Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1107903
J Health Sci Med 2022; 5(3): 893-900

Is there an association between thyroid function tests and 18F FDG PET/CT parameters in untreated cancer patients?

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Cite this article as: Kaplan İ, Can C, Kömek H, et al. Is there an association between thyroid function tests and 18F FDG PET/CT parameters in untreated cancer patients?. J Health Sci Med 2022; 5(3): 893-900.

ABSTRACT

Objectives: We aimed to investigate the association between the extent of disease, 18F FDG PET/CT parameters (SUVmax and the highest SUVmax) and thyroid function tests (TFT) (TSH, FT4, FT3, FT3/FT4 ratio, AntiTG, and AntiTPO) in untreated cancer patients.

Material and Method: One hundred and seventy-nine patients who underwent FDG PET/CT for metabolic characterization and staging in our clinic between May 2020 and November 2020 were included in the study. Patients were divided into two groups as malignant and benign according to histopathology findings. Thyroid function tests were ordered from all patients at the time of PET/CT imaging. The association between the presence of local lymph node metastasis, distant metastases and thyroid function tests as well as the association between PET/CT parameters and thyroid function tests in benign and malignant groups were statistically analyzed.

Results: Thyroid function tests did not exhibit a significant difference between patients with malignant and benign disease ($p > 0.05$). Univariate logistic regression analysis revealed that age, FT4 value, and the FT3/F4 ratio were significant parameters in predicting distant metastases. These parameters were also significant in predicting mortality. Multivariate logistic regression analysis showed that age was an independent prognostic factor predicting mortality.

Conclusion: Thyroid function tests are not decisive in differentiating malignant and benign lesions. While no statistically significant correlation was observed between thyroid function tests and PET/CT parameters, univariate analyses revealed that especially FT4 and FT3/FT4 ratio were significant in predicting disease extent and mortality in malignant disease. Age was found to be an independent prognostic factor in predicting mortality.

Keywords: PET/CT, SUVmax, thyroid hormones, malignancy, distant metastasis

INTRODUCTION

Thyroid hormones are regulated by the hypothalamic-pituitary-thyroid and peripheral tissue axes and affect cell development, differentiation, and growth (1). Thyroid hormones specifically bind to the membrane and nuclear receptors that activate various oncogenic pathways, resulting in the promotion of cell growth, inhibition of apoptosis, and stimulation of angiogenesis. As a result of these multiple actions, thyroid hormones can play a major role in carcinogenesis. Numerous studies have pointed to an association between the increased risk of both solid organ and hematological malignancies and elevated thyroid hormone levels and/or suppressed thyrotropin (TSH) levels (2-4). Also, many in vitro studies revealed the tumor-promoting effects of thyroid hormones (5-8). Hyperthyroidism is associated with poorer prognosis and increased mortality in cancer patients, while hypothyroidism is associated with improved prognosis and prolonged mortality (9,10).

The most common hormone pattern in euthyroid sick syndrome is normal T4 and thyroid stimulating hormone levels, and low total T3 and free T3 levels. Changes in hormone parameters are thought to be a response to systemic disease in different ways in response to oxidative stress. In addition, it can be observed in acute and chronic diseases, after operations and malignancies. It is not a true syndrome and approximately 75% of hospitalized

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Received: 25.04.2021 **Accepted:** 05.05.2022

patients have significant changes in the hypothalamic-pituitary-thyroid axis (11,12).

18F-fluorodeoxyglucose positron emission computerized tomography (18F FDG PET/CT) is one of the most commonly used functional imaging methods in clinical practice. This imaging technique is based on the demonstration of in vivo glucose metabolism (13,14). FDG uptake is routinely measured using the maximum standardized uptake value (SUVmax), which is an accurate and reliable imaging biomarker. 18F FDG PET/CT and SUVmax are widely used in the diagnosis, staging, and evaluating treatment response of various malignant diseases (15-19). A few recent systematic reviews and meta-analyses have shown that SUVmax can be used as a prognostic factor in numerous malignancies (20-23). SUVmax is closely associated with tumor size, number of metastatic lymph nodes, occurrence and progression of distant metastases, and mortality predictions (24).

