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^{18}F-FDG PET/CT Can Predict Development of Thyroiditis due to Immunotherapy for Lung Cancer

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Abstract

Objective:

For patients undergoing immunotherapy with nivolumab for lung cancer, determine if increased ^{18}F-FDG uptake in the thyroid gland predicts development of thyroiditis with subsequent hypothyroidism. Secondarily, determine if ^{18}F-FDG uptake in the thyroid gland correlates with administered cycles of nivolumab.

Materials and Methods:

Retrospective chart review over 2 years found 18 lung cancer patients treated with nivolumab and with ^{18}F-FDG PET/CT scans pre- and during therapy. Standardized uptake value (SUV) mean and maximum and total lesion glycolysis (TLG) of the thyroid gland were measured. SUVs were also measured for the pituitary gland, liver and spleen. Patients obtained monthly thyroid testing. PET/CT parameters were analyzed by unpaired t-test for differences between two groups (patients who developed hypothyroidism and those who did not). Correlation between development of thyroiditis and number of cycles of nivolumab received was also tested.

Results:

Six of eighteen patients developed hypothyroidism. T-test comparing the two groups (patients who developed hypothyroidism and those who did not) demonstrated significant differences in SUV_{mean} ($p = 0.04$), SUV_{max} ($p = 0.04$) and TLG ($p = 0.02$) of the thyroid gland. Two of four patients who developed thyroiditis and had increased ^{18}F-FDG uptake in the thyroid gland, had normal TSH at time of follow-up ^{18}F-FDG PET/CT. Patients who developed thyroiditis with subsequent hypothyroidism stayed longer on therapy (10.6 cycles) compared to patients without

thyroiditis (7.6 cycles), but the trend was not statistically significant. No significant difference in PET/CT parameters was observed for pituitary gland, liver or spleen.

Conclusion:

^{18}F-FDG PET/CT can predict the development of thyroiditis with subsequent hypothyroidism before laboratory testing. Further study is required to confirm the positive trend between thyroiditis and duration of therapy.

Introduction

Immunotherapy agents, which target programmed cell death protein-1 or -2 and interrupt tumor induced immune tolerance, have improved outcomes for patients with a variety of malignancies (*1-4*). Programmed cell death protein-1 (PD-1) is expressed on the surface of T-cells and bind to PD-1 and PD-2 ligands. This intercellular protein interaction modulates T-cell activation, proliferation and cytokine production (*5,6*). The activated T-cells either kill tumor cells directly or indirectly by producing cytokines.

Nivolumab is an IgG4 PD-1 immune checkpoint inhibitor antibody that interrupts cancer induced immune tolerance by disrupting the interaction between PD-1 and PD ligands 1 and 2 (*7*). Nivolumab initially demonstrated longer progression-free survival as a first-line treatment in patients with metastatic or unresectable melanoma (*8,9*). Further studies demonstrated the efficacy of nivolumab as second-line therapy in the treatment of non-small cell lung cancer (*1,2, and 10*). The same mechanism used to reduce immune tolerance to tumors can trigger immune related adverse events (irAEs) in the form of various autoimmune syndromes (*11*). One of the most common endocrine side effects is thyroid dysfunction. Studies in different cancers reported that 8 to 22% of patients treated with nivolumab, developed thyroiditis and hypothyroidism (*11-13*). Given this frequency, detecting and treating thyroid dysfunction is critical in patients undergoing therapy with nivolumab and other checkpoint inhibitors. Hepatitis and hypophysitis are less common adverse events related to immunotherapy (*14-16*).

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) plays a paramount role in oncologic staging and monitoring of response to therapy. ^{18}F-FDG is a radioactive glucose analog that is injected intravenously and taken up into cells through

glucose transporters. The PET scanner maps the distribution of ^{18}F-FDG in the body and the simultaneous CT provides anatomic correlation (*17,18*).

