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Diagnostic Accuracy of Flourodeoxyglucose-18 Positron Emission Computed Tomography in the Evaluation of Recurrent Papillary Thyroid Carcinoma with Patients' Raised Thyroglobulin Level in Lahore

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ABSTRACT

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, typically associated with good prognosis and high survival rates if diagnosed on time. However, recurrence occurs in approximately 20-30% of cases, most often presenting as loco regional disease in the thyroid bed or cervical lymph nodes. Symptoms of recurrence may include a palpable neck mass, hoarseness caused by laryngeal nerve palsy or other causes. Dysphagia or cervical discomfort are not specific symptoms and many cases remain asymptomatic and are detected through surveillance. Risk factors for recurrence include lymph node metastasis, extra thyroidal extension, and aggressive histological variants. Detection involves serum thyroglobulin levels, and imaging studies. Several biomarkers like HBME-1, cytokeratin 19 (CK19), and ret oncogene have been proposed to aid in diagnosis of thyroid cancers. **Objective:** To determine the diagnostic accuracy of fluorodeoxyglucose-18 Positron Emission Tomography (FDG-18-PET) in the evaluation of recurrent papillary thyroid carcinoma in patients with raised serum thyroglobulin levels. **Methods:** A cross-sectional analytical study was conducted at Institute of Nuclear Medicine and Oncology (INMOL), Hospital, Lahore, Pakistan. 39 patients aged 25-77 years (mean age: 50.08) with raised serum thyroglobulin levels, and a history of papillary thyroid carcinoma suspicious of recurrence were included in the study using convenience sampling. Data was analyzed using SPSS version 26. Each patient underwent 18-FDG-PET/CT and tissue biopsy for histopathological correlation afterwards. Diagnostic Odds Ratio (DOR) was used to determine statistical significance. **Results:** Out of 39 patients, 18-FDG-PET/CT was able to correctly detect the recurrence in 26 patients. It missed 10 with papillary thyroid carcinoma and falsely diagnosed 1 patient which was found to have no recurrence on histopathological correlation and the 2 patients was PET-CT negative. 18-FDG-PET/CT demonstrated a sensitivity of 77.8%, and a specificity of 66.66%, indicating its moderate ability to correctly identify both true positives and true negatives. The overall diagnostic accuracy was 76.9%. Notably, the positive predictive value (PPV) was high at 96.6%, signifying that a positive 18-FDG-PET/CT result strongly suggests recurrence. Conversely, the negative predictive value (NPV) was low at 20.0%, revealing that negative result was unreliable, with a considerable number of false negatives (8 out of 10 PET-negative cases were positive upon histopathological correlation). The diagnostic odds ratio (DOR) of 7.0 reflects a moderate discriminative capacity of the test. **Conclusion:** The study concludes that FDG PET/CT demonstrates high positive predictive power and moderate diagnostic accuracy in detecting recurrent papillary thyroid carcinoma among patients with elevated serum thyroglobulin levels, though moderate sensitivity and lower negative predictive value highlights the risk of false negatives. Therefore, PET/CT should be interpreted in conjunction with clinical, biochemical, and histopathological data.
Keywords: Papillary thyroid carcinoma, serum thyroglobulin levels, 18-FDG-PET/CT, histopathology, recurrence, imaging.