In this study, we aimed to investigate whether thyroid function tests (TSH, FT4, FT3, FT3/FT4 ratio, AntiTG, and AntiTPO) exhibit any difference between patients with untreated malignant or benign disease, and analyze the association between the extent of disease, FDG PET/CT parameters and thyroid function tests among these patients.

MATERIAL AND METHOD

The study was conducted with the permission of the Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.03.2020, Decision No: 736). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 179 patients who underwent FDG PET/CT for metabolic characterization and staging in our Nuclear Medicine Clinic between May 2020 and November 2020 were reviewed retrospectively. Patients were divided into two groups as malignant and benign according to histopathology findings. Thyroid function tests were ordered from all patients at the time of PET/CT imaging. SUVmax values were measured from all primary lesions as well as local lymph node and distant metastases in patients with malignant disease. The highest SUVmax was recorded for all patients. The association between the presence of local lymph node metastasis, distant metastases and thyroid function tests as well as the association between PET/CT parameters and thyroid function tests in benign and malignant groups were statistically analyzed.

Inclusion Criteria

Patients who had their thyroid function tests measured at the time of PET/CT imaging, did not yet undergo surgery or medical treatment, and had a histopathological diagnosis were included in the study.

Exclusion Criteria

Patients who are under thyroid hormone replacement for any reason and patients who had a previous history of Iodine-131 radionuclide treatment or thyroid surgery were excluded. Patients who underwent surgical treatment or chemotherapy/radiation therapy for the primary lesion or metastases were also excluded.

18F FDG PET/CT Protocol

All patients were asked to fast and stop intravenous (IV) glucose intake for at least 6 hours before undergoing scans. We confirmed blood glucose values to be ≤140 mg/dl by finger-stick method before FDG injection. One hour after the 18F FDG injection of 3.5 MBq/kg–5.5 MBq/kg, we obtained the CT images (120 kV, 80 mAs/slice, 700 mm transaxial FOV, no gap, 64x0.625 mm collimation, pitch 1.4, 0.5 s rotation time, 3.3 mm slice thickness, 512x512 matrix) from the vertex to the middle of the thigh in the supine position using the Discovery IQ 4 ring 20-cm axial FOV PET/CT device (GE Healthcare, Milwaukee, WI, USA). We then obtained the bedside PET (3D FOV 20 cm, ordered subset expectation-maximization algorithm [OSEM] 5 iterations/12 subset, full width at half maximum [FWHM] 3 mm) images at 2.5 minutes thereafter.

Image Analysis

Images were evaluated by two nuclear medicine attendings with at least 10-years of PET/CT experience. Volumes of interest (VOIs) were drawn from the primary lesion, local lymph nodes, and distant metastases. SUVmax of all lesions and the highest SUVmax of all patients were measured and recorded.

Statistical Analysis

IBM SPSS Statistics for Mac, version 25.0 (IBM Corporation, Armonk, New York) was used for statistical analyses. Normality of data was tested with Kolmogorov-Smirnov test. Comparison of two independent groups with nonparametric distribution was performed using Mann-Whitney U test, while categorical variables were compared with Pearson's chi-squared test using the results of Fisher's exact test. The prognostic role of thyroid parameters in predicting local lymph node metastasis, distant metastasis, and mortality was evaluated with univariate and multivariate logistic regression analysis. Quantitative data were expressed as mean±SD (standard deviation) or median (minimum-maximum), while categorical variables were expressed as percentage (%). Data were evaluated within 95% confidence interval. $p< 0.05$ was considered statistically significant.

RESULTS

Among the total of 179 patients, 97 (54.2%) were male. The mean age of all patients was 60 years (3-94). Fifty-three patients (29.6%) had benign and 126 (70.4%) had malignant histopathology findings. Histopathological diagnoses of the patients are listed in **Table 1**. Eighty-six (68.2%) out of 126 patients with malignant disease had local lymph node metastases and 44 (34.9%) had distant metastases.