Numerous ^{18}F-FDG PET/CT parameters such as the standardized uptake value (SUV) are used as imaging biomarkers to quantify the uptake of ^{18}F-FDG in malignant tissues as well as in inflammatory disorders (*19-22*). Hypothetically, activation of the immune system could result in increased ^{18}F-FDG activity in the spleen, and hypophysitis and hepatitis could show increased ^{18}F-FDG uptake from inflammation in the pituitary gland and liver, respectively. Therefore, increased ^{18}F-FDG uptake in these organs could potentially serve as markers for activation of the immune system by nivolumab. In this study, we evaluated this hypothesis by comparing the SUV parameters of these organs pre- and during therapy.

Inflammation of the thyroid gland associated with autoimmune thyroiditis can result in increased uptake of ^{18}F-FDG in the thyroid gland (*23,24*). We hypothesized that measuring ^{18}F-FDG uptake as a marker for inflammation in the thyroid gland may allow imaging to predict thyroid dysfunction before thyroid function tests become abnormal. Additionally, we evaluated the correlation between development of thyroiditis and greater duration of therapy with nivolumab.

Methods

Patient selection

This retrospective study was IRB approved by the institutional Human Subjects Protection Program. After approval by the United States Food and Drug Administration for use in advanced non-small-cell lung cancer (NSCLC) in October 2015, nivolumab was implemented into the

standard of care at our institution. A total of 382 patients with lung cancer were treated between October 2015 and February 2017. Of those 382, 25 patients with advanced NSCLC failed conventional treatment and received immunotherapy with nivolumab. Each cycle of therapy lasted four weeks and included two intravenous infusions of nivolumab at a standard dose of 240 mg over 60 minutes every two weeks. Serum thyroid stimulating hormone (TSH) was measured as standard of care approximately every month. Hypothyroidism was defined as TSH higher than upper limit of normal (normal institutional TSH range 0.35-4.0 μUL/ml). Of these 25 patients, 18 patients met the additional inclusion criteria of having received at least 2 cycles of therapy and ^{18}F-FDG PET/CT scans both before and during therapy. All 18 patients were followed until discontinuation of nivolumab for progression of disease or intolerable irAEs.

PET/CT scanning

A minimum of 4 hour fasting prior to the intravenous (IV) administration of ^{18}F-FDG was standard for all patients. Fingerstick blood glucose levels of the patients were measured before IV injection of ^{18}F-FDG at a weight-based dose of 3.7 MBq (0.1 mCi)/kg with a range from a minimum of 185 MBq (5 mCi) to maximum of 370 MBq (10 mCi). After injection of ^{18}F-FDG, the patients sat quietly awake for approximately 60 min. ^{18}F-FDG PET/CT was performed from vertex to the thigh using the General Electric 690 time-of-flight scanner. A matching low dose CT scan was obtained without IV contrast and with oral contrast before the PET acquisition. If possible, all patients were scanned with arms up. The acquisition time was 2.5 minutes per bed position, and seven to eight bed positions were obtained depending on the height of the patient. The PET data were reconstructed using an ordered-subsets expectation maximization algorithm (28 subsets, 2 iterations).

Analysis of PET/CT scans

The ^{18}F-FDG PET/CTs performed before and at 10-16 weeks after initiation of nivolumab were analyzed. Ten to sixteen weeks correlates approximately to 2-4 cycles of nivolumab therapy. The ^{18}F-FDG PET/CTs of these patients were analyzed for the ^{18}F-FDG uptake in the thyroid gland, pituitary gland, liver and spleen. The maximum standardized uptake value (SUV_{max}), mean standardized uptake value (SUV_{mean}), and total lesion glycolysis (TLG) were measured using ^{18}F-FDG PET/CTs software from Mirada XD version 3.6.5.28 (Oxford, UK). For measuring the TLG for the thyroid gland, a three-dimensional region of interest (ROI) was drawn around the larger lobe, since some patients had asymmetric glands with one lobe too small to accurately and reproducibly quantify. Activity in the thyroid gland greater than in the blood pool was deemed as increased visually. For the pituitary gland, a region of interest was drawn to encompass the entire gland. For the liver and spleen, a 3-cm spherical region of interest was drawn in the center of the organ. Thresholding of the region of interests was performed as necessary for optimal contouring. The resultant SUV_{max}, SUV_{mean} and TLG values were recorded in a Microsoft Excel spreadsheet.

