

**Diagnostic Accuracy of Flourodeoxyglucose-18 Positron Emission
Computed Tomography in the evaluation of Recurrent Papillary
Thyroid Carcinoma with Patient's Raised Thyroglobulin Level in
Lahore**



SUPERIOR UNIVERSITY

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Master of Science in Allied Health Sciences**

By

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Supervisor Name: Dr. Fahmida Ansari

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Certificate of Approval

This is to certify that the research work presented in this thesis, titled “**Diagnostic Accuracy Of Flourodeoxyglucose-18 Positron Emission Computed Tomography In The Evaluation Of Recurrent Papillary Thyroid Carcinoma With Patient’S Raised Thyroglobulin Level In Lahore**” was conducted by “**Loqman shah**” under the supervision of “**Dr. Fahmida Ansari**”

No part of this thesis has been submitted anywhere else for any other degree. This thesis is submitted to the Faculty of Allied Health Sciences, The Superior University, Lahore in partial fulfillment of the requirements for the degree of Master of Sciences in the field of “**Allied Health Sciences**” in Faculty of Allied Health Sciences at The Superior University, Lahore.

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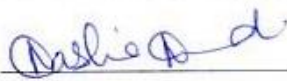
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Dedication

I dedicate this thesis to those who have supported me throughout my academic journey. I express my deepest gratitude to my parents, family, wife, Supervisor, Assistant Professor Dr. Fahmida Ansari, Co-supervisor Dr. Munir Ahmad, and Dr. Muhammad Numair Younis, for their expert guidance and valuable feedback. I also thank my loving parents for their support, encouragement, and love. And, I appreciate my Superior University for providing a conducive learning environment and necessary resources. Thank you.

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List of Abbreviations

Abbreviation	Full Form
FDG-18	Flourodeoxyglucose-18
PET	Positron Emission Tomography
CT	Computed Tomography
PTC	Papillary Thyroid Carcinoma
DTC	Differentiated Thyroid Carcinoma
RPTC	Recurrent Papillary Thyroid Carcinoma
Tg	Thyroglobulin
CK19	Cytokeratin 19
EANM	European Association of Nuclear Medicine
HBME-1	Hector Battifora Mesothelial-1

Abstract

Background:

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.

Chapter 1

INTRODUCTION

Among endocrine malignancies, the most frequently is thyroid carcinoma (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, with most cases occurring in individuals aged 25 to 65 years (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) with 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 Ten year's overall survival rates are 93% for papillary carcinoma, 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).

Previous studies have shown that the most significant prognostic indicators at the time of diagnosis were the presence of visible lymph node metastasis and hoarseness resulting from recurrent laryngeal nerve palsy (7).

Several biomarkers have been noticed to help 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 tumors (10, 11, 12, 13, 14).

The ret/PTC oncogenes represent a group of genetics 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 retain the intracellular tyrosine kinase domain of the normal RET receptor, allowing detection by immunohistochemistry with antibodies that recognize the protein's carboxy-terminal end (18).

PET/CT was particularly useful in those who had raised thyroglobulin levels and those with tumors not concentrating radioactive iodine. A negative PET/CT result, however, was not completely 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, a nuclear imaging technique which gives metabolic and functional data, necessary in detecting malignancies (20).

FDG-18 is a glucose 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 crucial in the diagnosis 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 raised 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 having advanced or recurrent PTC.

1.1. 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.

1.2. Problem Statement:

Recurrent papillary thyroid carcinoma (RPTC) remains challenging to diagnose in patients with raised thyroglobulin levels, often leading to delayed intervention. This study aims to assess FDG-18 PET scan's findings to identify and diagnose recurrent PTC in patients with elevated thyroglobulin to bridging current gaps and supporting evidence-based protocols for targeted imaging in recurrent papillary thyroid cancer cases.

AIM AND OBJECTIVES

To determine the diagnostic accuracy of fluorodeoxyglucose-18 positron emission tomography (FDG-18-PET) in the evaluation of recurrent papillary thyroid carcinoma (RPTC) with patient's elevated thyroglobulin level.