INTRODUCTION

Among endocrine malignancies, thyroid carcinoma is the most common (1). Thyroid cancers are relatively rare and can vary widely in their behavior, from slow-growing, localized papillary carcinomas to aggressive and often deadly anaplastic forms (2). Papillary carcinoma is the most frequently diagnosed thyroid cancer. Its appearance can vary significantly depending on the specific microscopic variant and on the presence of any degenerative changes. These histological subtypes can sometimes pose diagnostic challenges for pathologists, and certain variants carry important implications for a patient's prognosis. This brief review outlines a practical approach to diagnosing papillary carcinoma, explores common diagnostic challenges and debates, and highlights supportive tools like immunohistochemistry and molecular testing that can aid in clarifying complex cases(3). Detailed pathological investigations have revealed small papillary cancers in 6% to 13% of autopsied individuals in the United States. However, Scandinavian researchers reported an unexpectedly high prevalence of 36% in autopsies conducted in Finland. Thyroid carcinoma represents 1.1% of all cancers. It is more prevalent in women than in men, with most cases occurring in individuals aged 25 to 65 years. Since the early 1990s, the new cases of thyroid cancer has been on the rise(4). Thyroid carcinoma is a frequently occurring cancerous tumor, with about 37,000 of new cases annually identified in the United States of America (USA) and an associated mortality rate of roughly 1,600 deaths per year. Over the past few decades, its incidence has more than doubled. The most common histological subtypes, papillary and follicular thyroid cancer, are collectively known as differentiated thyroid cancer (DTC) and typically have favorable outcomes. The 10-year overall survival rates are 93% for papillary carcinoma and 85% for follicular carcinoma(5). Several symptoms can be caused by thyroid cancer including a lump in any part of neck, swelling in the neck, neck pain which might radiate towards ears, consistent hoarseness, dysphagia, dyspnea, or persisting cough that might not go away easily, even after medication. However, no symptom is specific to thyroid carcinoma itself as some non-cancerous conditions can cause some of these symptoms as well(6). It was seen in previous studies that the most important indicators of prognosis were the presence of visible lymph node metastasis and hoarseness caused by recurrent laryngeal nerve palsy at the time of diagnosis(7). Several biomarkers have been proposed to aid in the diagnosis of thyroid cancers, particularly those of follicular epithelial origin. These include HBME-1, cytokeratin 19 (CK19), and the ret oncogene, each associated with specific characteristics of papillary carcinoma (PC). HBME-1, traditionally known as a mesothelial cell marker. They have shown diagnostic value in identifying malignant thyroid tumors that originate from follicular cells. Its expression in such tumors generally points towards malignancy, although it does not specifically confirm papillary differentiation(8,9). Cytokeratin 19 (CK19) is often strongly and diffusely expressed in papillary thyroid carcinomas, appearing as widespread cytoplasmic staining. While this marker can occasionally be detected in non-cancerous thyroid tissue, such as in reactive follicular cells, most studies report that diffuse CK19 positivity is not typically seen in follicular adenomas or carcinomas (10, 11, 12, 13, 14). The ret/PTC oncogenes is a key molecule connected with the growth of medullary carcinoma represent a group of genetic rearrangements involving the ret gene on chromosome 10q (15, 16). These alterations are unique to papillary thyroid carcinomas and have been found in up to 77% of cases (17). The resulting chimeric proteins contain the intracellular tyrosine kinase domain of the normal RET protein, making them detectable by immunohistochemistry using antibodies that target the carboxy-terminal end of the protein (18). PET/CT was particularly useful for patients with elevated thyroglobulin levels and those with tumors not concentrating radioactive iodine. A negative PET/CT result, however, was not sufficiently reliable to exclude further investigation(19). Among various PET tracers, fluorodeoxyglucose-18 (FDG-18) has emerged as a prominent imaging agent due to its utility in cancer imaging. PET/CT scan is a nuclear imaging technique that give metabolic and functional data, necessary in detecting malignancies(20). FDG-18 is a glucose analog-labeled with the radioactive isotope fluorine-18, enabling it to track metabolic activity, particularly within malignant tissues that exhibit increased glycolysis, commonly referred to as the Warburg effect. The FDG-18 PET scan thus serve as a functional diagnostic tool to identify active and aggressive malignancies based on metabolic activity rather than structural abnormalities alone(21). FDG-18-PET/CT is exceptionally important in the diagnostic landscape of residual thyroid cancers, including papillary thyroid carcinoma (PTC), for its lethargic course yet potential for recurrence(22). The metabolic insights provided by FDG-PET are particularly valuable in scenarios of elevated thyroglobulin (Tg) levels but negative iodine scans, indicate potential residual or metastatic disease despite negative conventional imaging(23). Thyroglobulin, a protein produced by the thyroid gland, serves as a biomarker for PTC; elevated Tg levels post-thyroidectomy and radioiodine ablation are suggestive of recurrent disease and necessitate further evaluation through sensitive imaging modalities(24). Additionally, the diagnostic role of FDG-18-PET/CT has expanded to assessing aggressiveness of PTC by providing insights into tumor behavior and potential response to treatment. Studies have shown that FDG uptake correlates with certain clinicopathological features of PTC, like as increased size of tumor, extra extension of thyroid, and metastatic potential(25). This study has reinforced FDG-PET as a valuable tool not only in identifying disease recurrence but also in characterizing the nature of the malignancy, aiding clinicians in personalized treatment planning for patients with advanced or recurrent PTC. **Rationale of study:** The main purpose of the research is to provide data regarding the sensitivity, specificity and validating overall effectiveness of Flourodeoxyglucose-18 PET/CT for evaluating recurrent papillary thyroid carcinoma in patients having raised thyroglobulin level. Particularly in cases where conventional imaging and iodine scans are inconclusive to the medical community, it provides the early diagnosis of recurrent papillary thyroid carcinoma with standard staging. We can also come up with an early treatment and design plan according to the patient profile status.