Statistical analysis

Patients were divided into two groups, patients who developed irAE thyroiditis (hypothyroidism) and those who did not. For the thyroid, liver, spleen and pituitary gland, PET/CT parameters pre- and during therapy were analyzed with an unpaired t-test to assess for significant differences between the two groups. Correlation analysis with z-tests for significance was used to assess the relationships among PET/CT parameters, development of irAE thyroiditis and number of cycles of nivolumab received.

Results:

18 patients with advanced NSCLC were treated with nivolumab between October 2015 and February 2017 and met the inclusion criteria for this study as described in the methods. The mean age of patients was 69 years (range 31-86). 11/18 patients (61%) were female. 14/18 (78%) presented with adenocarcinoma of the lung and 4/18 (22%) with squamous cell lung carcinoma. The average blood glucose measured before injection of ^{18}F-FDG was 99 mg/dl with a range from 64 to 180 mg/dl. The average uptake time of ^{18}F-FDG was 60 minutes with a range from 50 to 80 minutes.

Chart review of the monthly thyroid testing divided the patients into two groups: patients who developed immune-related thyroiditis with subsequent hypothyroidism (n=6) and those who did not (n=12). 16 of the 18 patients had normal TSH prior to initiation of the immunotherapy. Two patients had history of hypothyroidism prior to starting nivolumab and were already on thyroid hormone replacement; however, adding or removing these 2 patients did not affect overall statistical significance. Five of the six patients who developed hypothyroidism were female. The average onset of hypothyroidism was after 3 cycles (range 3-6 cycles) of nivolumab. The timing of serum TSH measurements was within 2 weeks before or after the ^{18}F-FDG PET/CT. Four out of six patients who developed hypothyroidism during the course of therapy had normal TSH at the time of follow-up ^{18}F-FDG PET/CT. For the 6 patients who developed irAE thyroiditis with subsequent hypothyroidism , the average serum TSH at the time of follow-up ^{18}F-FDG PET/CT was just slightly higher than the upper limit of normal at 4.31 μUL/ml with a range of 0.3-12.15 μUL/ml (normal range 0.35-4.0 μUL/ml). Two of four patients with irAE thyroiditis with subsequent hypothyroidism and increased ^{18}F-FDG uptake in the thyroid gland had normal TSH at time of follow-up ^{18}F-FDG PET/CT. For the two patients with elevated serum TSH at time of

follow-up ^{18}F-FDG PET/CT and increased ^{18}F-FDG uptake in the thyroid gland, the serum TSH average was 9.2 μUL/ml with range of 6.18-12.15 μUL/ml (Figure 1).

Average number of cycles of nivolumab received was 8.6 (range 2-20) with each cycle lasting 4 weeks. The patients who developed hypothyroidism stayed longer on therapy (10.6 cycles) compared to patients who had no immune related thyroid dysfunction (7.6 cycles) during the nivolumab treatment, but the trend was not statistically significant. Table 1 provides the characteristics of the study population.

Diffuse increase of ^{18}F-FDG uptake in the thyroid gland during the nivolumab therapy was seen visually in four of six patients who developed thyroiditis with subsequent hypothyroidism (Figure 2). Two out of six patients who developed immune related hypothyroidism by laboratory analysis demonstrated no increased ^{18}F-FDG uptake in the thyroid gland during the nivolumab therapy (Figure 3). Table 2 provides the SUV_{mean}, SUV_{max} and TLG for patients who developed hypothyroidism during the nivolumab therapy.

The baseline/pre-therapy ^{18}F-FDG PET/CT's showed no statistical difference between patients who developed irAE thyroiditis with subsequent hypothyroidism and those who did not for the parameters SUV_{mean} 0.28 (P = 0.23), SUV_{max} 0.28 (P = 0.28) and TLG 0.43 (P = 0.13). PET/CT during therapy showed statistically significant differences between the two groups for SUV_{mean} 0.77 (P = 0.04), SUV_{max} 0.96 (P = 0.04) and TLG 0.96 (P = 0.02). Table 3 displays the ^{18}F-FDG uptake parameters and statistical analysis.