Chapter 2

LITERATURE REVIEW

It is essential to demonstrate the significance of accurately diagnosing recurrent PTC, the cancerous tumor of thyroid gland, in patients having raised thyroglobulin (Tg) levels. After studying many relevant research studies it is concluded that the 18-FDG-PET/CT is a crucial imaging modality for identifying recurrent or metastatic ailment when conventional imaging fails to localize lesions. This review examines existing studies on the diagnostic accuracy of FDG-PET/CT in evaluating repeated PTC, highlighting its sensitivity, specificity, and clinical utility in guiding patient management.

Schlüter B, et., al. (2000) study in Germany argued that the function of FDG-18-PET imaging in guiding remedy for differentiated thyroid carcinoma (DTC) in patients having raised thyroglobulin levels and negative I^{131} scans. A sum of 118 FDG-18-PET/CT scans were conducted on 64 patients, having follow-up data for all. Imaging was done using a PET scanner one hour after injecting 370 MBq (10 mCi) of FDG. Suspicious findings were assessed through histology, cytology, I^{131} uptake, CT/MRI, and high Tg levels. True-positive results were confirmed in 34, while 7 had false positive, 15 had false negative, correlating strongly with high Tg levels above 10 mg/L. Treatment was modified in 19 patients, including surgeries, external irradiation, and palliative care. The study highlights FDG-18-PET/CT as a useful detecting tool for DTC patients in optimizing treatment strategies(26).

Nahas Z, et., al. (2005) study in Maryland United States of America (USA) argued to assess the role of integrated PET/CT imaging in detecting recurrent PTC. A 33 patients retrospective study analysis was performed, comparing PET/CT with conventional imaging techniques to evaluate its effect on management. In 67% cases, PET-CT provided more details that confirmed treatment plans. The sensitivity, specificity, and positive predictive value of PET/CT were 66%, 100%, 100%, respectively, with the correctness of 70%. PET-CT is particularly useful in patients having thyroglobulin levels >10 ng/mL was no longer concentrating radioactive iodine. While PET/CT was a reliable guide for surgical planning when positive, negative results were not sufficient to exclude further investigation(27).

Sundram F. et., al. (2006)This systematic review explore the diagnostic accuracy of FDG-18-PET in identifying recurrent papillary or follicular thyroid carcinoma. Fourteen studies met the inclusion criteria, but most had evidence levels of 3 or 4, limiting quantitative analysis. Methodological issues included poor validity of reference tests and lack of blinding. FDG-PET consistently provided anatomical localization in those patients having raised thyroglobulin and negative I-131 scans. While findings suggest its potential, further research is needed before routine clinical implementation(28).

Shammas A, et., al. (2007) study investigate that the diagnostic accuracy of FDG-18-PET/CT in recurrent PTC varies serum thyroglobulin (Tg) levels. Studies have indicated that FDG-PET's sensitivity increases with higher Tg levels. For instance, one study reported sensitivities of 60% for Tg levels below 5 ng/mL, 62.5%, Tg levels between 5 to 10 ng/mL, 72% Tg levels above 10 ng/ml. This indicates that FDG-PET is highly effective in identifying recurrent disease with higher Tg levels in patients. In patients having low Tg levels, the sensitivity of FDG-PET is comparatively lower, suggesting limited utility in this subgroup. Therefore, while FDG-PET is valuable in identifying recurrent PTC, its diagnostic performance is less robust with low Tg levels in patients(29).

Bertenga et., al. (2009) conducted a study in Italy, assessed the diagnostic efficacy of FDG-18- PET/CT in detecting differentiated thyroid carcinoma in patients with negative I-131 scans and raised thyroglobulin (Tg) levels. A total 52 post-thyroidectomy patients with remnant ablation and high Tg levels (mean = 156 ng/mL) were included. F-18-FDG-PET/CT positivity significantly correlated having Tg levels but showed no association with Thyroid Stimulating Hormone levels, size of tumor, or combined Thyroglobulin/TSH levels. Findings were independent of levothyroxine therapy regimens. FDG-18-PET/CT demonstrated the highest correctness in patients with Tg levels above 21 ng/mL, confirming its utility as a diagnostic tool in this context(30).