Table 1. Patient numbers and tumor types in malignant and benign groups

Malignant Group (126)	**N**
Lung cancer	28
Breast cancer	21
Gastric cancer	15
Colorectal cancer	13
Prostate cancer	9
Pancreatic cancer	6
Lymphoma	5
Hepatic cancer	3
Cervical cancer	2
Endometrial cancer	2
Ovarian cancer	2
Esophageal cancer	2
Duodenal cancer	2
Multiple myeloma	2
Bladder cancer	2
Renal cancer	2
Gallbladder cancer	2
Tongue cancer	2
Glioblastoma Multiforme	1
Neuroblastoma	1
Paraganglioma	1
Liposarcoma	1
Ampullary tumor	1
Peritoneal carcinomatosis	1
Benign Group (53)	**N**
Solitary pulmonary nodule	21
Pleural thickening	8
Cervical-Mediastinal-Abdominal lymphadenopathy	5
Bone lesion	5
Tumor of unknown origin	3
Pancreatic mass	3
Hepatic mass	2
Cerebral mass	1
Esophageal mass	1
Breast lump	1
Cervical mass	1
Testicular mass	1
Peritoneal lesionv	1

Our patients had a median TSH value of 1.25 mU/L (0.01-131.00), a median free thyroxin (FT4) value of 1.36 ng/dL (0.10-2.58), and a median free triiodothyronine (FT3) of 3.03 pg/mL (0.61-6.20). The median anti-thyroglobulin antibody (AntiTG) level was 13.73 IU/mL (1.71-3125.00) and the median anti-thyroid peroxidase antibody (AntiTPO) level was 13.80 IU/mL (5.08-538.20). The median FT3/FT4 ratio vas 2.29 (0.79-6.10). A primary lesion was observed in 157 of our patients with a median SUVmax of 8.84 (0.59-91.17) and the median highest SUVmax of 156 patients (primary or metastatic lesion) was 10.34 (0.59-91.17) (**Table 2**).

The Association of Malignant/Benign Lesions with Thyroid and PET/CT Parameters

The median values of age, TSH, FT4, FT3, FT3/FT4 ratio, AntiTG, and AntiTPO levels did not exhibit a statistically significant difference between patient with malignant or benign disease. The median primary lesion SUVmax and the median highest SUVmax were significantly higher in malignant lesions than benign lesions (p<0.001 for both) (**Table 3**).

Table 2. Descriptive Parameters

	Total			
	N	**Mean**	**Std. Deviation**	**Median (Min-Max)**
Age	179	58.41	17.111	60 (3-94)
TSH	178	2.2185	9.76901	1.25 (0.01-131)
FT4	179	1.3676	0.30567	1.34 (0.1-2.5)
FT3	173	3.0601	0.73522	3.03 (0.61-6.2)
FT3/FT4	173	2.3385	0.70569	2.29 (0.79-6.1)
AntiTG	165	55.544	266.148	13.73 (1.71-3125)
AntiTPO	168	27.5317	67.2994	13.80 (5.08-538.2)
Primary Lesion SUVmax	157	11.4343	11.7915	8.84 (0.59-91.1)
Highest SUVmax	156	12.2935	11.7178	10.34 (0.59-91.1)

TSH: Thyrotropin, FT4: Free thyroxin, FT3: Free triiodothyronine, AntiTG: Anti-thyroglobulin, AntiTPO: Anti-thyroid peroxidase, SUVmax: Maximum standardized uptake value

Table 3. The Association of Malignant/Benign Lesions with TFT and PET/CT Parameters

	Benign			**Malign**			
	N	**Median (Min-Max)**	**Std. Deviation**	**N**	**Median (Min-Max)**	**Std. Deviation**	**p**
Age	53	55 (7-80)	15.01	126	63 (3-94)	17.82	0.079
TSH	53	1.35 (0.01-6.84)	1.36	125	1.23 (0.01-131)	11.63	0.104
FT4	53	1.32 (0.78-1.92)	0.26	126	1.34 (0.1-2.58)	0.32	0.769
FT3	50	3.11 (1.94-6.2)	0.75	123	2.97 (0.61-4.96)	0.72	0.126
FT3/FT4	50	2.44 (1.27-5.27)	0.71	123	2.23 (0.79-6.1)	0.69	0.142
AntiTG	49	13.94 (10-185)	38.11	116	13.46 (1.71-3125)	316.01	0.268
AntiTPO	50	14.56 (6.76-538.2)	85.1	118	13.55 (5.08-515.1)	58.1	0.154
Primary Lesion SUVmax	45	2.17 (0.59-24.1)	4.66	112	12.11 (1.2-91.17)	12.46	0
Highest SUVmax	44	2.35 (0.59-24.1)	5.12	112	13.39 (1.2-91.17)	12.19	0