MATERIAL AND METHODS

This was cross sectional analytical study performed at the Institute of Nuclear Medicine and Oncology (INMOL) from March 2025 to 30 June 2025 having 39 patients sample size. The Nonprobability sampling technique was used. Inclusion criteria was including patients of both genders, age more than 18, who had completed treatment of papillary thyroid cancer in the past and underwent surgery and/or Iodine therapy, who presented with raised thyroglobulin as a marker for recurrence, with raised thyroglobulin, suspected diagnosis of recurrent papillary thyroid carcinoma, inconclusive conventional imaging scans, inconclusive iodine scan and exclusion criteria was patients with age less than 18, all the patients presented with carcinoma other than papillary carcinoma, with normal thyroglobulin level, confirmed recurrence on conventional and iodine scans. Primary data was collected through organized questionnaire patient detail including age, gender and patient history, Histopathological findings after ethical approval was obtained from the Institutional Review Board (IRB) of Superior University before commencing the study and take proper permission from INMOL Hospital, Lahore. Primary data was analyzed and verified by using the SPSS, version 24 SPSS Inc. Chicago, II, USA software. Chi square Test was used to find out significant association

among various variables. Diagnostic Odd Ration was used for determination of the diagnostic accuracy of FDG-18-PET/CT(2).

RESULTS

The study was performed to determine the diagnostic accuracy of flourodeoxyglucose-18 positron emission computed tomography in the evaluation of recurrent papillary thyroid carcinoma in patients with raised thyroglobulin level in Lahore. A total of 39 patients with raised Tg levels and a history of PTC suspicious of recurrence were included in the study conducting was INMOL Hospital, Lahore. 25 (64.1%) were females, while 14 (35.9%) were males. Age range was 25-77 years. 18-FDG was injected intravenously after preparing the patient for PET/CT. Histopathological evaluation was kept the gold standard for diagnosis.

Table 4.1

Frequency of Patients Gender

Gender			
		Frequency	Percent
Valid	F	25	64.1
	M	14	35.9
	Total	39	100.0

Table 4.1 shows 25(64.1%) patients out of 39 are female and 15(35.9%) out of 39 are male. The data indicate the higher prevalence of recurrence papillary thyroid carcinoma among female population as compared to male population.

Figure 4.1

Figure.4.1 shows graphical representation of Gender distribution

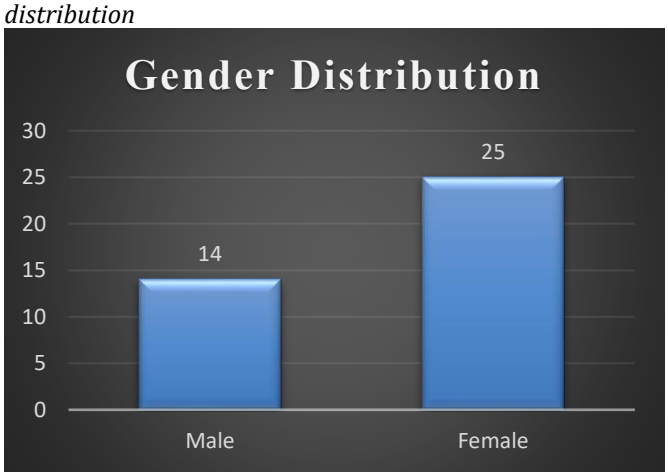

Table 4.2

Patients division into Age Groups

Age		
Age Group	Frequency	Percentage
25-37	9	23.08%
38-50	18	46.15%
51-63	6	15.38%
64-77	6	15.38%
Total	39	100%

Table 4.2 shows that 9 (23.08%) patients lie in the 25-37 age group, 18(45.15%) lie in the 38-50, 6(15.38%) lie in the 51-63, 6(15.38%) lie in the 64-77 out of 39(100%). Mostly patients lie in 38-50 age group.

