Can FDG-PET-CT Predict L.N. Capsular Invasion in Metastatic Nodes in Patients with Locoregional Recurrent Differentiated Thyroid Cancer?

Ahmed Mohamed Amer, MD; Sharif Ahmed Abdelkarim, MD; Hossam Mohamed Farid, MD
Department of Surgical Oncology, National Cancer Institute, Faculty of Medicine, Cairo University, Egypt

Introduction: To assess the ability of (PET-CT to detect L.N. affection with tumor in differentiated thyroid cancer, and to assess L.N. capsular invasion which may be an important factor for subsequent locoregional tumor recurrence.

Ain of work: The 2015 American Thyroid Association (ATA) guidelines state that 18 F-FDG PET-CT is highly advised for the evaluation of therapy response, the identification of lesions in metastatic disease, and outcome prediction in high-risk patients who have elevated thyroglobulin levels and negative whole-body iodine scans (I131). It is not advised as a standard pre-operative scan or for the assessment of thyroid nodules.[21]

Patients and methods: cross-sectional study included patients admitted to National cancer institute with recurrent well differtiated thyroid cancer (WDTC) aged between 35 and 70 years. The patients were diagnosed by elevated thyroglobulin (Tg) level, neck U.S., or C.T. Then FDG- PET CT was performed to assess regional recurrence and level of SUV nodal activity. Resection of recurrence was performed, and pathological results were obtained.

Results: in the 15 patients who did PET- CT it was able to detect nodal metastasis in all of the 15 patients, with all of them had pathologically proven nodal metastasis. 11 patients out of the 15showed nodal activity of 10 SUV or more, with three of them showed nodal activity of 10 or more in their second nodal metastasis. All patients with nodal activity of 10 SUV or more showed L.N.s capsular invasion with the tumor.

Conclusion: 18- FDG- PET CT may be an important tool for detection of locoregional WDTC recurrence, the diagnose of L. Ns affection and infiltration nodal capsule. It seemed that SUV activity was related more to tumor biology, activity, and the presence of tumor infiltration of L.N capsule. It seemed that SUV activity of 10 or more may be indicator of L.N. capsular invasion, and hence correlated with more incidence of recurrence.

Key words: Well differentiated thyroid cancer, diagnose, FDG-PET CT.

Introduction

Approximately 1.0 to 1.5% of all malignancies reported annually are thyroid cancers, making them the most prevalent endocrine tumours.[1] The most prevalent kind of thyroid cancer, differentiated thyroid carcinoma (DTC), often has a favourable prognosis with a 20% chance of recurrence.[2,3] Of them, aggressive tumours are less common and have a poorer prognosis and result.[3]

Histological subtypes of primary thyroid cancer are commonly used to classify the disease into common kinds, such as anaplastic carcinoma (ATC), follicular thyroid carcinoma (FTC), hurtle cell carcinoma, medullary carcinoma (MTC), and papillary thyroid carcinoma (PTC). Anaplastic carcinoma is known as undifferentiated cancer, while papillary and follicular thyroid carcinoma are categorised as well-differentiated thyroid cancers (DTCs). Each of these types of thyroid cancer exhibits unique biology and clinical characteristics.[4]

With 97% and 94% disease-specific 10-year survival rates for papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), respectively, patients with differentiated thyroid cancers (DTCs) have good prognoses.[5,6] Hurtle cell and medullary thyroid cancer patients, on the other hand, had far lower survival and recurrence rates, with 73% 10-year survival rates for each.[7] With a 1-year survival rate of less than 20% and a median survival length of 5 months, anaplastic thyroid carcinoma (ATC) has extremely poor results.[8,9]

Surgery and radioactive iodine ablation are the usual treatments for well-differentiated thyroid cancer, with the exception of tumours that are smaller than 1 cm and do not have risk factors. Despite having a good prognosis, well-differentiated thyroid carcinoma requires regular clinical monitoring since the probability of recurrence is around 10–35% [10,11]

Neck ultrasonography, thyroglobulin antibody levels (Tg-Ab), and thyroglobulin levels (Tg) are routinely measured in individuals with differentiated thyroid carcinoma (DTC). Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), which may assist provide crucial anatomical linkages and information regarding the thyroid gland and surrounding structures, are two further imaging modalities that may aid in the work-up and diagnosis of thyroid cancer.[12] Patients with chronic illness who are at high or moderate risk are frequently screened with the 123I/131I whole body scan.[13,14]