Measurements of the pituitary gland pre-therapy and during therapy demonstrated no significant differences in SUV_{mean} (-0.10, P = 0.63) and SUV_{max} (-0.19, P = 0.33). The liver pre-therapy

and during therapy showed no significant differences in SUV_{mean} (-0.07, P = 0.57) and SUV_{max} (-0.33, P = 0.26). Similarly, the spleen displayed no significant differences in SUV_{mean} (-0.33, P = 0.86) and SUV_{max} (-0.43, P = 0.41) pre-therapy and during therapy. Review of the medical records revealed no evidence of autoimmune disorders of these organs.

Discussion:

To our knowledge, this is the first study evaluating ^{18}F-FDG PET/CT parameters of the thyroid gland, pituitary gland, liver and spleen in patients with advanced NSCLC before and during therapy with nivolumab. 33% (6/18) of patients developed thyroiditis with subsequent hypothyroidism during the immunotherapy, which is high compared to prior studies (*11,25*). The onset of hypothyroidism during therapy was between the 3rd and 6th cycles of therapy which was in-line with prior published studies (*25,26*). Like the study from Filette et al., most patients who developed hypothyroidism during the immunotherapy were female. Presumably, this finding is related to the higher prevalence of autoimmune thyroid disease in women (*27*).

^{18}F-FDG PET/CT is a critical imaging modality for staging and assessing response to therapy for lung cancer (*28-29*). Studies and case reports have demonstrated the use of ^{18}F-FDG PET/CT in monitoring of response after immunotherapy (*30-33*). The ability of ^{18}F-FDG PET/CT to detect the irAE thyroidits in melanoma patients treated with pembrolizumab was reported in a study from Filette et al. In our study, visually increased FDG uptake in the thyroid gland on the PET/CT during therapy was observed in four of six patients who developed hypothyroidism. The SUV_{max} of the thyroid gland in these four patients ranged from 2.4 to 4.5. Comparing the patients who developed irAE thyroiditis and those who did not, statistically significant differences in the parameters SUV_{mean}, SUV_{max} and TLG were demonstrated in the thyroid gland on the PET/CT

during therapy. Correlation with serum TSH checked monthly demonstrated normal TSH at time of follow-up ^{18}F-FDG PET/CT in 2 of 4 patients who had increased ^{18}F-FDG uptake in the thyroid gland and developed thyroiditis with subsequent hypothyroidism later while on therapy. Diffusely increased ^{18}F-FDG uptake is consistent with inflammation of the thyroid gland associated with autoimmune thyroiditis (*23*,*24*). This study demonstrated the ability of ^{18}F-FDG PET/CT to detect irAE thyroiditis before elevation of serum TSH. Therefore, detecting an increase in activity in the thyroid gland on ^{18}F-FDG PET/CT could alert the oncologist and patient to be more vigilant for signs or symptoms of hypothyroidism.

Hepatitis and hypophysitis are also adverse events related to immunotherapy (*14-16*). Hypothetically, activation of the immune system could result in increased ^{18}F-FDG activity in the spleen. Comparing the patients who developed irAE thyroiditis and those who did not, ^{18}F-FDG uptake in liver and spleen demonstrated no significant change. Likewise, no significant changes in ^{18}F-FDG uptake in the pituitary gland were seen. which also decreases the likelihood of secondary hypothyroidism due to hypophysitis due to immunotherapy.

One of the strengths of this study is the long duration of follow up. A potentially vital finding of this study is the trend that patients who developed irAE thyroiditis received more cycles of nivolumab therapy than patients without irAE thyroiditis. At our institution, patients are continued on nivolumab as long as disease is stable or improved and side effects are tolerable. The number of cycles of nivolumab that a patient received may be considered a surrogate for progression free survival.

The development of irAEs including thyroid dysfunction may be a marker for concomitant activation of the immune system against tumor. A similar correlation of good response with the

occurrence of irAEs was observed in patients with metastatic melanoma treated with immunotherapy (*34*). A limitation of our study was the relatively small sample size. While our study was statistically significant for the ability of ^{18}F-FDG PET/CT to predict development of irAE thyroiditis, larger number of patients would have been required to establish statistical significance for predicting response to nivolumab, and such a study is ongoing. If subsequently proven, ^{18}F-FDG PET/CT could potentially detect the irAE thyroiditis before blood testing and therefore act as an early predictor for good response to immunotherapy.