Lee J et., al. (2012) the purpose of the study to assess the diagnostic value of ¹²⁴I-PET/CT and FDG-18-PET/CT in detecting iodine and non-iodine-transport recurrences compared to conventional imaging from July 2009 to June 2010, Nineteen DTC patients with raised Tg having negative pathological findings on conventional imaging were prospectively studied. All cases had undergone total thyroidectomy follow-up for an average of 13 months post-treatment. Combined FDG-18-PET/CT and ¹²⁴I-PET/CT detected recurrent lesions 47.4% of

patients, with disease management modified in 66.7% and surgical planning optimized in 21.1%. The findings suggest that this imaging combination offers a useful diagnostic tool for guiding treatment decisions in DTC patients having high Tg levels and no detectable lesions on traditional imaging(31).

Khan, et., al. (2016) study was investigated in the North Waziristan (Pakistan) having a total number of patients in 73 under the age of 40 years diagnosed thyroid cancer in which 26% n=19 with 14 (73.7%) being diagnose PTC and 5 (26.3%) follicular TC was associated tremendously with recent increase in high TSH level, mean TSH values $P < 0.05$ and size of swelling, found not significantly associated with age, gender, ATg and Thyroglobulin values $P > 0.05$ (32).

Hassan A, et., al. (2016) study was conducted in Shaukat Khanum Memorial Cancer Hospital and RC in Lahore (Pakistan) analyzed 689 PTC cases over a 20-year period. The findings showed that the 5years disease free survival rates were 54% for low risk cases, 26% for moderate risk, 5% for high risk groups. Twenty years disease free survival rates were 43% for stage I, 28% for stage II, 18% for stage III, and 2% for stage IV patients. These statistics recommended that recurrence rates are higher among patients with advanced stages or higher risk classifications(33).

Kiran N, et., al. (2022) Another retrospective study from Rai Medical College Sargodha Hospital reported that among 56 malignant thyroid neoplasms were diagnosed by biopsies, 76.78% were PTC, 10.71% were follicular carcinoma, 8.92% were medullary carcinoma, and 1.78% were anaplastic carcinoma. Out of 374 patients 56 were malignant. Among these 43 (76.78%) contains PTC, 6 (10.71%) follicular TC followed by 5 (8.92%) of medullary and 1 (1.78%) of anaplastic carcinoma(34).

Furqan S, et., al. (2024) study conducted at Aga Khan Hospital in Karachi (Pakistan) found that the majority of cases were identify as stage I papillary thyroid carcinoma (PTC), accounting for 49.0%, with a heal rate of 52.94%, a persistence rate of 28.43%, and a recurrence rate of 18.62%. Among patients with follicular carcinoma, 33.3% were diagnosed at stage IV, showing no cases of cure, with a persistence rate of 25% and a recurrence rate also at 25%. For those with the Hürthle cell variant of follicular carcinoma, most cases (60.0%) were diagnosed at stage I, with an 80% cure rate, 0% persistence, and a 20% recurrence rate(35).

Nanni C, et.al, (2006) conducted a study to assess the function of 18F-FDG-PET and PET/CT imaging in patients having DTC, who were previously treated and had undergone whole body Iodine-131 scan, had raised levels of Tg. They concluded that both modalities have proven roles in evaluation of thyroid cancer and have increased sensitivity and specificity which could change the prognosis and provide better management (36).

Vrachimis A, et.al, (2015) performed a study among patients having suspected DTC or those among whom it had dedifferentiated by comparing the roles of PET/MRI and PET/CT with FDG-18. 31 thyroidectomized and remnant ablated patients were included. All the patients went through PET/MRI and PET/CT with FDG. Among 26 patients having recurrent tumor, 25 were correctly identified by both ¹⁸F-FDG PET/CT and PET/MRI. Detection rate of PET/CT and PET/MRI was 97 % and 85 % for malignant lesions, and 100 % and 77 % (37 of 48 lesions) for benign lesions, respectively(37).