Undifferentiated thyroid cancer cells have a decreased avidity and capacity to capture radioiodine, despite the fact that most tumour cells in well-differentiated thyroid cancer can retain iodine. Additionally, due of the change of tumour cells into less differentiated cells, differentiated thyroid carcinoma (DTC) may lose its capacity to concentrate (131I) in metastatic illness. The therapy of these patients remains difficult since whole body scans may have low sensitivity in these individuals, yielding negative findings in 10–15% of cases.[15]

The treatment of cancer patients has evolved

DOI: 10.21608/asjs.2025.387515.1204

since Positron Emission Tomography/Computerized Tomography (PET/CT) was first used in clinical settings as an imaging and diagnostic tool.[16] 2. Because less differentiated cells overexpress regulating glycolytic enzymes and transporters, [18F]-fluoro-2-deoxy-d-glucose (FDG) has been confirmed as a marker of cell metabolism.[17,19]

The development and application of 18F-FDG PET-CT as a crucial tool for the treatment of patients with differentiated thyroid cancer (DTC) was initially documented in 1987, and aggressive tumours have shown a higher uptake of this technique.[20]

The 2015 American Thyroid Association (ATA) guidelines state that 18 F-FDG PET-CT is highly advised for the evaluation of therapy response, the identification of lesions in metastatic disease, and outcome prediction in high-risk patients who have elevated thyroglobulin levels and negative whole-body iodine scans (I131). It is not advised as a standard pre-operative scan or for the assessment of thyroid nodules.[21]

Although distant metastasis has been very uncommon, occurring in around 4–27% of cases, recurrent illness typically presents as local recurrence or neck lymph node metastases.[10]

After surgical radioactive iodine ablation, an elevated thyroglobulin level might indicate a chronic or recurring illness. In patients with differentiated papillary thyroid carcinoma, radioactive iodine has a 99% specificity rate for detecting recurrence and metastatic disease,[22] however, in patients with recurrent or metastatic disease, negative findings have been observed in around 30–50% of cases. Patients with tiny or poorly differentiated tumours may have a negative radioiodine scan.[23]

Although other prior studies showed varying levels of thyroglobulin (Tg) ranging between 2-30ng/ml,[12,22,25,26] as well as the role of thyroglobulin antibodies (Tg Ab), which may lead to difficulties in interpreting Tg levels,[12] F-18 FDG-PET-CT may be clinically useful in detecting locoregional lymph node or distant metastasis in patients with thyroid stimulating hormone (TSH) stimulated Tg levels higher than 10ng/ml following radioiodine therapy .[12]

This study aimed to evaluate the role of F-18 FDG-PET/CT in the diagnosis and treatment of patients with recurrent well-differentiated thyroid cancer. It also evaluated the ability of FDG- PET CT to detect nodal affection and L.N. capsular invasion with tumor, which may be a sign of a high risk of recurrences and necessitate more aggressive treatment, closer monitoring, or a change in treatment regimens for these patients.

Patients and methods

Convenience sampling was used to choose participants for this cross-sectional study from the National Cancer Institute's inpatient surgery facilities in Egypt between June 2014 and June 2015. Every patient in the group had a recurrent well-differentiated thyroid cancer diagnosis (WDTC). The research comprised 15 patients, 7 of whom were male and 8 of whom were female, ranging in age from 35 to 70.

The patients were diagnosed with recurrent (WDTC) by elevated thyroglobulin level (Tg) and imaging either by neck U.S. or C.T, followed by FDG -PET -CT to assess regional recurrence (operative bed and nodal), and to assess level of SUV nodal activity.

A PET scan machine was employed. Prior to scanning, all patients were instructed to fast for six hours and to maintain a stringent blood glucose level (diabetic < 8.3 mmol/L, non-diabetic < 6.1 mmol/L). 14 FDG [4.4 MBq/kg] was given intravenously to the patients in amounts ranging from 270 to 370 MBq. Patients had to empty their bladders after 60 minutes and before scanning. The patient's feet and the basilar region were the collection ranges. It was a 16-slice helical C.T. scan machine. Coronal, sagittal, and cross-sectional CT, PET, and PET-CT fusion imaging were obtained by analysing the data using image fusion and interactive reconstruction.

Two radiologists independently evaluated the PET-CT imaging and determined the SUV activity of the questionable neck nodes. With the recurrent metastatic WDTC, an uptake value of 10 or above was standardised as a sign of L.N. capsular invasion.

Then Resection of recurrences with unilateral or bilateral modified radical neck dissection (MRND) with bilateral level VI dissection was performed to all patients, and pathological results of nodal status were obtained regarding pathological type and L.N. capsular invasion.