Figure 4.2

Graphical representation of Age distribution

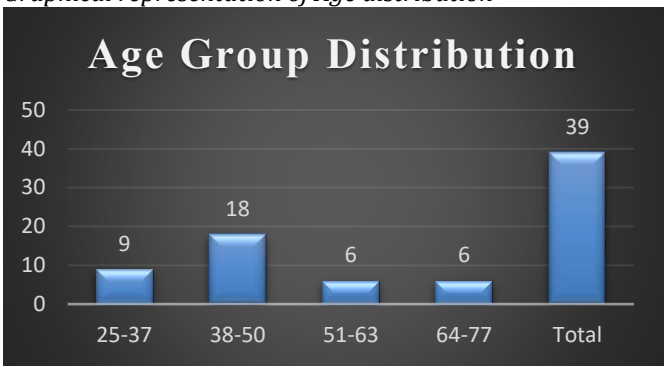

Table 4.3

*Cross-tabulation of PET/CT findings * Histopathology findings*

PETCTFINDINGS * Histopathological Findings Cross-tabulation				
Count				
		Histopathological Findings		
		No papillary carcinoma	Papillary carcinoma	Total
Petctfindings	No papillary carcinoma	2	8	10
	Papillary carcinoma	1	28	29
Total		3	39	39

Table 4.3: Shows 39 patients, 28 patients were True positive, 1 False positive, 8 False negative, 2 True negative Calculation of Sensitivity and Specificity:

Table 4.4

Sensitivity

Sensitivity:
Sensitivity=TP/TP+FN×100
=28/28+8*100
=28/36*100=77.8%

Table 4.4 shows 77.8% sensitivity value indicate the PET/CT correctly identified ~78% of patients who had recurrent cancer.

Table 4.5

Sensitivity

Specificity:
Specificity=TN/TN+FP*100
=2/2+1*100
=2/3*100=66.66%

Table 4.5 show 66.66% specificity value, indicate the PET/CT correctly ruled out recurrence in ~67% of truly disease-free patients.

Table 4.6

Overall Accuracy

Overall Accuracy:
Accuracy=TP + TN/Total Population×100
=28+2/39*100
=30/39*100=76.9%

Table 4.6 show 76.9% Overall accuracy value indicate the overall PET/CT was correct in ~76.9% of the cases.

Table 4.7

Positive Predictive Value (PPV)

Positive Predictive Value (PPV):
PPV=TP+FP/TP*100
=28+1/28*100
=29/28*100=96.6%

Table 4.7 show 96.6% Positive predictive value indicate when PET/CT was positive, there was a 96.6% chance it was truly recurrent PTC.

Table 4.9

Negative Predictive Value (PPV)

Negative Predictive Value (NPV)
=TN/TN+FN
=2/2+8*100
=2/10*100=20.0%

Table 4.9 show 20.0% Negative predictive value indicate a negative PET/CT scan only excluded cancer correctly 20.0% of the time.

Table 4.10

Diagnostic Odd Ratio

Diagnostic Odd Ratio (DOR)
DOR= TP*TN/FP*FN
=28*2/1*8
=56/8=7.0

Table 4.10 show 7.0 value indicate a moderate level of discrimination (DOR > 1 indicates PET/CT has value)

Explanation of Findings

Out of the total 39 patients, PET/CT was able to detect the recurrence in 28 patients correctly. It missed 8 patients with PTC, and falsely diagnosed 1 patient with no PTC. PET/CT demonstrated a sensitivity of 77.8% and a specificity of 66.66%, indicating its moderate ability to correctly identify both true positives and true negatives. The overall diagnostic accuracy was 76.9%. Notably, the positive predictive value (PPV) was high at 96.6%, signifying that a positive PET/CT result strongly correlates with actual recurrence. Conversely, the negative predictive value (NPV) was low at 20.0%, revealing that a negative result was unreliable, with a considerable number of false negatives. The diagnostic odds ratio (DOR) of 7.0 reflects a moderate discriminative capacity of the test.

DISCUSSION

Papillary thyroid carcinoma is the most common type thyroid tumors. It constitutes of about 70% of thyroid malignancies. Presence of a cold nodule is a common finding seen on iodine scans. Involvement of cervical lymph nodes can also be seen(26). Recurrence of papillary carcinoma is an evident problem which need early diagnosis for better prognosis. We evaluated 18-FDG-PET/CT for its ability to diagnose the recurrence of papillary thyroid carcinoma in patients with raised thyroglobulin levels along with negative iodine scans. Histopathological findings were kept as a gold standard for it. This study aimed to determine the diagnostic accuracy of PET/CT in cases where other conventional tests like X-Ray, CT, MRI, etc. are not of much help.

A total of 39 patients with a history of PTC and elevated Tg indicative of possible recurrence were evaluated using PET/CT, and findings were compared against histopathological results as the gold standard. The results demonstrated that PET/CT had a sensitivity of 77.8%, specificity of 66.66%, an overall diagnostic accuracy of 76.9%, PPV of 96.6% and NPV of 20.0%, suggesting moderate diagnostic utility.