Choi, et.al, (2006) performed a retrospective study, 1,763 patients undergoing 18F-FDG PET/CT for various reasons, excluding known thyroid disease, were evaluated. The researchers with a purpose to determine whether combining PET uptake patterns with CT imaging features could enhance to distinguish benign and malignant thyroid lesions beyond what standardized uptake values (SUVs) alone could provide. The findings revealed that focal thyroid lesions were incidentally identified in a subset of patients. Among these, a significant proportion were malignant, underscoring the importance of not overlooking such incidental findings. Notably, the study determine that integrating PET and CT imaging characteristics improved diagnostic accuracy compared to relying solely on SUV measurements. This research emphasize the potential of FDG-18 PET/CT not only detecting incidental thyroid lesions but also in providing valuable information that can guide clinical decision-making. The enhanced characterization of these lesions through combined imaging modalities may lead to more accurate diagnoses and better-informed management strategies for patients(38).

Shammas A, et.al, (2007) evaluated patients having suspected recurrence of thyroid carcinoma using FDG-18 PET/CT. In this prospective study, patients having raised serum thyroglobulin levels and negative radioiodine scans underwent FDG-18F PET/CT imaging. The results demonstrated that 18F-FDG PET/CT effectively diagnostic area of recurrent or metastatic ailment that were not detected by conventional imaging modalities. The study found that PET/CT had a significant impact on clinical management, leading to changes in

treatment plans based on the imaging findings. They concluded that FDG-18F PET/CT is a useful diagnostic tool in the assessment of patients with suspected recurrent or metastatic DTC, particularly when traditional imaging techniques yield inconclusive results. The integration of PET/CT into the diagnostic workflow can enhance the identification of disease recurrence to guide appropriate therapeutic interventions (39).

Larg MI, et.al, (2019) conducted a study at Oncological Institute Cluj-Napoca. In this retrospective analysis, the researchers assessed 173 PET/CT scans from DTC patients presenting having elevated Tg levels, negative anti-Tg antibodies, and no clinical or imaging evidence of recurrence or metastasis. The study found that 38% of these scans were positive for disease recurrence or metastasis. The diagnostic performance metrics were notable, having a sensitivity of 88.09%, specificity of 98.6%, positive predictive value of 93.1%, and overall accuracy of 96.53%. Importantly, the PET/CT findings led to significant changes in patient management. Among those with positive scans, 29 patients underwent surgery, 24 continued with radioiodine therapy, and 5 initiated treatment with tyrosine kinase inhibitors or external radiotherapy. Overall, treatment strategies were altered in 89.2% of cases based on PET/CT results. The study concluded that FDG-18F PET/CT is a valuable imaging modality for identifying recurrence in DTC patients having elevated Tg levels and negative radioiodine imaging. Its integration into follow-up programs can enhance diagnostic accuracy and inform treatment decisions, particularly in cases where traditional imaging fails to localize disease(40).

Alnafisi, et.al, (2000) conducted a study in University of Western Ontario, London and McMaster University, Hamilton, Ontario, Canada, in which they included 11 patients who had persistently raised levels of thyroglobulin, negative 131-I scans, total thyroidectomy, a history of carcinoma, and had underwent all known treatments for metastasis. FDG uptake was observed in the neck or upper mediastinum of all 11 patients, initially in 10 and on follow-up in 1. Biopsy confirmed malignancy in six cases, was inconclusive in two, and normal in one; two patients had normal ultrasound with no biopsy. FDG findings altered management in seven patients, leading to surgery and/or radiotherapy. One declined treatment, and four remained under observation. Surgical pathology confirmed thyroid cancer in all treated cases, with no evidence of aggressive histologic patterns on review. It was concluded that FDG-18F PET is helpful in guiding patients having thyroid cancer for further evaluation specially when 131-I shows unpredictable or normal results(41).

Kim HJ, et.al, (2016) conducted a study to assess FDG-18F PET/CT as preoperative tool as a first step in identification of PTC. The study contains 197 cases and 246 tumor sites, was observing FDG uptake in 63% of cases, with 3.6% of patients showing incidental non-thyroid malignancies. Among patients with lateral neck metastasis, FDG-PET/CT indicate high specificity and negative predictive value, particularly when ultrasound or CT findings were inconclusive. Key factors linked to FDG avidity included tumor size, BRAF mutation, Hashimoto's thyroiditis, and extrathyroidal extension, the latter showing the strongest correlation. Although FDG uptake did not predict recurrence-free survival, it proved useful in identifying metastatic nodes and guiding surgical planning in uncertain cases. (42)

JS Bae, et.al, (2006) conducted a retrospective analysis of 3,379 patients undergoing FDG-PET/CT between 2003 and 2005 found that 8.4% showed thyroid FDG uptake. Among 99 patients who underwent further evaluation, 23.2% were diagnosed with thyroid cancer. Focal uptake carried a significantly higher malignancy risk (30.9%) compared to diffuse uptake (6.4%). Malignant nodules had notably higher SUVmax values than benign ones, and SUVmax correlated with tumor size. These findings indicate that focal FDG uptake with elevated SUVmax on PET/CT may suggest an develop risk of thyroid cancer and warrant further investigation (43).