Results

The study was conducted on recurrent well differentiated thyroid cancer (WDTC) at National Cancer Institute. Neck US was used to detect first recurrence in 24 patients from 40 patients recruited to the study as shown in **Table 1**. Ultrasound detected mass in thyroid remnant in the majority of patients who had recurrence and 58.8% of lesions were less than 2 cm and detected enlarged lymph nodes with malignant features in 73.9% of patients.

During first recurrence of WDTC as shown in **Table 2**, 57.5% of patients had CT scan and it detected mass present in thyroid remnant or operative bed in 87% of patients and infiltration of surrounding tissue in 13% of cases, Distant metastases were found in 26.1% of patients. Enlarged lymph nodes with malignant features were present in 96.6% of patients who had CT scan.

Iodine 131 (I 131) was used to diagnose recurrence in 6 patients (15%). Local recurrence was found in 83.3% of them as demonstrated in **Table 3**.

PET-CT was used to detect recurrence in 15 patients (37.5%) as shown in **Table 4**. PET-CT was able to detect loco regional recurrence in 12 patients. Also, PET-CT was used to detect second recurrence in 6 patients and detected regional recurrence in 6 cases and one of them had also distant recurrence. Cutoff point for SUV was determined at 10. Median SUV of first recurrence was 11.4 while median of lymph node was 14.4 in first recurrence and 10 in second recurrence.

Validity of ultrasound, CT., I131 and PET-CT in detection of locoregional recurrence was assessed compared to recurrence confirmed by histopathology and results are demonstrated in **Table 5**. Sensitivity was 100% in ultrasound, I131 and PET-CT in first recurrence. Specificity was low in CT to detect loco-regional recurrence while sensitivity was high (92.3%). Overall diagnostic accuracy was the highest in CT (90%). Validity wasn't assessed for PET-CT in second nodal recurrence due to low number of cases as it was assessed in patients with available SUV values.

Validity was assessed in US, CT and PET-CT in detection of lymph nodes recurrence in comparison to histopathology in **Table 6**. Sensitivity was high in US (80%) while specificity was 50%. While specificity was high in CT and SUV of second recurrence (100%). Validity of SUV detection of first nodal recurrence couldn't be assessed as all nodes detected by PET-CT was found to be affected in pathology. Overall diagnostic accuracy was the highest in CT (78.3%) followed by ultrasound (77.3%).

All patients with suspicious recurrent nodes had undergone neck dissection guided by the imaging done. In the 15 patients who did FDG-PET/CT, 10 patients undergone bilateral modified radical neck dissection (BMRND), including bilateral level VI (66.7%), 4 patients unilateral modified radical neck dissection with bilateral level VI dissection (26,6%), and one patient had undergone resection of operative bed recurrence (6,6%).

As shown in **Table 7**, four patient with nodal activity of 10 or more SUV showed L.N capsular invasion with the tumor and 2 patients with SUV less than 10 showed capsular invasion. One patient with nodal recurrences with SUV < 10 showed no L.N Capsular invasion with tumor in first recurrence. All patients with SUV were all with papillary classic pathology. 4 patients of the 5 with nodal activity 10 or more in first recurrence were females (80%), and one was a male (20%). All patients were 45 years or less (100%). Three patients with nodal activity less than 10 SUV were females (100%), two with age less than 45y. and the other one with age more than 45y.

In **Table 8**, from the 6 patients with second recurrence, three patients out of the four with SUV more than 10 showed L.N. Capsular invasion, and two patients out of two with SUV less than 10 (Between 5-9) showed L.N capsular invasion. From the 4 patients with SUV more than 10, three were female (75%), three were 45y or less (75%), three were with classic papillary pathology (75%) and one papillary collumnar pathology (25%). The two patients with SUV less than 10 were cemales, less than 45y, with one with classic papillary, and one with hurtle cell pathology.

Table 1: Neck ultrasound in first recurrence of WDTC

Factors		N (%)
Neck US (n=40)	Done	24 (60)
	Not done	16 (40)
Mass present in thyroid remnant or operative bed (n=23)	present	17 (73.9)
	absent	6 (26.1)
Size of recurrent lesion by US (n=17)	≤ 2 cm	10 (58.8)
	> 2cm	7 (41.2)
Enlarged lymph nodes with malignant features by US (n=23)	Present	17 (73.9)
	absent	6 (26.1)
Size of enlarged nodes (n=17)	≤ 1 cm	3 (17.6)
	> 1 cm	14 (82.4)