These findings are consistent with those reported in prior literature. Numerous studies have demonstrated that FDG-PET/CT is particularly helpful in patients with biochemical recurrence of PTC but negative radioiodine scans, where it plays a complementary role. For instance, S Riaz et. Al, (2017) a study from Lahore assessed 93 patients post-treatment for head & neck malignancies. The study concluded that FDG PET/CT showed strong diagnostic accuracy 88% overall, with PPV of 88% and also had significant prognostic value, as PET-negative patients demonstrated better disease-free survival. This supports the findings, particularly the trend that PET/CT identifies true positives well yet negative scans don't always guarantee absence of recurrence(27).

T Haslerud et.al, in 2016, conducted a study based in the US, to assess the role of 18-FDG-PET/CT in thyroid carcinoma. They calculated a sensitivity of 79% which is close to the above calculated results(28).

One of the most compelling results in this study was the high positive predictive value (PPV) of 96.6%, indicating that a positive PET/CT scan is highly likely to represent true recurrence. This supports the use of PET/CT in confidently confirming disease recurrence when the scan is positive. Zhi Lu et.al, in 2016 conducted a study in China in which they determined the usefulness of 18-FDG-PET/CT in diagnosing recurrence of thyroid carcinoma. They calculated a PPV of 91.40% which is close to what we calculated(28). Another study by Ali Razfar et.al, (2010) on clinical usefulness of PET-CT in recurrent thyroid carcinoma showed a PPV of 94% further validating the results(30).

However, the negative predictive value (NPV) was low at 20.0%, suggesting that a negative result does not reliably exclude the disease. This is of clinical importance, as it highlights the risk of false reassurance in patients with PET-negative findings. Of the 10 patients who were PET-negative, 8 were actually found to have recurrent disease on histopathology, underscoring the limitations of PET/CT in detecting small-volume or low-metabolic activity lesions. Moustafa, H. et. al., in 2012, indicates the causes of false-negative results may arise due to several biological and technical factors. Commonly include low metabolic activity, small lesion usually <5 mm, Micro-metastasis, low Thyroid stimulating hormones at the time of scan may reduce FDG-18(31).

Similarly, Choi JW, et.al, in 2011, included 115 consecutive patients who underwent 18-FDG PET/CT for initial evaluation and were diagnosed with PTC by postoperative permanent biopsy. They concluded that factors like tumor size, and low metabolic activity, affect the imaging. Micro-papillary carcinomas, lymph node carcinomas, or small metastatic carcinomas are difficult to detect with 18-FDG-PET/CT due to their partial volume effect on PET/CT. In their study, the group with false negative results was noted to have small tumor size and less common extra-thyroid and lymphovascular invasion. This also suggested that prognosis in those with negative pre-operative findings is better than those with positive findings. They concluded that the absence of perithyroidal and lymphovascular invasion were independent predictors of false-negative results on initial ^{18}F-FDG PET/CT in patients with papillary thyroid carcinomas (PTCs). Moreover, negative preoperative ^{18}F-FDG PET/CT findings may be indicative of less aggressive tumor behavior in primary PTC. (32)

Some studies have reported that results of 18-FDG-PET/CT can be affected by serum Tg levels(33,34,35,36).
The diagnostic odds ratio (DOR) of 7.0 further supports the moderate diagnostic strength of PET/CT in this context. This value shows that the test provides meaningful differentiation between disease presence and absence.
From a practical standpoint, the findings reinforce the critical role of integrating PET/CT results with clinical and biochemical markers like Tg levels, rather than relying on imaging in isolation. In addition, due to its limited NPV, a negative PET/CT scan should not preclude further investigation, especially when Tg remains elevated or clinical suspicion is high.
In conclusion, this study supports the moderate diagnostic value of 18F-FDG PET/CT in detecting recurrent papillary thyroid carcinoma, particularly in Tg-positive patients. While a positive scan strongly indicates recurrence, a negative scan does not reliably exclude disease. These results emphasize the need for a multimodal diagnostic approach, combining PET/CT with serum markers and possibly other imaging modalities. Future studies with larger sample sizes and multicenter designs are needed to better establish PET/CT's role and refine its predictive metrics in this clinical setting.

CONCLUSIONS

This study concludes that FDG PET/CT demonstrates high positive predictive power and moderate diagnostic accuracy in detecting recurrent papillary thyroid carcinoma among patients with elevated thyroglobulin levels. While it is highly effective in confirming recurrence when positive, its lower negative predictive value and moderate sensitivity underscore the risk of false negatives. Hence, PET/CT should be interpreted alongside clinical, biochemical, and histopathological findings to avoid misdiagnosis or delayed treatment.