Chapter 3

METHODOLOGY

3.1. Research Design

The cross-sectional analytical research that was investigate diagnostic accuracy of Flourodeoxyglucose-18 Positron Emission Computed Tomography in the evaluation of recurrent PTC with Patient's Raised Thyroglobulin Level In Lahore

3.2. Clinical Settings

This research study was performed at Institute of Nuclear Medicine and Oncology (INMOL) Hospital, Lahore.

3.3. Sample Size

The Cochran's formula for computing the size of sample is given below;

$$n = \frac{Z^2 \times p \times (1 - p)}{d^2}$$

$$(p) = 2.6\% = 0.026$$

$$Z = 95\% (Z = 1.96)$$

$$d = 5\% = 0.05$$

$$n = \frac{(1.96)^2 \times (0.026) \times (1 - 0.026)}{(0.05)^2}$$

n=39 patients(49).

3.4. Sampling Technique

Convenient sampling technique was used for this research.

3.5. Duration of Study

The study was completed within 4 months after the approval of the synopsis

3.6. Selection Criteria

3.6.1. Inclusion Criteria

- Patients of both genders
- Patients with age more than 18
- Patients who had completed treatment of PTC in the past and underwent surgery and/or Iodine therapy
- Patients who presented with raised thyroglobulin as a marker for recurrence
- Patients with inconclusive conventional imaging scans
- Patients with inconclusive iodine scan

3.6.2. Exclusion Criteria

- Patients with age less than 18
- All the patients presented with carcinoma other than papillary carcinoma.
- All the patients with normal thyroglobulin level
- Patients with confirmed recurrence on conventional and iodine scans

3.7. Equipment

- PET-CT Machine (GE Discovery STE PET-CT with 16 slices)

3.8. Procedure and patient preparation

Fasting 4-6 Hours to the patient before starting the scan. Intravenously Radioactive FDG-18 injecting in small amount to patient. After it, the patient waited for uptake of radiopharmaceuticals for distribute into the body. The patient already lies on to PET scanner couch, gamma rays emitted by FDG-18 detect by PET scanner forming the detailed images of the metabolic activity. Consultant Nuclear Physician interpreted the high uptake areas show disease on PET scan. Time taken by this scan was almost 1-2 Hours. Better add the scan procedure from European Association of Nuclear Medicine (EANM) guidelines if detail is required.

3.9. Ethical Consideration

- Participants were provided with clear information regarding the study, including its purpose and benefits, and their right to withdraw per will. The informed consent document was written in understandable language and addressed any questions participants may have.
- Confidentiality was maintained by ensuring all data is anonymized and securely stored.
- The ethical approval was acquired from the Institutional Review Board (IRB) of Superior University, Lahore before commencing the study. The IRB will reviewed the research proposal to ensure it adhered to ethical guidelines and protected participant rights.

3.10. Data Collection Procedure

Data was collected by patient detail including age, gender and patient history, Histopathological findings through questionnaire with PET/CT scan procedures from INMOL Hospital, Lahore.

3.11. Data Analysis

This data was analyzed and verified through the SPSS, version 24 SPSS Inc. Chicago, IL, USA software. Diagnostic Odd Ratio was used for determination of the diagnostic accuracy of FDG-18F-PET/CT(2).

Chapter 4

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

Table 4.1 shows 25(64.1%) patients out of 39 are female and 14(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.