Table 2: CT in first recurrence of WDTC

Factors		N (%)
CT (n=40)	**Done**	23 (57.5)
	Not done	17 (42.5)
Mass present in thyroid remnant or operative bed (n=23)	present	20 (87.0)
	absent	3 (13.0)
Infiltration of surrounding tissue (n=23)	Yes	3 (13.0)
	No	20 (87.0)
Size of recurrent lesion by CT (n=20)	≤ 2 cm	6 (30.0)
	> 2cm	14 (70.0)
Presence of distant metastasis by CT (n=23)	yes	6 (26.1)
	no	17 (73.9)
Enlarged lymph nodes with malignant features by CT (n=23)	Present	16 (96.6)
	absent	7 (30.4)
Size of enlarged nodes (n=15)	≤ 1 cm	1 (6.7)
	> 1 cm	14 (93.3)

Table 3: I 131 in recurrence of WDTC

Factors		N (%)
I 131 (n=40)	Done	6 (15.0)
	Not done	34 (85.0)
Local recurrence in operative bed by I 131 (n=6)	yes	5 (83.3)
	no	1 (16.7)
Presence of distant metastasis by I 131 (n=6)	yes	0 (0.0)
	no	6 (100.0)

Table 4: PET.CT in recurrence of WDTC

Factors		N (%)
PET.CT (n=40)	Done	15 (37.5)
	Not done	25 (62.5)
Regional recurrence detected by PET-CT (n=13)	present	12 (92.3)
	absent	1 (7.7)
SUV of regional recurrence by PET-CT (n=8)	≤ 10	3 (37.5)
	> 10	5 (62.5)
SUV of regional recurrence by PET- CT(n=8)	Median (range)	11.4 (3.6-46.0)
SUV of lymph nodes by PET-CT (n=8)	≤ 10	3 (37.5)
	> 10	5 (62.5)
SUV of lymph nodes by PET-CT (n=8)	Median (range)	14.4 (1.8-30.0)
Site of second recurrence by PET-CT (n=15)	regional	5 (33.3)
	Reginal &distant	1 (6.7)
	Not done	9 (60.0)
SUV of second regional recurrence by PET-CT (n=2)	≤ 10	2 (100.0)
	> 10	0 (0.0)
SUV of second regional recurrence by PET-CT (n=2)	Median (range)	4.5 (3.9-5.0)
SUV of second nodal recurrence (N=6)	≤ 10	4 (66.7)
	> 10	2 (33.3)
SUV of second nodal recurrence (N=6)	Median (range)	10.0 (2.9-69.0)

Table 5: Validity of US, CT, I 131 in detection of recurrent loco regional tissue lesions

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall diagnostic accuracy (%)
Ultrasound (n=23)	100.0	46.2	58.8	100.0	69.6
CT (n=23)	92.3	20.0	60.0	66.7	90.0
I 131 (n=6)	100.0	50.0	80.0	100.0	83.3
PETCT in first recurrence (n=13)	100.0	14.3	50.0	50.0	53.8
SUV in first recurrence (n=8)	50.0	0.0	60.0	0.0	37.5

Table 6: Validity of US, CT in detection of lymph nodes

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall diagnostic accuracy (%)
Ultrasound (N=22)	80.0	50.0	94.1	20.0	77.3
CT (N=23)	76.2	100.0	100.0	28.6	78.3
SUV in second recurrence (n=6)	40.0	100.0	100.0	25.0	50.0

Table 7: SUV nodal first recurrence in relation to patients' characteristics

Factors		≤10 N =3	>10 N=5	P value
Sex	Male	0 (0)	1 (20)	NA
	Female	3 (100)	4 (80)	
Age	≤45	2 (66.6)	0(0)	NA
	> 45	1 (33.3)	5 (100)	
Pathology	Papillary classic	3 (100)	5 (100)	NA
L.N capsular invasion	Yes	2 (66.6)	4 (80)	NA
	No	1 (33.3)	1 (20)	

Table 8: SUV nodal second recurrence in relation to patients' characteristics

Factors		≤10 N =2	>10 N=4	P value
Sex	Male	0 (0.0)	1 (25.0)	NA
	Female	2 (100.0)	3 (75.0)	
Age	≤45	0 (0.0)	1 (25.0)	NA
	> 45	2 (100.0)	3 (75.0)	
Pathology	Papillary classic	1 (50.0)	3 (75.0)	NA
	Papillary columnar	0 (0.0)	1 (25.0)	
	Follicular (Hurtle)	1 (50.0)	0 (0.0)	
L.N affection	Yes	2 (100.0)	3 (75.0)	
	No	0 (0.0)	1 (25.0)	
L.N capsular invasion (n=6)	Yes	2 (100.0)	3 (75)	NA
	No	0 (0.0)	1 (25)	