TSH:Thyrotropin, FT4:Free thyroxin, FT3:Free triiodothyronine, AntiTG:Anti-thyroglobulin, AntiTPO:Anti-thyroid peroxidase, SUVmax: Maximum standardized uptake value

The Correlation between Thyroid and PET parameters

There was no significant correlation between the primary tumor SUVmax, the highest SUVmax, and thyroid function tests in 126 patients with malignant disease. AntiTG level was significantly correlated with sex (r: -1.99, p: 0.033). Age also had a significant correlation with TSH, FT3, AntiTG, and FT3/FT4 ratio (r: .242, p: 0.020; r: .780, p: <0.001; r: .307, p: <0.001; and r: .033, p: 0.006, respectively). Local lymph node metastasis was significantly correlated with FT3/FT4 ratio as well (r: .462, p: 0.045). Distant metastasis, on the other hand, was significantly correlated with age, FT4 level, and FT3/FT4 ratio (r: -.193, p: 0.030; r: -.221, p: 0.013; and r: .241, p: 0.007, respectively). Mortality was also significantly correlated with age, FT4 level, and FT3/FT4 ratio (r: -.280, p: 0.002; r: -.242, p: 0.006; and r: .245, p: 0.005, respectively) (**Table 4**).

Logistic Regression Analysis on Predicting Local Lymph Node Metastasis

Univariate logistic regression analyses for age, TSH, FT4, FT3, FT3/FT4 ratio, AntiTG, and AntiTPO levels failed to demonstrate a significant parameter in predicting local lymph node metastasis (**Table 5**).

Logistic Regression Analysis on Predicting Distant Metastasis

Univariate logistic regression analyses revealed age, FT4 levels, and FT3/FT4 ratio to be significant for predicting distant metastasis (OR: .977, p: 0.046; OR: .172, p: 0.008; and OR: .957, p: 0.005, respectively). However, multivariate logistic regression analyses failed to demonstrate an independent prognostic variable (**Table 6**).

Table 4. Correlation of TFT and PET/CT Parameters among Patients with Malignant Disease

		Sex	Age	Primary Lesion SUVmax	Highest SUVmax	Local Lymph Node Metastasis	Distant Metastasis	Mortality
Sex	r		.146	.008	-.010	.090	.022	.029
	p		.104	.930	.918	.319	.811	.750
Age	r	.146		.107	.155	-.056	-.193	-.280
	p	.104		.259	.104	.531	.030	.002
TSH	r	-.106	-.208	-.098	-.076	.017	-.004	-.041
	p	.242	.020	.308	.428	.853	.963	.649
FT4	r	-.075	.067	-.058	-.062	-.104	-.221	-.242
	p	.405	.454	.547	.517	.246	.013	.006
FT3	r	.026	-.344	-.080	-.135	.159	.115	.096
	p	.780	.000	.408	.162	.079	.206	.293
FT3/FT4	r	.093	-.319	.000	-.071	.181	.241	.254
	p	.307	.000	.999	.462	.045	.007	.005
AntiTG	r	-.199	-.253	-.075	-.128	-.077	.147	.117
	p	.033	.006	.450	.195	.410	.115	.212
AntiTPO	r	-.092	.004	-.050	-.171	.097	-.006	-.116
	p	.325	.966	.609	.080	.294	.949	.212

TSH:Thyrotropin, FT4:Free Thyroxin, FT3:Free Triiodothyronine, AntiTG:Anti-Thyroglobulin, AntiTPO:Anti-Thyroid Peroxidase, SUVmax:Maximum Standardized Uptake Value