This study has limitations with regards to the assessment of thyroid status. Euthyroid state does not exclude the diagnosis of thyroiditis, since hypothyroidism is a relatively late consequence of thyroiditis. Since biopsy of the thyroid gland to evaluate for inflammation is impractical, grouping patients according to euthyroid or hypothyroid state by TSH is the most clinically relevant. When the patients stopped immunotherapy, the oncologist also stopped checking TSH levels. Therefore, the analysis would miss the unlikely scenario of a patient developing subclinical hypothyroidism after discontinuing immunotherapy.

Conclusion:

Since lung cancer patients treated with immunotherapy are staged and followed with ^{18}F-FDG PET/CT, standard of care use of this imaging could predict the development of the irAE thyroiditis before laboratory testing. Thus, oncologists and patients can be more vigilant for signs or symptoms of early hypothyroidism and initiate thyroid hormone replacement optimally. Further work is required to establish more strongly the predictive power of finding increased ^{18}F-FDG activity in the thyroid and progression free survival.

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Table 1: Overview of patient characteristics

		Total (n=18)	Thyroid irAE (n=6)	No Thyroid irAE (N=12)
Characteristic				
Age (years)	**Mean (range)**	69 (31-86)	65 (31-79)	72 (51-86)
Gender	**Female**	11 (61%)	5 (83%)	6 (50%)
	Male	7 (39%)	1 (17%)	6 (50%)
No. cycles of therapy	**Mean (range)**	8.6 (3-20)	10.6 (6-20)	7.6 (3-15)

irAE: immune related adverse event

Table 2: ^{18}F-FDG uptake in the thyroid gland in patients who developed thyroiditis

	Pre-Therapy			During Therapy			Differences		
No. Patient	**SUV_{mean}**	**SUV_{max}**	**TLG**	**SUV_{mean}**	**SUV_{max}**	**TLG**	**SUV_{mean}**	**SUV_{max}**	**TLG**
1	1.5	1.5	0.7	3.3	4.1	3.5	1.8	2.6	2.8
2	1.7	2.1	1.5	3.7	4.5	2.9	2	2.4	1.4
3	1.3	1.7	0.9	3.5	4.3	2.3	2.2	2.6	1.4
4	0.9	1.1	0.7	1.9	2.4	1.6	1	1.3	0.9
5	2.4	2.8	1.9	1.6	1.8	1.6	-0.8	-1	-0.3
6	2	2.2	0.2	1.6	1.8	0.3	-0.4	-0.4	0.1

SUV_{mean}: Mean standardized uptake value, $SUV_{max:\ Maximum}$ standardized uptake value, TLG: total lesion glycolysis.

Table 3: Comparison of thyroid ^{18}F-FDG uptake during therapy between groups that did or did not develop thyroiditis

	Thyroid irAE (n=6)	No Thyroid irAE (n=12)	
	Mean (SD)	**Mean (SD)**	**Difference (P-Value)**
SUV $_{mean}$	2.41 (1.04)	1.64 (0.44)	0.77 (0.04)
SUV $_{max}$	2.96 (1.28)	2.00 (0.5)	0.96 (0.038)
TLG	1.96 (1.05)	1.00 (0.47)	0.96 (0.016)

irAE: immune related adverse event, SUV: standardized uptake value. TLG: total lesion glycolysis. SD: standard deviation.