Discussion

A tomographic technique called PET imaging makes it possible to quantitatively evaluate functional and metabolic processes without causing any harm. This method employs a ring detector device that uses a radionuclide that emits positrons to identify coincidences. Numerous positron-emitting radionuclides are used in PET imaging, and as many of them have short half-lives, a costly cyclotron manufacturing plant must be located nearby. Due to their comparatively lengthy half-lives, which enable them to be transported from the manufacturing plant to the imaging location, 18F (half-life 110 minutes) and 124I (half-life 4.2 days) are the most often used PET radiopharmaceuticals.[27]

Compared to using either modality alone, combining PET and CT in one unit offers a number of benefits, including as more precise localisation and characterisation of vague lesions with indefinite criteria.Additionally the incorporation of CT results in the performance of attenuation correction, which is required for the evaluation of certain regions, such as the chest, neck, and brain. Additionally, standardised uptake values (SUV) and other quantitative measurements of tracer uptakes are provided by PET/CT.[27]

The most widely used radiotracer in oncologic imaging for staging and assessing the response to treatment in a variety of tumours is the glucose analogue 18F-FDG.[28,29] Since it cannot be converted to FDG 6 phosphate, it is taken up by glucose transporters (GLUT) and represents both normal and aberrant metabolic activity as well as the identification of tumour cells. Lesions with poor radioiodine uptake and high 18F-FDG uptake have been shown to behave more aggressively in individuals with well-differentiated thyroid carcinoma.[30,31]

Determining an appropriate therapy strategy and surgical extent for patients with well-differentiated thyroid carcinoma (DTC) requires preoperative staging and assessment of the main tumour and nodal involvement. Ultrasound, CT, and MRI are traditional imaging modalities utilised in thyroid cancer work-ups. These techniques can yield crucial anatomical details about the thyroid gland and its relationships to surrounding tissues.[32]

Ultrasound is accessible, simple to use, free of ionising radiation, helpful for tiny needle biopsies, and can identify worrisome thyroid nodules with an accuracy of up to 85% (33). Its drawbacks, however, include operator reliance, restricted assessment of the posterior mediastinal and retrosternal areas, and poor localisation of cervical metastases, particularly in the central compartment.[34] The American Thyroid Association (ATA) states that ultrasonography is advised for the preoperative assessment of the neck nodes and contralateral lobe.[35]

When working up more advanced thyroid cancer, CT and MRI are helpful because they provide information about the tumor's extension and relationship to the surrounding and L.N. affection. The sensitivity of C.T. for identifying cervical metastases ranges from 80 to 90.6%.[36]

By contrasting their findings with pathological specimens, Choi et al. assessed the diagnostic accuracy of U.S., CT, and the combination of both in assessing cervical nodal affection in well-differentiated thyroid carcinoma. When it came to identifying nodal metastases in levels II–V, ultrasound and CT showed a higher sensitivity than CT alone (95.9% vs. 81.7%; n=53, p=0,025); nevertheless, when it came to identifying nodal metastases in level VI, CT was more sensitive than ultrasound (66.7% vs. 53.2%; p=0.04).[37]

The benefit to risk ratio should be reviewed among the treating team since the use of iodinated contrast material can postpone the administration of postoperative radioactive iodine, which is one of the limits of CT scans in the treatment of thyroid cancer patients.[37]

Since gadolinium-based contrast agents may be administered without interfering with the delivery of radioiodine, MRI might be an additional imaging option. A benefit of MRI over CT is its superior tissue contrast and radiation-free nature. However, the signal characteristics are non-specific and the MRI durations are prolonged.[38]

Most patients with recurrences in this research had masses found in their operation beds or thyroid remnants by ultrasound, which also found lymph nodes. A CT scan was performed on 57.5% of patients, and in 87% of cases, it found a tumour in the surgical bed or thyroid remnant. 96.6% of patients with CT scans exhibited enlarged lymph nodes with malignant characteristics. Six individuals (15%) were diagnosed with recurrence using iodine 131 (I 131). 15 patients (37.5%) had recurrences found with PET-CT.

In the first recurrence, the sensitivity of PET-CT, I-131, and ultrasonography was 100%. The sensitivity of CT to detect loco-regional recurrence was high (92.3%), while the specificity was poor. CT had the best overall diagnosis accuracy at 90%.