Table 5. Logistic Regression Analysis on Predicting Local Lymph Node Metastasis

	Univariate analysis					Multivariate analysis				
	B	OR	95% C.I.for EXP(B)		p	B	OR	95% C.I.for EXP(B)		P
			Lower	Upper				Lower	Upper	
Sex	.393	1.481	-	-	.316	-	-	-	-	-
Age	-.008	.992	3	94	.456	-	-	-	-	-
TSH	-.037	.964	.01	131.00	.731	-	-	-	-	-
FT4	-.575	.563	.10	2.58	.352	-	-	-	-	-
FT3	.456	1.578	.61	4.96	.100	-	-	-	-	-
FT3/FT4	.447	1.564	.79	6.10	.116	-	-	-	-	-
AntiTG	.001	1.001	1.71	3125.00	.314	-	-	-	-	-
AntiTPO	.001	1.001	5.08	515.10	.818	-	-	-	-	-
Primary Lesion SUVmax	.014	1.014	1.20	91.17	.363	-	-	-	-	-
Highest SUVmax	.005	1.005	1.20	91.17	.749	-	-	-	-	-

TSH:Thyrotropin, FT4:Free thyroxin, FT3:Free triiodothyronine, AntiTG:Anti-thyroglobulin, AntiTPO: Anti-thyroid peroxidase, SUVmax: Maximum standardized uptake value

Logistic Regression Analysis on Predicting Mortality

Univariate logistic regression analyses revealed age, FT4 levels, and FT3/FT4 ratio to be significant for predicting distant metastasis (OR: .947, p: 0.004; OR: .223, p: 0.042; and OR: .3.970, p: 0.006, respectively). Age was determined to be significant prognostic marker for mortality in multivariate analyses (OR: .949, p: 0.018) (**Table 7**).

DISCUSSION

In this prospective study investigating the association of thyroid function tests with the extent of malignant disease in patients with a tumoral lesion, we did not observe a significant difference in thyroid function tests between malignant and benign groups. Also, PET/CT parameters and thyroid function tests did not exhibit a statistically significant correlation. FT3/FT4 ratio was significantly correlated with local lymph node metastasis and was shown to be a prognostic factor predicting distant metastasis and mortality in univariate analyses.

Thyroid hormones specifically bind to the membrane and nuclear receptors that activate various oncogenic pathways, resulting in the promotion of cell growth, inhibition of apoptosis, and stimulation of angiogenesis. Therefore, thyroid hormones can play a major role in carcinogenesis. Numerous studies indicate an association between increased risk of both solid organ and hematological malignancies and elevated thyroid hormone levels and/or suppressed TSH levels (2-4).

In a study performed with 158 patients with various types of cancer and 100 healthy controls, no statistically significant difference was observed between the groups in terms of the prevalence of thyroid dysfunction (16% and 14%, respectively; p: 0.51). However, the authors reported that thyroid dysfunctions are usually overlooked in cancer patients (25). In their prospective study with more than ten thousand participants, Khan et al. (26) found that elevated FT4 levels were associated with a higher risk of solid organ malignancies, but this association was weaker when corrected for patients under thyroid medications. Still, the highest FT4 level was associated with 13% increase in the risk of solid organ malignancies compared to the lowest FT4 level. TSH level was not associated with the overall risk of cancer. In our study, we did not observe any difference in thyroid function tests between the malignant and benign groups.

Table 6. Logistic Regression Analysis on Predicting Distant Metastasis

	Univariate analysis					Multivariate analysis				
	B	OR	95% C.I. for EXP(B)		p	B	OR	95% C.I. for EXP(B)		p
			Lower	Upper				Lower	Upper	
Sex	.091	1.095	-	-	.809	-	-	-	-	-
Age	-.023	.977	3	94	.046	-.019	.981	-	-	.127
TSH	.029	1.030	.01	131.00	.658	-	-	-	-	-
FT4	-1.762	.172	.10	2.58	.008	-1.239	.290	-	-	.127
FT3	.229	1.257	.61	4.96	.391	-	-	-	-	-
FT3/FT4	.957	2.605	.79	6.10	.005	.434	1.544	-	-	.318
AntiTG	.009	1.009	1.71	3125.00	.317	-	-	-	-	-
AntiTPO	.010	1.010	5.08	515.10	.413	-	-	-	-	-
Primary Lesion SUVmax	.009	1.009	1.20	91.17	.598	-	-	-	-	-
Highest SUVmax	-.012	.988	1.20	91.17	.458	-	-	-	-	-