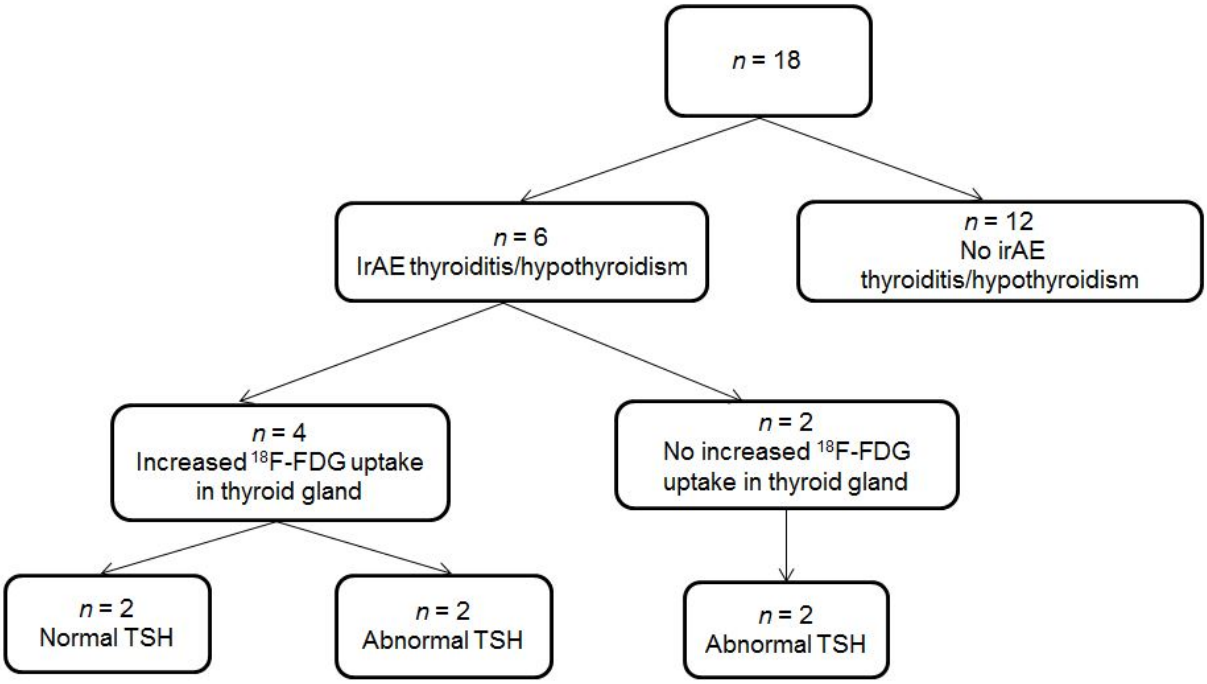

Figure 1: Flow chart showing the distribution of patients by development of thyroiditis, ^{18}F-FDG uptake in the thyroid gland, and value of TSH at time of PET/CT.

