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Research Article

Is Thyroid Stimulating-Hormone related to Functional Tumor Burden in Patients with Advanced Medullary Thyroid Cancer?

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Abstract

Objectives: To investigate the relation between thyroid-stimulating-hormone (TSH) and metabolic tumor volume (MTV) in patients with advanced medullary thyroid cancer.

Methods: Ga-68-DOTA-TATE-PET/CT findings such whole-body somatostatin receptor-expressing metabolic tumor volume (SSR-E MTV) and total lesion volume (SSR-E TLV) were calculated, and correlation analysis was performed for TSH and whole-body SSR-E MTV and SSR-E TLV.

Results: Totally twenty-eight patients were included in the study. The median TSH level was 2.90 mU/L and median free T4 was 2.70 ng/L. The median calcitonin level was 6671.6 pg/mL and the median carcinoembryonic antigen level was 202.8 ng/mL. Median whole-body SSR-E MTV was calculated as 37.2 cm3 and median SSR-E TLV was calculated 198.6 cm3. There was a significantly positive correlation between TSH and whole-body SSR-E MTV and SSR-E TLV (rho=0.739, p<0.001 and rho=0.595, p=0.006). In the linear regression analysis, only calcitonin was found as a significant factor in terms of correlated with for SSR-E MTV (p<0.001). there were found that calcitonin and TSH were statistically significant factors in terms of correlated with SSR-E TLV (p<0.001 and p=0.005, respectively).

Conclusion: This is the first study shown that a positive correlation between TSH and SSR-E MTV in patients with advanced medullary thyroid cancer.

Keywords: medullary thyroid cancer, metabolic tumor volume, somatostatin receptor, thyroid stimulating-hormone, total lesion volume

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Medullary thyroid cancer (MTC) is a rare type of neuroendocrine tumor, accounts for approximately 1-2 % of all thyroid cancer cases. MTC originates from parafollicular, calcitonin-secreting cells. MTC may occur either sporadically or in a hereditary form as a component of type 2 multiple endocrine neoplasia (MEN2) syndromes. The familial or hereditary form accounts for about 25% of all MTC and is inherited as an autosomal dominant mutation and overexpression of the RET (Rearranged during Transfection) proto-oncogene. The sporadic form accounts for about 75% of all MTC and it mostly occurs in adults aged between 40 and 60 years. Only curative treatment modality is surgery for MTC in all patients without distant metastases and extra-nodal involvement. In advanced stage diseases, tyrosine kinase inhibitors (TKIs) such as vandetanib and cabozantinib were approved.[1]

Calcitonin (Ctn) and carcinoembryonic antigen (CEA) are used as markers for medullary thyroid cancer. Postoperatively, results may provide a prognostic factor or indicate biochemical cure. In advanced stages, doubling times of

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these markers may be prognostic.[2-8] In radiologic evaluation, computed tomography (CT) for lung and mediastinal imaging, three-phase contrast-enhanced multi-detector liver CT and/or contrast-enhanced magnetic resonance imaging (MRI) for liver imaging and bone scintigraphy plus axial MRI for skeletal imaging are used in cases of suspected metastatic disease. Functional imaging techniques are used commonly in oncologic practice such as 2-(fluorine-18) fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET)/CT scan but FDG PET/CT is less sensitive in medullary thyroid cancer.[9] In recent years, Gallium-68 (Ga-68) DOTA-TATE PET/CT as a new method, has been used to detect metastatic or recurrent disease. In Ga-68 DOTA-TATE PET/CT, some parameters such as whole-body somatostatin receptor-expressing metabolic tumor volume (SSR-E MTV) and total lesion volume (SSR-E TLV) may be used as indicators for functional tumor burden. Total tumor volume is important for both choosing treatment modality and follow-up period.

Thyroid-Stimulating Hormone (TSH) is secreted by the pituitary gland and regulate the secretion of thyroid hormones. In differentiated thyroid cancer, TSH suppression is important in terms of tumor growth.[10,11]

We aimed to investigate the relation TSH and tumor volume parameters such as SSR-E MTV and SSR-E TLV in patients with advanced MTC.