TSH: Thyrotropin, FT4:Free Thyroxin, FT3:Free Triiodothyronine, AntiTG:Anti-Thyroglobulin, AntiTPO:Anti-Thyroid Peroxidase, SUVmax: Maximum Standardized Uptake Value

Table 7. Logistic Regression Analysis on Mortality

	Univariate analysis					Multivariate analysis				
	B	OR	95% C.I. for EXP(B)		p	B	OR	95% C.I. for EXP(B)		p
			Lower	Upper				Lower	Upper	
Sex	.160	1.174	-	-	.748		-	-	-	-
Age	-.054	.947	3	94	.004	-.052	.949	-	-	.018
TSH	.024	1.025	.01	131.00	.772	-	-	-	-	-
FT4	-1.501	.223	.10	2.58	.042	-1.189	.304	-	-	.262
FT3	.359	1.432	.61	4.96	.328	-	-	-	-	-
FT3/FT4	1.379	3.970	.79	6.10	.006	.658	1.931	-	-	.300
AntiTG	.010	1.010	1.71	3125.00	.567	-	-	-	-	-
AntiTPO	.003	1.003	5.08	515.10	.666	-	-	-	-	-
Primary Lesion SUVmax	-.018	.982	1.20	91.17	.295	-	-	-	-	-
Highest SUVmax	-.016	.985	1.20	91.17	.397	-	-	-	-	-

TSH: Thyrotropin, FT4: Free Thyroxin, FT3: Free Triiodothyronine, AntiTG: Anti-Thyroglobulin, AntiTPO: Anti-Thyroid Peroxidase, SUVmax: Maximum Standardized Uptake Value, OR: Odds Ratio, CI: Confidence Interval

Among the various values determined with 18F-FDG PET/CT, the most widely used parameter is SUVmax, which measures the metabolic rate of glucose uptake by tumor cells. Recent systematic reviews and meta-analyses have shown that SUVmax can be used as a prognostic factor in numerous malignancies (20-23). Increased SUVmax is associated with aggressive tumor behavior and patients with higher SUVmax have a higher risk of recurrence and progression (27). Therefore, aggressive treatments are more effective in patients with higher SUVmax and are associated with progression free survival (PFS) and/or overall survival (OS) advantage. Tumor size and the number of metastatic lymph nodes are well-defined prognostic factors in various types of cancer as they are closely related to distant metastasis and progression (28). However, there is no study in the literature about how SUVmax and the highest SUVmax, which are PET/CT parameters, and thyroid parameters are related. In the current study, SUVmax and the highest SUVmax had no significant correlation with thyroid function tests.

In their study evaluating the relationship of suppressed TSH levels and mortality, Ittermann et al. (29) failed to show a significant association between low serum TSH levels and cancer mortality. Similarly, Zhang et al. (30) observed no association between thyroid hormone levels within the reference range and mortality. In concordance with the above-mentioned studies, we found no statistically significant association between TSH levels and tumor extent and mortality.

The effect or ineffectiveness of thyroid hormones on tumor progression and the efficacy of systemic anticancer therapies has been previously described but has not yet been clearly demonstrated or thoroughly understood. The association between worse survival and decreased FT3 levels, also named as low T3 syndrome, is documented in a variety of clinical scenarios (31,32). The mortality rate of critical patients with distinct alterations in serum thyroid parameters is significantly increased. Also, preclinical experiences point to an association between low serum FT3 levels and mortality in the frail elderly (33,34). In their study on the association of thyroid hormone levels within the reference range with mortality, Zhang et al. (30) found that FT3 levels were negatively correlated with cancer mortality. In another study on patients with lung cancer, 33% of patients demonstrated abnormalities in their thyroid function tests, and most of them had euthyroid sick syndrome (ESS) (a low T3 variant), indicating poorer prognosis (35). In our study, FT3 levels did not significantly predict mortality and were not associated with the extent of primary tumor.

