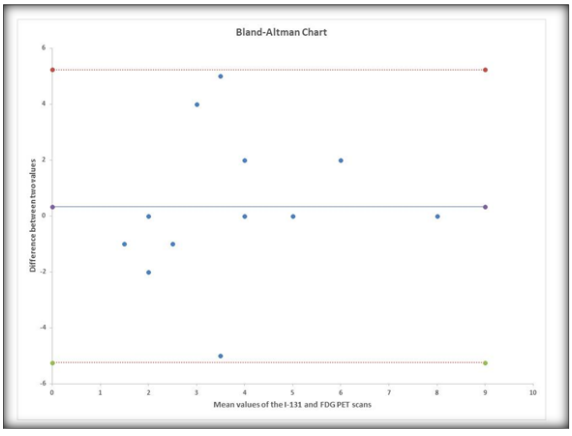

Figure 2: Presents the Bland-Altman diagram showing the plot of the difference between the number of positive lesions between I-131 WBS and F-18 FDG PET scan against the mean value of the pair (n=12). The diagram shows that the standard deviation of the difference is estimated as 2.67 and the 95% limits of agreement by -5.24 and 5.24. The coordinates are very scattered indicating a poor agreement between the two tests.

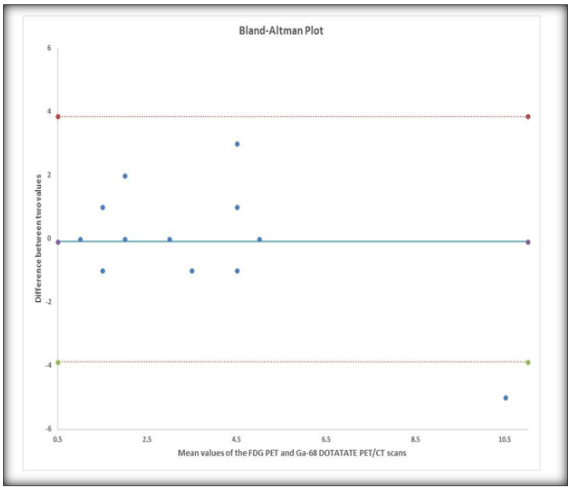

Figure 3: Presents the Bland-Altman diagram showing the plot of the difference between the number of positive lesions between F-18 FDG PET and Ga-68 DOTATATE PET/CT scans against the mean value of the pair (n=12). The diagram shows that the standard deviation of the difference is estimated as 1.975 and the 95% limits of the agreement by -3.87 and 3.87. Most coordinates are close to the mean difference indicating an excellent agreement between the two tests.

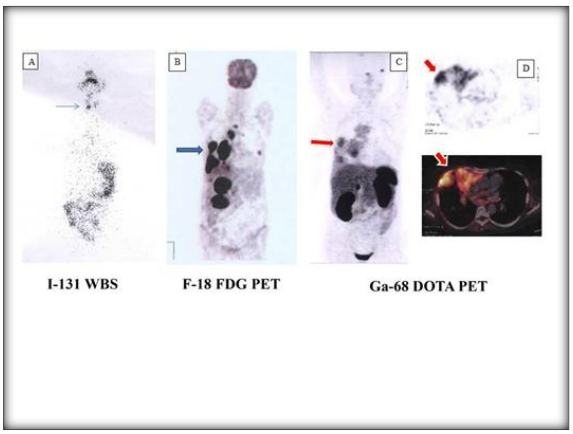

Figure 4: A 58-year-old female with advanced DTC: (A) WBS showed focal I-131 concentration in neck (thin arrow), no significant uptake in lung and mediastinum; (B) FDG-avid metastatic lesions in the mediastinum & lung (blue arrow) on Maximum intensity projection (MIP) image; (C) MIP showed Ga-68 DOTATATE-avid lesions in mediastinum and right lung, (D) Axial and Fused Ga-68 DOTATATE PET/CT axial images showed SSTR expressing lesions in anterior mediastinum and right lung and pleura (red arrows).