Limitation

Several limitations might affect the generalizability of the findings. The sample size was relatively small, limiting the diversity of the population studied because the research was conducted under constraints of time and resources which may not reflect the broader population spectrum.

Recommendations

FDG PET/CT is a valuable tool in detecting recurrent papillary thyroid carcinoma, especially due to its high positive predictive value and overall diagnostic accuracy. A positive PET/CT scan strongly indicates true recurrence, making it highly useful for guiding timely clinical decisions. Despite moderate sensitivity and low negative predictive value, the strengths of PET/CT in identifying true positives support its use as a frontline imaging modality in patients with elevated thyroglobulin levels, complemented by clinical and laboratory correlation where necessary.

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CA THYROID FDG-PET-CT
Case No: 01

- Diagnosed case of Papillary Ca Thyroid April 2020, Status Post left lobectomy, Isthmectomy and left neck dissection & 2 times Radioactive iodine ablation first in 2020 and second in 2021. Rising Tg. PET Imaging for Suspected recurrence.
- **Hypermetabolic left neck mass – known primary**
- **Hypermetabolic bilateral neck nodes – metastatic**
- **Mild metabolically active chest nodes – inflammatory? CT based follow up may be done**

Figure 1
PET-CT & CT Chest (Axial Plane)

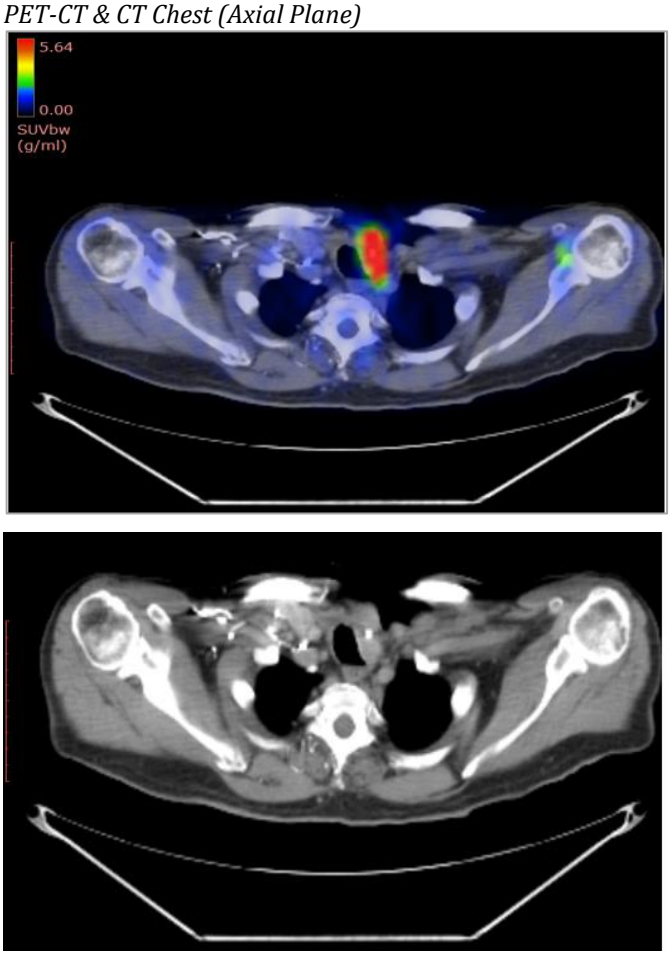
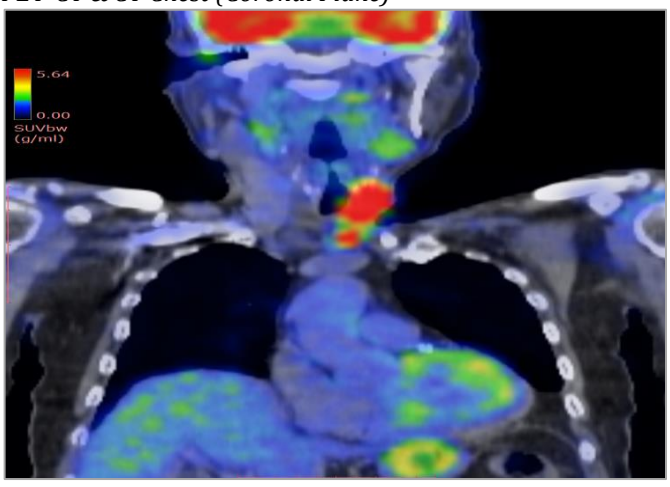


Figure 2
PET-CT & CT Chest (Coronal Plane)