Methods

Study Population

This trial was planned as a retrospective single-center study. Medical information was obtained from the archive files of patients who were treated and followed-up between 2017-2019 years, for advanced stage medullary thyroid cancer in the outpatient of the medical oncology. Patients were under 18 age, had localized disease and patients not performed Ga-68 DOTA-TATE and with no laboratory test results were excluded. Disease staging was performed according to TNM eight edition.

68Ga-DOTA-TATE imaging Protocol

A fully automated Scintomics GRP synthesis module with Scintomics Control Center and GRP-Interface software was used for the radiolabeling of 68Ga-DOTA-TATE. The 68Ge/68Ga generator was purchased from iThemba LABS, South Africa. DOTA-TATE was purchased from Scintomics GRP, Germany via a local distributor. Whole-body PET/CT scans were performed using LSO-based full-ring PET scanner (Siemens Biograph 6, Chicago, IL, USA). 2 MBq/kg 68Ga-DOTA-TATE was injected intravenously. After 1-hour, whole-body CT scans were obtained from the base of the skull to the upper thigh with slice collimation of 5 mm and a slice interval of 3.4 mm. The emission data were acquired for 2,5min per bed (6–7 beds), which were later attenuation corrected with the digital CT data. Image reconstruction used the ordered subsets expectation-maximization algorithm of 2 iteration and 8 subsets. Image analysis was carried out on the Esoft multimodality computer platform (Siemens Medical Solutions, Erlangen, Germany).

Imaging Analysis

Images were visually interpreted by consensus between two experienced nuclear physicians. The foci of uptake were identified as representing a tumor if the accumulation of 68Ga-DOTA-TATE was increased relative to comparable normal contralateral or surrounding tissues. The SUVmax, SUVmean, and SSR-E MTV (cm^3) for each lesion were produced automatically from the VOIs by the workstation. The margin of the target lesion inside the VOI was automatically produced and voxels greater than a threshold of 41% of SUVmax in the VOI were defined to measure SSR-E MTV and SUVmean. The results were checked by comparison with the fused CT images to determine if the adjustment was needed in the percentage threshold. If the percentage threshold was not appropriate, further adjustment of the percentage threshold was performed until a satisfactory outcome was achieved. The whole-body SSR-E MTV of each patient was defined as the sum of SSR-E MTVs of all lesions. The SSR-E TLV was obtained by multiplying the SSR-E MTV of each lesion for the corresponding SUVmean determined in the selected volume by is contouring. The whole body SSR-E TLV of each patient was defined as the sum of SSR-E TLVs of all lesions. The SUVmax was defined as the one lesion which has the highest SUVmax.

Statistical Analysis

For statistical analysis, IBM Statistical Package for the Social Sciences 15.0 for Windows was used. Descriptive statistics were given as number and percent for categoric variables and as mean, standard deviation, minimum and maximum for numerical variables. The relations between numerical variables was evaluated Spearman Correlation Analysis because the parametric test condition is not provided. Statistically alpha significant was accepted as $p<0.05$. Institutional ethics committee approval was received.

Results

For this purpose, twenty-eight patients with advanced MTC who were treated and followed up our clinic were included in the study. 19 (67.9%) patients were women and 9 (32.1%) patients were men. The mean age of patients was 55 (standard deviation (SD) ±13.1) years. 20 (71.4%) of patients had

sporadic form and 8 (28.2%) of familial form MTC. ECOG performance status of all patients was 0-1. 7 (25%) of patients had stage IVa disease and 21 (75%) of patients had stage IVc disease. Metastasis locations were cervical and mediastinal lymph node, bone, lung and brain, respectively. 9 (32.1%) of patients received TKIs because of inoperable (7 patients vandetanib and 2 patient cabozantinib) and 19 (67.9%) patients received surgical treatment only. Patients number received levothyroxine was 20 (71.4%) (Table 1).