Sensitivity in detection of lymph nodes was high in US (80%) while specificity was 50%. While specificity was high in CT and SUV of second recurrence (100%).

Several studies have evaluated the role of FDG PET-CT in the diagnose and management of recurrent and metastatic thyroid cancer, and have been published, and meta-analysis of such studies have been performed.

FDG PET-CT had a high sensitivity of 93.5% in identifying metastasis and recurrence in thyroid cancer in the absence of radioiodine uptake, according to Dong et al.'s evaluation of 25 studies including 789 patients.[39]

After examining 12 investigations, Mill et al. also discovered that FDG PET-CT showed a 94% sensitivity for identifying recurrence in thyroid carcinoma that was well-differentiated.[40]

About 57% of patients had recurrent or metastatic thyroid illness that could be identified by ultrasonography, according to Weber et al..[41]

Seo and associates. reported that in 21.1% of patients with thyroid cancer, PET-CT tests were able to identify the involvement of the lymph nodes and the presence of metastatic disease, something that ultrasound investigations were unable to do.[42]

Although a significant correlation was not found between level of SUV activity and L.N capsular invasion in our study, however, it seemed that SUV activity of 10 or more may be indicator of L.N. capsular invasion, and hence correlated with more incidence of recurrence. A larger sample size may be needed to verify this note, and to verify whether SUV activity of PET- CT may be used as a predictor factor for recurrence.

It has been shown that aggressive illness and a poor prognosis are linked to FDG uptake.[43] Positive FDG PET shows a strong negative prognostic value for average all survival ($p<0.001$), according to Robbins et al.,[44] SUV max, or maximum standardised uptake value, has also been demonstrated to be a major predictive factor.

In comparison to other imaging modalities, several investigations have demonstrated the comparatively high sensitivity of FDG PET for hurtle cell cancer on Talat ion. According to Rieman et al.'s multicenter investigation, FDG PET had a 92% sensitivity and a 95% specificity in hurtle cell carcinoma, while the comparable values for an I-131 whole body scan were 65% and 94%, and for an ultrasound, they were 37% and 94% (n=327).[45]

Also, Vurel et al. has observed higher positivity of PET CT in patients older than 40 years compared with younger patients (70% vs 53%).[46]

Conclusion

FDG- PET/CT is considered now an important tool in diagnosis and management of patients with well differentiated thyroid cancer, especially in the initial evaluation in patient with intermediate to high-risk disease, and during follow up in patient with elevated serum thyroglobulin level and negative whole body radioiodine scan.

FDG PET/CT may play an important role in detecting neck nodes affection with metastatic thyroid cancer, and may have a prognostic value in detecting patients with high incidence of recurrence, according to SUV max which may indicate L.N.s capsular invasion. According, FDG- PET/CT may focus on such group of patients with high incidence of recurrence to adopt modified or more aggressive plan of treatment to prevent or delay recurrence of disease.

References

1. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al: Cancer incidence in five continents, Volume IX. IARC Press, *International Agency for Research on Cancer.* 2007.
2. Eustatia-Rutten CF, Corssmit EP, Biermasz NR, Pereira AM, Romijn JA, Smit JW: Survival and death causes in differentiated thyroid carcinoma. *The Journal of Clinical Endocrinology & Metabolism.* 2006; 91(1): 313-319.
3. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al: Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: Using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid.* 2010; 20(12): 1341-1349.
4. Nix P, Nicolaides A, Coatesworth AP: Thyroid cancer review 2: Management of differentiated thyroid cancers. *International Journal of Clinical Practice.* 2005; 59(12): 1459-1463.
5. Davies L, Welch HG: Thyroid cancer survival in the United States: Observational data from 1973 to 2005. *Archives of Otolaryngology–Head & Neck Surgery*. 2010; 136(5): 440-444.
6. Yu XM, Schneider DF, Leverson G, Chen H, Sippel RS: Follicular variant of papillary thyroid carcinoma is a unique clinical entity: A population-based study of 10,740 cases. *Thyroid.* 2013; 23(10): 1263-1268.
7. Goffredo P, Roman SA, Sosa JA: Hurthle cell carcinoma: A population-level analysis of 3311 patients. *Cancer.* 2013; 119(3): 504-511.
8. Chen J, Tward JD, Shrieve DC, Hitchcock YJ: Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: Analysis of the surveillance, epidemiology, and end results 1983–2002. *American Journal of Clinical Oncology.* 2008; 31(5): 460-464.
9. O'Neill JP, Shaha AR: Anaplastic thyroid cancer. *Oral Oncology.* 2013; 49(7): 702-706.
10. Bertagna F, Bosio G, Biasiotto G, Rodella C, Puta E, Gabanelli S, Alavi A: F-18 FDG-PET/CT evaluation of patients with differentiated thyroid

cancer with negative I-131 total body scan and high thyroglobulin level. ***Clinical Nuclear Medicine***. 2009; 34(11): 756-761.