Pinter et al. (36) reported consistent data indicating elevated FT4 levels to be a poor prognostic factor in patients with advanced hepatocellular carcinoma. On the other hand, some studies have shown a direct association between high FT4 levels and better physical performance or survival in elderly patients (34,37). In their before-mentioned study, Zhang et al. (30) did not observe any association between FT4 and mortality. The univariate analyses of the current study showed FT4 level to be a factor predicting distant metastasis and mortality.

Serum levels of the active forms of thyroid levels depend on the iodothyronine deiodinases, an enzyme family that can convert biological precursor T4 to active T3 (deiodinases 1 and 2) and inactive rT3 and T2 (deiodinase 3) (38, 39). Aside from their roles, the three deiodinases differ in their tissue of expression: D1 is expressed in liver and kidneys, while D2 is expressed in skeletal muscle cells where most of the T3 is produced. D3 is accepted as an inactivating enzyme and is vital for placental and fetal tissues (39). Chronic diseases, cachexia, hepatic or renal failure, and chronic systemic inflammation lower the activity of D1 and D2, but augment the activity of D3, causing decreased FT3 levels (40,41). These clinical scenarios are prevalent in cancer patients, especially in the terminal stage, and are typically associated with worse prognosis. Most of our patients had malignancy, some of them were being followed up in the intensive care unit due to chronic disease and malignancy. Therefore, changes in thyroid hormones may be affected by euthyroid sick syndrome.

Using FT3/FT4 ratio rather that the mean of two hormone levels can act as a more functional marker for peripheral deiodination activity and can even help classifying patients with normal FT3 levels (32). To date, limited data are available regarding the prognostic impact of thyroid hormone levels in patients with advanced cancer and the potential role of the FT3/FT4 ratio remains undiscovered (36,42,43). Two recently published studies have shown that low FT3/FT4 ratio better predicts OS and PFS in patients with metastatic colorectal cancer, independent of other prognostic factors (44,45).

Another recent study on hospitalized elderly patients with acute illnesses showed that peripheral thyroid hormone conversion dysfunctions evaluated by FT3/FT4 ratio is closely associated with frailty and survival, even if FT3 is within reference range (38). Low FT3/FT4 ratio is reported to be a strong prognostic factor for both PFS and PS in patients with metastatic renal cell carcinoma (46). In the current study, univariate analyses revealed the FT3/FT4 ratio to be a prognostic factor for both the extent of disease and mortality.

Aging is known to trigger functional and structural changes in the hypothalamic-pituitary-thyroid axes, causing ESS (47). Tellini et at. (48) investigated the

incidence of ESS in 220 geriatric patients hospitalized for cancer and observed that the risk of ESS is higher in elderly cancer patients with recent major weight loss and worse clinical conditions. The incidence of thyroid dysfunction in the normal population may vary depending on iodine deficiency, geographical differences, and ethnic factors. NHANES III, a wide population screening study, showed that subclinical and clinical hyperthyroidism and hypothyroidism potentially contributes to morbidity in especially the elderly in the US (49). Patients with malignant disorders have a higher risk of thyroid dysfunction than the normal population. Increasing age and lower performance score is also significantly associated with thyroid dysfunction (50). In our study age was both correlated with thyroid function tests and was a factor predicting the extent of disease in univariate analyses and an independent prognostic factor predicting mortality.

The limitations of our study include the limited number of patients and therefor the inability to group then according to tumor types, the numerical inequality in malignant and benign groups and the inability to follow-up patients for long term.

CONCLUSION

Thyroid function tests did not exhibit a significant difference between malignant and benign lesions. No statistically significant correlation was observed between thyroid function tests and PET/CT parameters. Univariate analyses revealed that especially FT4 and FT3/FT4 ratio were significant in predicting disease extent and mortality in malignant disease, while age was found to be an independent prognostic factor in predicting mortality. Even though further studies are needed, we recommend cancer patients with advanced age to have thyroid function test as a part of their first clinical screening.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of the Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.03.2020, Decision No: 736).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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