The median Ctn level was 6671.6 pg/mL (min-max 2-102148 pg/mL) and median CEA level was 202.8 ng/mL (min-max 1.56-3271 ng/mL). The median TSH level was 2.90 mU/L (min-max 0.04-22 mU/L) and the median free T4 was 2.70 ng/L. Median whole-body SSR-E MTV was calculated as 37.2 cm^3 (min-max 3-582.7 cm^3) and median whole-body SSR-E TLV was calculated 198.6 (min-max 14-3262.8). The median SUVmax was 11.1 (min-max 2-34.6) (Table 2).

In the correlation analysis, there was a significantly positive correlation between TSH and whole-body SSR-E MTV (rho=0.739 and p<0.001). Similarly, significantly a positive correlation was observed between TSH and whole-body SSR-E TLV (rho=0.595 and p=0.006). This correlation was not shown between TSH and SUV max (rho=0.150 and p=0.529) (Table 3 and Fig. 1). There was a significantly positive correlation between Ctn and whole-body SSR-E MTV (rho=0.503 and p=0.008). Also, a positive correlation was observed between Ctn and whole-body SSR-E TLV (rho=0.436 and p=0.023). But there was no correlation between Ctn and SUVmax (rho=0. 284 and p=0.151). There were similar correlations CEA and whole-body SSR-E MTV and TLV (rho=0.488 p=0.010 and rho=0.436 p=0.023) (Table 3).

In the linear regression analysis for whole-body SSR-E MTV, only Ctn was found as significant factor in terms of correlated with SSR-E MTV (p<0.001). The same method was

Table 1. Patients characteristics

	n	%
Sex		
Male	9	32.1
Female	19	67.9
Age Med. (SD)	55.0 (13.1)	
Hereditary		
Sporadik	20	71.4
Familial	8	28.6
Stage		
IV a	7	25.0
IV c	21	75.0
Metastasis Site		
Neck LN	17	60.7
Bone	15	53.6
Inferior mediastinal LN	7	25.0
Lung	3	10.7
Treatment		
Surgery	19	67.9
Cabozantinib	2	7.1
Vandetanib	7	25.0
Levothyroxine	20	71.4

SD: Standard Deviation; LN: Lymph Node.

Table 2. Patients laboratory tests and Ga-68 DOTA-TATE PET/CT findings

	Median±SD	Min- Max
Laboratory		
TSH mU/L	2.90±5.22	0.04-22
fT4 ng/L	2.70±3.14	0.45-9.45
CEA ng/mL	202.8±641.0	1.56-3271
Calcitonin pg/mL	6671.6±19771.4	2-102148
Ga-68 DOTA PET		
Whole-body SSR-E MTV cm^3	37.2±112.5	3-582.7
Whole-body SSR-E TLV	198.6±629.9	14-3262.8
SSR-E SUVmax	11.1±9.6	2-34.6

SD: Standard Deviation; Min: Minimum; Max: Maximum; TSH: Thyroid-Stimulating Hormone; fT4: free thyroxine; CEA: Carcinoembryonic Antigen; MTV: metabolic tumor volume; TLV: total lesion volume; SUVmax: Standard Uptake Value maximum, SSR-E: Somatostatin receptor-expressing.

Table 3. Correlation analysis between laboratory tests and Ga-68 DOTA-TATE PET/CT findings

	Whole body SSR-E MTV cm^3		Whole body SSR-E TLV		SSR-E SUVmax	
	rho	p	rho	p	rho	p
TSH	0.739	<0.001	0.595	0.006	0.150	0.529
fT4	-0.446	0.056	-0.295	0.221	0.144	0.557
CEA	0.488	0.010	0.436	0.023	0.241	0.227
Calcitonin	0.503	0.008	0.436	0.023	0.284	0.151

TSH: Thyroid-Stimulating Hormone; fT4: free thyroxine; CEA: Carcinoembryonic Antigen; MTV: metabolic tumor volume; TLV: total lesion volume; SUVmax: Standard Uptake Value maximum, SSR-E: Somatostatin receptor-expressing.