11. Smooke-Praw S Ro K, Levin O, Ituarte PH, Harari A, Yeh MW: Thyroglobulin antibody levels do not predict disease status in papillary thyroid cancer. ***Clinical Endocrinology.*** 2014; 81(2): 271-275.
12. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Tuttle RM: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer. ***Thyroid***. 2009; 19(11): 1167-1214.
13. Mazzaferri EL, Kloos RT: Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation?. ***The Journal of Clinical Endocrinology & Metabolism***. 2002; 87(4): 1490-1498.
14. Jeon MJ, Kim WG, Park WR, Han JM, Kim TY, Song DE, Kim WB: Modified dynamic risk stratification for predicting recurrence using the response to initial therapy in patients with differentiated thyroid carcinoma. ***European Journal of Endocrinology.*** 2014; 170(1): 23-30.
15. Heston TF, Wahl RL: Molecular imaging in thyroid cancer. ***Cancer Imaging.*** 2010; 10(1): 1.
16. Townsend DW: Dual-modality imaging: Combining anatomy and function. ***Journal of Nuclear Medicine.*** 2008; 49(6): 938-955.
17. Vander Heiden MG, Cantley LC, Thompson CB: Understanding the Warburg effect: The metabolic requirements of cell proliferation. ***Science.*** 2009; 324(5930): 1029-1033.
18. Grabellus F, Nagarajah J, Bockisch A, Schmid KW., Sheu SY: Glucose transporter 1 expression, tumor proliferation, and iodine/glucose uptake in thyroid cancer with emphasis on poorly differentiated thyroid carcinoma. ***Clinical Nuclear Medicine.*** 2012; 37(2): 121-127.
19. Schönberger J, Rüschoff J, Grimm D, Marienhagen J, Rümmele P, Meyringer R, et al: Glucose transporter 1 gene expression is related to thyroid neoplasms with an unfavorable prognosis: An immunohistochemical study. ***Thyroid***; 2002; 12(9): 747-754.
20. Joensuu H, Ahonen A: Carcinoma with fluorine-18. ***J Nucl Med***. 1987; 28(910â): 910-914.
21. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel S J, Nikiforov YE, Wartofsky L: 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. ***Thyroid.*** 2016; 26(1): 1-133.
22. Schlüter B, Bohuslavizki KH, Beyer W, Plotkin M, Buchert R, Clausen M: Impact of FDG PET on patients with differentiated thyroid cancer who present with elevated thyroglobulin and negative 131I scan. ***Journal of Nuclear Medicine***. 2001; 42(1): 71-76.
23. Lubin E, Mechlis-Frish S, Zatz S, Shimoni A, Segal K, Avraham A, Levy R, Feinmesser R: Serum thyroglobulin and iodine-131 whole-body scan in the diagnosis and assessment of treatment for metastatic differentiated thyroid carcinoma. ***Journal of Nuclear Medicine.*** 1994; 35(2): 257-262.
24. Abraham T, Schöder H: Thyroid cancer-indications and opportunities for positron emission tomography/computed tomography imaging. In: Seminars in nuclear medicine, ***WB Saunders.*** 2011; 41(2): 121-138.
25. Ozkan E, Aras G, Kucuk NO: Correlation of 18F-FDG PET/CT findings with histopathological results in differentiated thyroid cancer patients who have increased thyroglobulin or antithyroglobulin antibody levels and negative 131I whole-body scan results. ***Clinical Nuclear Medicine.*** 2013; 38(5): 326-331.
26. Seo JH, Lee SW, Ahn BC Lee J:Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: Special emphasis on using 18F-FDG PET/CT. ***Clinical Endocrinology.*** 2010; 72(4): 558-563.
27. Wechalekar K, Sharma B, Cook G: PET/CT in oncology—a major advance. ***Clinical Radiology***. 2005; 60(11): 1143-1155.
28. Wartski M, Sauvanet A: 18F-FDG PET/CT in pancreatic adenocarcinoma: A role at initial imaging staging?. ***Diagnostic and Interventional Imaging.*** 2019; 100(12): 735-741.
29. Palmieri LJ, Coriat R: 18F-FDG PET/CT in pancreatic adenocarcinoma: On the edge of a paradigm shift?. ***Diagnostic and Interventional Imaging***. 2019; 100(12): 731-733.
30. Schlumberger MJ:Papillary and follicular thyroid carcinoma. ***New England Journal of Medicine***. 1998; 338(5): 297-306.