irAE: immune related adverse event

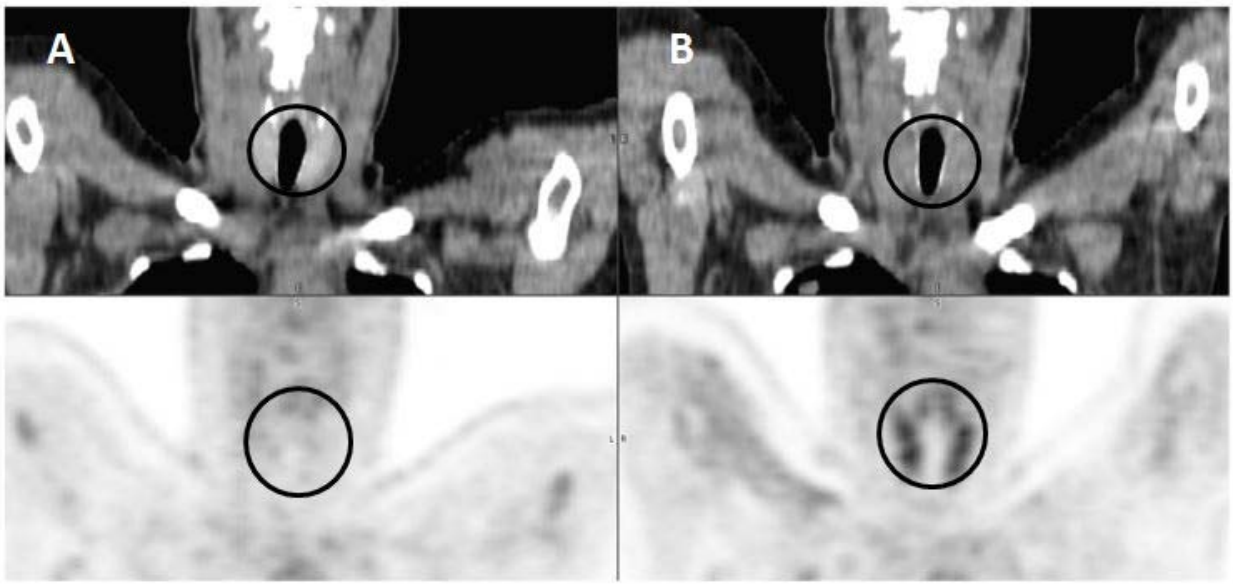

Figure 2: Patient with increased ^{18}F-FDG uptake in thyroid gland during nivolumab therapy. Coronal images from the pre-therapy (A), CT (top left) and ^{18}F-FDG PET (bottom left) displayed normal uptake in the thyroid gland with SUV_{max} =1.7 (A). Coronal images from the during therapy (B), CT (top right) and ^{18}F-FDG PET (bottom right) showed increased thyroid uptake with SUV_{max} =4.3. Black circle denotes the region of the thyroid gland.

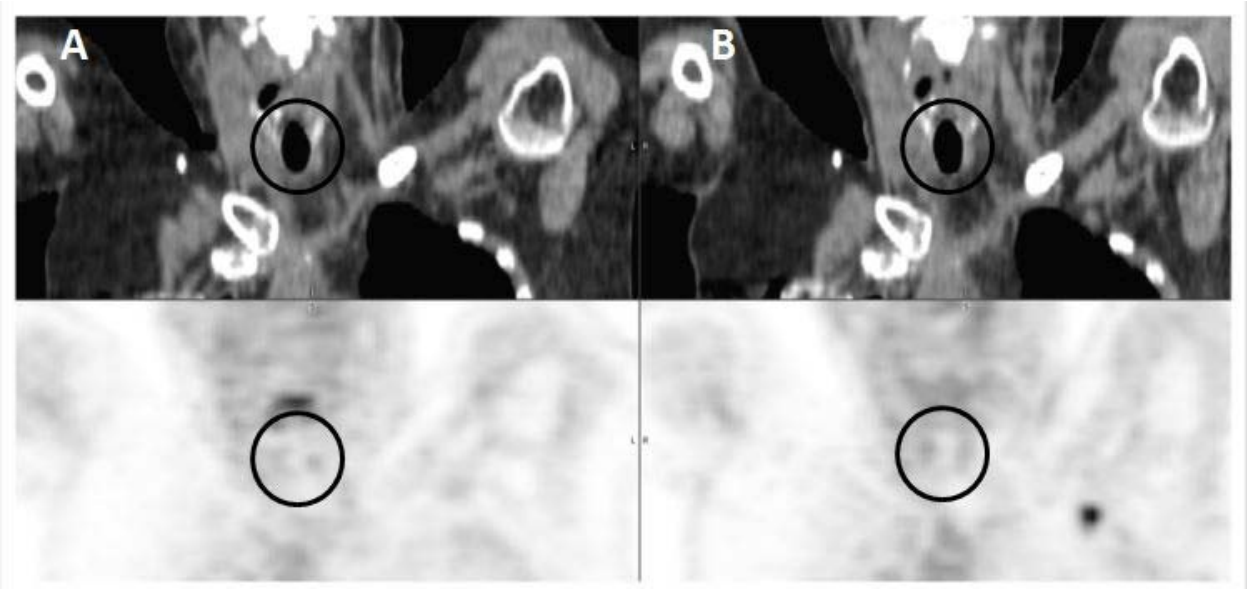

Figure 3: Patient with normal ^{18}F-FDG uptake in thyroid gland during nivolumab therapy. Coronal images from the pre-therapy (A), CT (top left) and ^{18}F-FDG PET (bottom left) displayed normal uptake in the thyroid gland with SUV_{max} =2.2. Coronal images from the during therapy (B), CT (top right) and ^{18}F-FDG PET (bottom right) showed increased thyroid uptake with SUV_{max} =1.8. Black circle denotes the region of the thyroid gland.