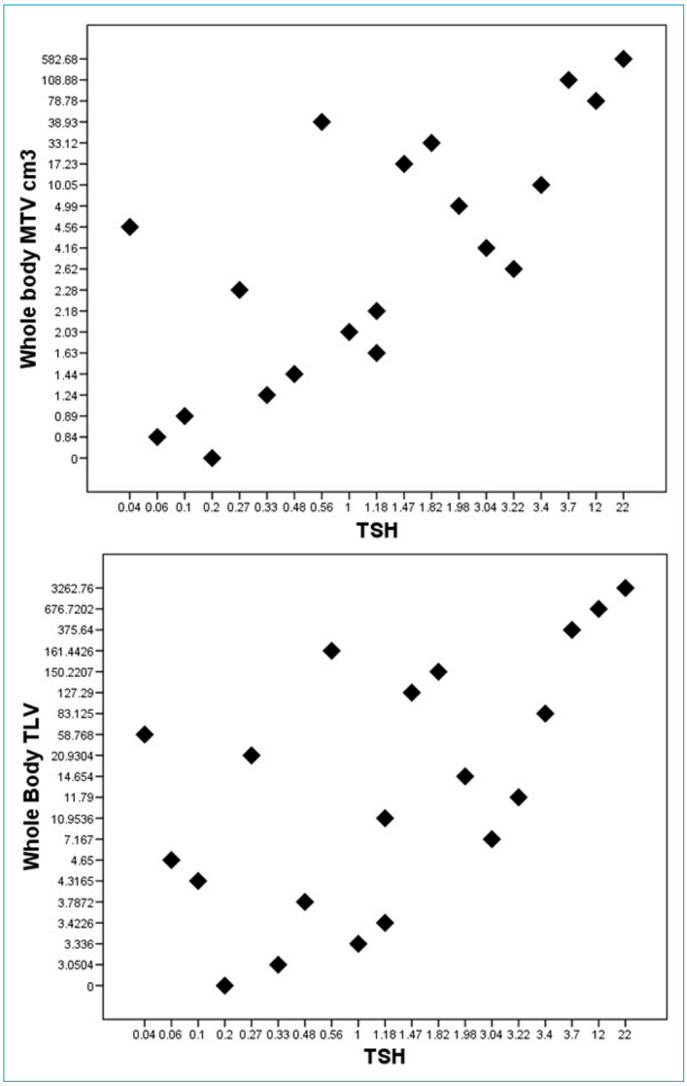

Figure 1. The correlation between TSH and tumor volume parameters in Ga-68 DOTA-TATE PET/CT.

performed for whole-body SSR-E TLV and there were found that Ctn and TSH were statistically significant factors in terms of correlated with SSR-E TLV (Tables 4,5).

We also examined patients who treated with TKIs. After 3 months of treatment starting, we performed Ga-68 DOTA-TATE. Totally 4 patients had stable disease, 2 patients had a partial response and 1 patient had progressive disease according to PET Response Criteria in Solid Tumors (PERCIST). These patient's TSH level was stabile according to pre-treatment tests but number of patients was not sufficient for statistical analysis.

Discussion

TSH suppression is very important in patients with differentiated thyroid cancer to prevent tumor growth but there was not any study focused on TSH suppression of other cancer types. We examined whether or not is there any relation TSH and tumor volume in patients with advanced-stage MTC.

In the literature, there are a few studies investigated the effects of TSH on different cancer types other than differentiated thyroid cancer. The first study published in 2015, totally 86 patients with newly diagnosed breast cancer were examined and found that there was a negative correlation between Ki-67 and free T3 levels in HER-2 positive subgroup but there was no any correlation between TSH or free T4 and Ki-67 levels.[12] In another study, 676 patients with breast cancer were included and assessed whether or not a relation between pre-diagnostic TSH, free T3, and free T4 levels and tumor subgroups and aggressiveness. High free T4 level was found associated with a higher risk for overall, especially less aggressive, breast cancer.[13] The recent trial examined to relation TSH and free T4 with breast