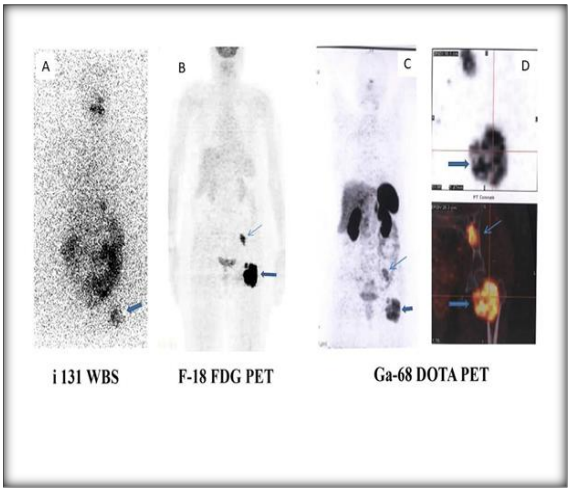

Figure 5: A 70-year-old female with metastatic FCT: (A) Increased I-131 uptake in left femur on WBS, (B) FDG PET MIP showed FDG-avid lesions in left iliac bone (thin arrow) and left femur (thick arrow); (C) Ga-68 DOTATATE PET-CT MIP and Fused coronal images showed SSTR expressing lesions in left iliac (thin arrow) and left femur (thick arrow).

Table 1: Number of lesions detected in each patient by all 3 scans – I-131 WBS, FDG PET and Ga-68 DOTATATE PET/CT scans

Patient ID	I-131 scan	FDG PET scan	Ga-68 DOTATATE PET/CT scan
P1	1	2	2
P2	7	5	4
P3	5	1	1
P4	8	8	13
P5	4	4	5
P6	2	3	3
P7	1	3	1
P8	6	1	2
P9	5	3	4
P10	2	2	1
P11	1	6	3
P12	5	5	5
Total	47	43	44

Table 2: Concordant lesions detected by all 3 scans – I-131 WBS, FDG PET and Ga-68 DOTATATE PET/CT scans

Counts	I-131 scan	FDG PET scan	Ga-68 DOTATATE PET/CT scan
27 out of total 65 lesions	positive	positive	positive
19 bone lesions out of total 37 skeletal lesions	positive	positive	positive

DISCUSSION

Follicular cell-derived DTC is the most commonly seen endocrine cancer with an indolent course. A small fraction of thyroid malignancy is aggressive having high malignant potential and can metastasize mainly to regional nodes, lungs and bones and rarely to the brain, liver, renal, colon and adrenal glands. DTCs are generally managed with radio-active iodine after total or completion thyroidectomy and followed-up with clinical evaluation, estimation of serum TSH, serum Tg as a tumor marker, along with serum anti-thyroglobulin antibody (ATG), neck ultrasound and whole-body radio-iodine scintigraphy (WBS). Advanced and aggressive thyroid malignancies demonstrate a reduced ability to retain radio-iodine either at the onset of disease or over some time.

The lesions with high grade F-18 FDG uptake in the patients with DTCs usually showed low grade radio-iodine uptake and are more clinically aggressive.[24]

Normal thyroid expresses SSTR2, SSTR3 and SSTR5 mRNAs with only faint expression of SSTR1 mRNA. Likewise, follicular cell-derived carcinoma cell-lines have similar expression patterns. SST and its analogues inhibit the proliferation of neoplastic tissue.

Oncocytic thyroid carcinoma (previously known as Hurthle cell carcinoma) accounts for 3% to 5% of all thyroid cancer cases having an unpredictable clinical course and demonstrates more aggressive

biological characteristics. As compared to other DTCs including the papillary and follicular varieties and non-oncocytic poorly-differentiated thyroid carcinomas, Oncocytic thyroid carcinoma (OTC) generally exhibit RAI-refractory characteristics and having a worse prognosis.[25,26,27]

Jaap J M Teunissen et.al [28,29] reported that several metastases of PTC, FTC and majority of Hurthle cell thyroid cancer (HCTC) metastases could express SSTR and In-111 Pentetreotide Scintigraphy as a promising tool for the localization of metastases especially in HCTC. In addition, it would be useful for the selection of possible candidates for therapeutic radiolabelled beta-emitting SST analogues. Lutetium-177 DOTATATE therapy may be beneficial for patients with progressive DTCs who lack alternative treatment options and showed high grade In-111 Octreotide uptake in metastatic lesions on In-111 Octreotide scintigraphy. These findings are especially important in patients diagnosed with OTC in which no much benefit from radio-iodine therapy owing to non–iodine avid lesions presented at the time of diagnosis.

Thakur S et.al[30] demonstrated that SSTR2 may serve as a molecular target in the diagnosis and treatment of a subset of thyroid cancer patients and showed high Ga-68 DOTATATE uptake in patients with OTC suggesting PRRT might be beneficial in these patients, which are currently lacking effective therapeutic options.