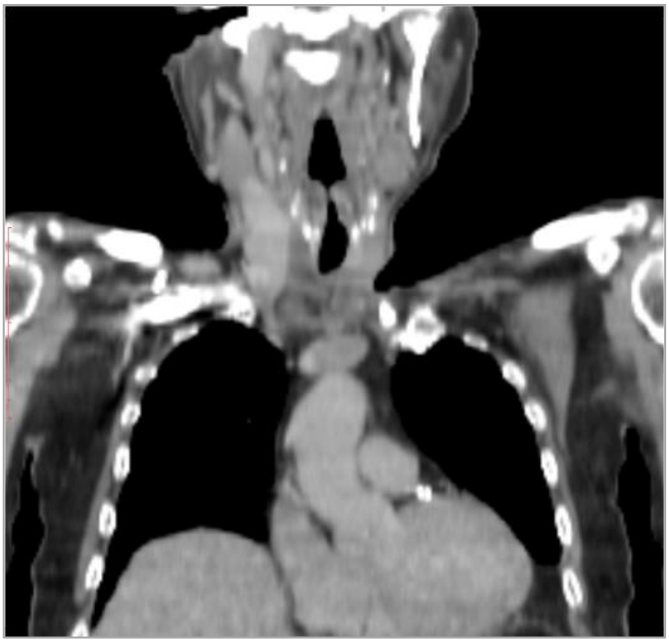
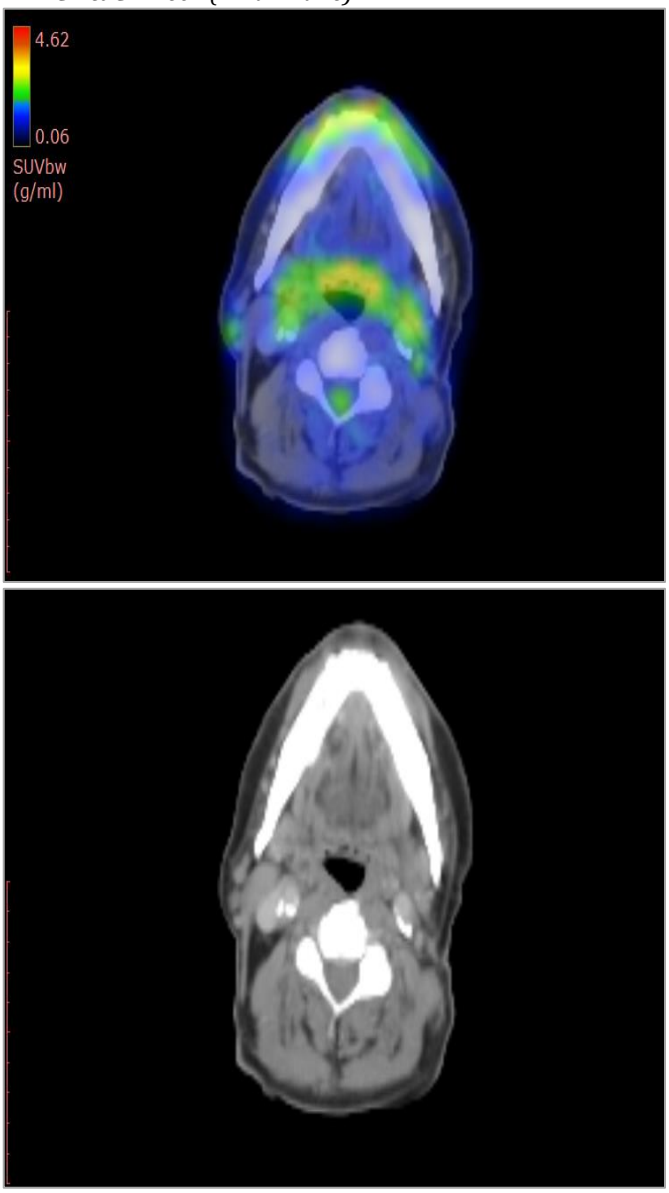


Figure 3
PET-CT & CT Neck (Axial Plane)



Case No: 02

- Very small sized lymph nodes not significant on CT
- PET positive

Figure 1

PET-CT & CT Chest (Axial Planes)