Table 4. Linear regression analysis for whole-body SSR-E MTV

Dependent Variable: Whole body MTV cm³	**B**	**Beta**	**p**
Enter Model			
MPV	3.363	0.041	0.447
PDW	-2.076	-0.038	0.434
TSH	2.990	0.121	0.295
fT4	-0.533	-0.013	0.756
CEA	0.028	0.158	0.408
Calcitonin	0.004	0.709	0.011
Backward Model			
Calcitonin	0.006	0.989	<0.001

MPV: Mean Platelet Volume; PDW: platelet distribution width; TSH: Thyroid-Stimulating Hormone; fT4: free thyroxine; CEA: Carcinoembryonic Antigen; MTV: metabolic tumor volume; SSR-E: Somatostatin receptor-expressing.

Table 5. Linear regression analysis for whole-body SSR-E TLV

Dependent Variable: Whole body TLV	**B**	**Beta**	**p**
Enter Model			
MPV	-4.718	-0.010	0.847
PDW	-14.631	-0.048	0.384
Phosphorus	-9.997	-0.009	0.879
TSH	45.788	0.329	0.027
fT4	-3.269	-0.014	0.789
CEA	0.259	0.264	0.219
Calcitonin	0.014	0.439	0.118
Backward Model			
TSH	37.039	0.266	0.005
Calcitonin	0.024	0.742	<0.001

MPV: Mean Platelet Volume; PDW: platelet distribution width; TSH: Thyroid-Stimulating Hormone; fT4: free thyroxine; CEA: Carcinoembryonic Antigen; TLV: total lesion volume, SSR-E: Somatostatin receptor-expressing.

cancer risk, published in 2015, 62,546 women involved, within median 4.8 years follow up period, totally 834 women developed breast cancer and found that both low TSH and high free T4 levels associated with increased breast cancer risk.[14] In an experimental study, changes of thyroid function tests were investigated in sarcoma transplanted 44 rats and showed that tendency to TSH increasing and free T3 decreasing when liver metastasis developed and these changes were interpreted as low T3/T4 syndrome.[15] Chan et al.[6] examined the relationship between TSH and free T4 with cancer incidence and cancer-related mortality. For this purpose, 3836 older men prospectively investigated and totally 864 men developed cancer, most common prostate, colorectal and lung cancers, respectively. There was found a relation between higher TSH and colorectal cancer, but not prostate and lung cancer also not related to cancer-related mortality. In a trial examined associations between TSH and disease progression in patients with uveal melanoma. In this study, TSH levels were found lower in uveal melanoma patients than the healthy control group and TSH was significantly associated with survival.[17] In most of these trials other than the last were found a negative correlation between TSH and cancer types.

We found a positive correlation between TSH and tumor volume in patients with advanced medullary thyroid cancer. This positive relation was not observed in other cancer types so strongly. There was no patient with liver metastasis in our study. Also, there was no change in TSH levels of patients with partial response to TKIs. For these reasons, we associated this relation medullary thyroid cancer-specific possible molecular effects. In the literature there was a trial supporting our results, totally 30 patients with thyroid cancer were included, 6 of these patients had MTC and was shown that 3 of 6 patients expressed TSH-receptor mRNA.[18]

Our study has a few limitations, firstly the trial was planned retrospectively but MTC is seen very rare for this reason, prospective trial focusing on this specific issue is very difficult. Secondly, there were no pre-diagnosis TSH data of patients. There are strengths of our study, this trial is the first study examining the relation TSH and tumor volume in patients with MTC also we used Ga-68 DOTA-TATE to determine the tumor volume.

Conclusion

The presented study was shown that a positive correlation between TSH and tumor volume in patients with advanced MTC but there are needed the studies whether TSH growth the MTC like in differentiated thyroid cancer or whether TSH increases because of tumor volume. This trial may highlight the new studies focusing on TSH suppression in MTC.

Disclosures

Ethics Committee Approval: The Okmeydani Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 25.06.2019, number: 48670771-514.11.

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Conflict of Interest: None declared.

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