Maghsoomi Z et.al[22] undertook a systematic to investigate the safety and efficacy of PRRT in patients of advanced radio-iodine refractory PTC and MTC and concluded that in the absence of established treatment for patients with refractory DTC and metastatic MTC, PRRT could be effective with less adverse effects.

In this study, we investigated the potential role of FDG PET and Ga-68 DOTATATE PET/CT scans in the evaluation of patients diagnosed with advanced thyroid malignancy. One of the highlighting points of this study is that a substantial number of lesions that were not concentrating radio-iodine on I-131 WBS, were either positive on FDG PET (18.46%) or Ga-68 DOTATATE PET/CT scan (16.9 %).

This is important since it gives a true indication of the extent of disease, and makes the lesions that express SSTR amenable to PRRT. Secondly, Lin's concordance correlation coefficient between I-131 WBS and FDG PET scan was 0.317 with a 95% confidence interval (-0.27 – 0.73) indicating a poor concordance between the two methods for detecting lesions and Pearson's correlation coefficient between I-131 WBS and FDG PET scan was r=0.31 indicating a poor agreement – the conventional 'flip-flop' concept where lesions not expressing Sodium Iodide Symporter (NIS) would be positive on FDG PET scan.[31,32]

It is possible that multiple expressions in these lesions could be due to multiple clones of cells of varying biology and also reflect the aggressiveness of the lesions. Aggressive forms of thyroid malignancies are more likely to metastasize early and at the same time to be more metabolically active and therefore are likely to demonstrate more FDG-avid lesions. It is a known fact that the cells of high-grade tumours usually lose some of their differential functions such as uptake of radio-iodine and therefore likely to be missed on diagnostic as well as post-therapy radio-iodine scans. The combination of lesions that concentrated radio-iodine and those that did not show radio-iodine uptake but were avid on FDG PET scan is a demonstration of gradual de-differentiation of tumor tissue clones. Better differentiated clones have preserved NIS expression and are therefore amenable to radio-iodine therapy. While those FDG-avid lesions that show no radio-iodine concentration tend to be more aggressive and may become refractory to radio-iodine treatment.[33]

F-18 FDG PET or Ga-68 DOTATATE PET/CT scans could play an important role in staging aggressive variants of thyroid malignancies and may alter management in a substantial number of these patients.

In contrast to I-131 WBS scan, in which radio-iodine uptake was mostly present in the neck especially in the thyroid bed area in aggressive and advanced thyroid cancers, we have demonstrated that the FDG PET scans and Ga-68 DOTATATE PET/CT scans were more likely to reveal foci of radio-tracer uptake in locations outside the thyroid bed region. Ga-68 DOTATATE PET/CT scan detected an additional 4(10.8%) osseous metastatic lesions that were not radio-iodine-avid and not FDG-avid. Most of those lesions expressing SSTR on Ga-68 DOTATATE PET/CT scan were making them amenable to PRRT.

Our pilot study emphasized that both F-18 FDG PET and Ga-68 DOTATATE PET/CT scans could be of prognostic value in the initial evaluation of patients diagnosed with advanced DTC as majority of the metastatic lesions were either FDG-avid or Ga-68 DOTATATE-avid.

Therefore, the initial value of F-18 FDG PET and Ga-68 DOTATATE PET/CT scans in patients of advanced DTC is to demonstrate radio-iodine and FDG-avidity or Ga-68 DOTATATE-avid lesions as well as the lesions that are not I-131 avid but positive either on F-18 FDG PET or Ga-68 DOTATATE PET/CT scans. We hypothesized that the former (radio-iodine positive and FDG or Ga-68 DOTATATE positive) lesions may precede the development of non-radioiodine avid but FDG or Ga-68 DOTATATE-avid lesions. SSTR expression in these lesions opens up the possibility for further management of this advanced disease at an earlier stage with PRRT.

CONCLUSION

In patients with advanced follicular cell-derived thyroid cancers, both F-18 FDG PET and Ga-68 DOTATATE PET/CT imaging should be performed

in addition to routine radio-iodine scan. SSTR expression in a substantial number of lesions with advanced thyroid carcinoma probably reflects the variable biology of metastases as compared to the primary and makes them amenable to PRRT.

Limitations

1. The low number of patients included in this pilot study is a shortcoming of the study. Though lesion-based analysis was possible, with a higher number of patients both lesion-based and patients-based analysis can be done, thereby reflecting the number of patients who actually benefited from undergoing additional diagnostic procedures in terms of change in management.
2. Due to ethical issues, the final results of the inter-modality comparison could not be compared with the pathology of the lesions which is considered as a gold standard.

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