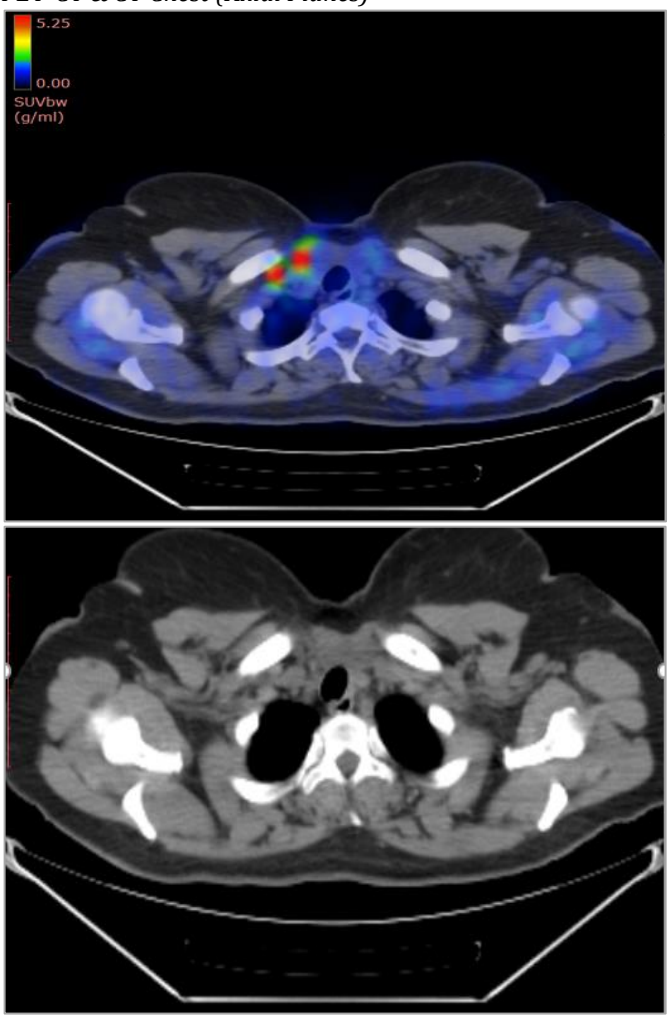
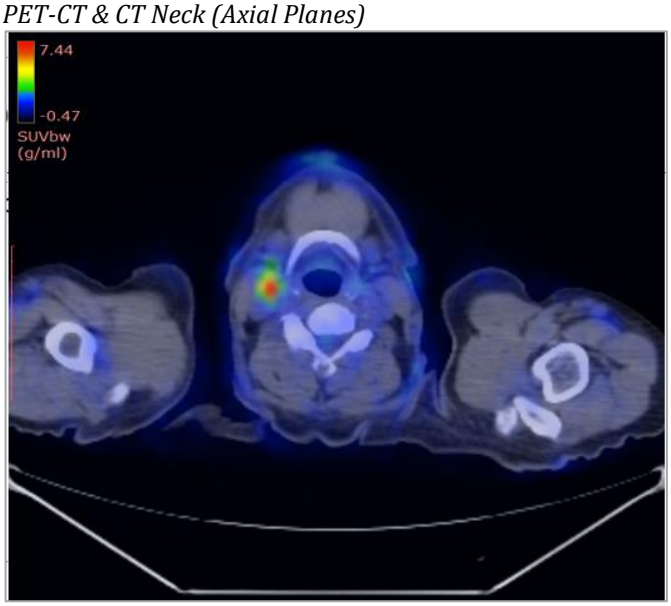


Figure 2

PET-CT & CT Neck (Axial Planes)



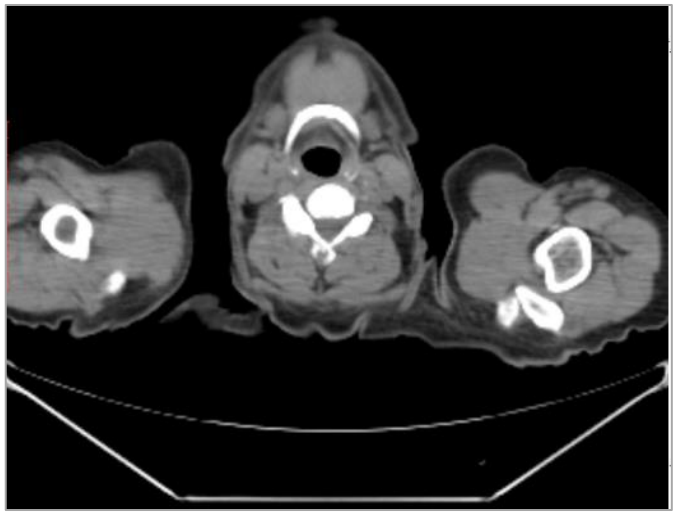


Figure 3

PET-CT & CT Neck & Chest (Coronal Planes)