31. Kukulska A, Krajewska J, Kołosza Z, Cieślik E, Puch Z, Gubała E, et al: The role of FDG-PET in localization of recurrent lesions of differentiated thyroid cancer (DTC) in patients with asymptomatic hyperthyroglobulinemia in a real clinical practice. ***European Journal of Endocrinology***. 2016; 175(5): 379-385.

32. Loevner LA, Kaplan SL, Cunnane ME, Moonis G: Cross-sectional imaging of the thyroid gland. ***Neuroimaging Clinics of North America***. 2008; 18(3): 445-461.

33. Niu LJ, Hao YZ, Zhou CW: Zhonghua er bi yan hou tou jing wai ke za zhi, ***Chinese Journal of Otorhinolaryngology Head and Neck Surgery.*** 2006; 41(6): 415-418.

34. Blank W, Schuler A, Wild K, Braun B: Transthoracic sonography of the mediastinum. ***European Journal of Ultrasound***. 1996; 3(2): 179-190.

35. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Tuttle RM: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer. ***Thyroid***. 2009; 19(11): 1167-1214.

36. Küçük ÖN, Gültekin S.S, Aras G, Ibis E: Radioiodine whole-body scans, thyroglobulin levels, 99mTc-MIBI scans and computed tomography: Results in patients with lung metastases from differentiated thyroid cancer. ***Nuclear Medicine Communications***. 2006; 27(3): 261-266.

37. Choi JS, Kim J, Kwak JY, Kim MJ, Chang HS, Kim EK: Preoperative staging of papillary thyroid carcinoma: Comparison of ultrasound imaging and CT. ***American Journal of Roentgenology***. 2009; 193(3): 871-878.

38. Urhan M, Velioglu M, Rosenbaum J, Basu S, Alavi A: Imaging for the diagnosis of thyroid cancer. ***Expert Opinion on Medical Diagnostics***. 2009; 3(3): 237-249.

39. Dong MJ, Liu ZF, Zhao K, Ruan LX, Wang GL, Yang SY, Luo XG: Value of 18F-FDG-PET/PET-CT in differentiated thyroid carcinoma with radioiodine-negative whole-body scan: A meta-analysis. ***Nuclear Medicine Communications***. 2009; 30(8): 639-650.

40. Miller, ME, Chen Q, Elashoff D, Abemayor ESt, John M: Positron emission tomography and positron emission tomography-CT evaluation for recurrent papillary thyroid carcinoma: Meta-analysis and literature review. ***Head & Neck,*** 2011; 33(4): 562-565.

41. Weber T, Ohlhauser D, Hillenbrand A, Henne-Bruns, D, Reske SN, Luster M: Impact of FDG-PET computed tomography for surgery of recurrent or persistent differentiated thyroid carcinoma. ***Hormone and Metabolic Research,*** 2012; 44(12): 904-908.

42. Seo JH, Lee SW, Ahn BC, Lee J: Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: Special emphasis on using 18F-FDG PET/CT. ***Clinical Endocrinology***. 2010; 72(4): 558-563.

43. Schönberger J, Rüschoff J, Grimm D, Marienhagen J, Rümmele P, Meyringer R, Eilles C: Glucose transporter 1 gene expression is related to thyroid neoplasms with an unfavorable prognosis: An immunohistochemical study. ***Thyroid***. 2002; 12(9): 747-754.

44. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, Larson SM: Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F] fluoro-2-deoxy-D-glucose-positron emission tomography scanning. ***The Journal of Clinical Endocrinology & Metabolism***. 2006; 91(2): 498-505.

45. Riemann B, Uhrhan K, Dietlein M, Schmidt D, Kuwert T, Dorn R, Schober O: Diagnostic value and therapeutic impact of 18F-FDG-PET/CT in differentiated thyroid cancer. ***Nuklearmedizin-NuclearMedicine***. 2013; 52(01): 1-6.

46. Vural GU, Akkas BE, Ercakmak N, Basu S, Alavi A: Prognostic significance of FDG PET/CT on the follow-up of patients of differentiated thyroid carcinoma with negative 131I whole-body scan and elevated thyroglobulin levels: correlation with clinical and histopathologic characteristics and long-term follow-up data. ***Clinical Nuclear Medicine***. 2012; 37(10): 953-959.