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

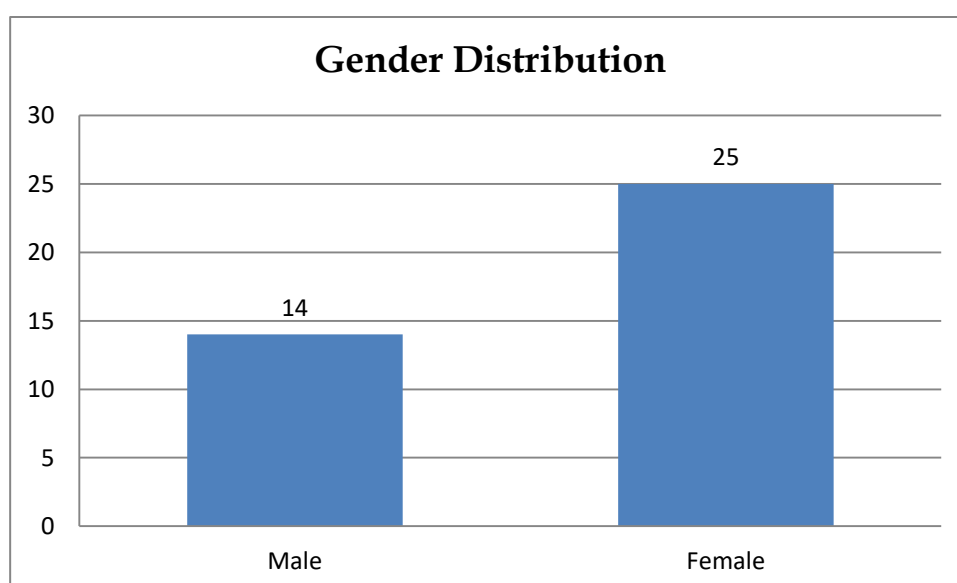


Figure 4.1 shows graphical representation of Gender distribution

Table 4.2: Patients division into Age Groups

Table 4.2 shows that 9 (23.08%) patients lie in the 25-37 age group, 18(46.15%) 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.

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%

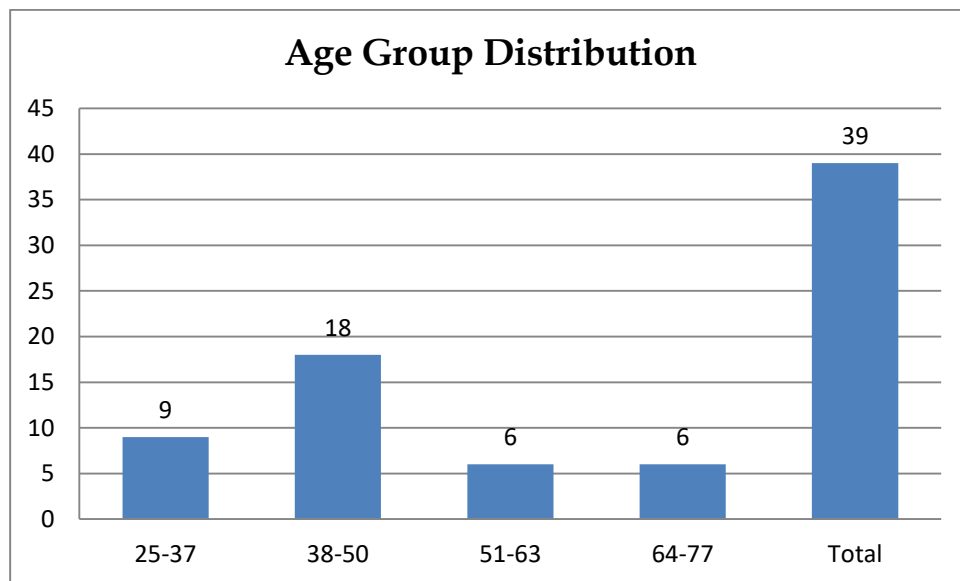


Figure 4.2: Graphical representation of Age distribution

Table 4.3: Cross-tabulation of PET/CT findings * Histopathology findings

PETCTFINDINGS * Histopathological Findings Cross-tabulation				
Count				
		Histopathological Findings		Total
		No papillary carcinoma	Papillary carcinoma	
PETCTFINDINGS				
	No papillary carcinoma	2	8	10
	Papillary carcinoma	1	28	29
Total		3	36	39

Table 4.3 shows 28 patients was True positive, 1 False positive, 8 False negative, 2 True negative out of 39 patients

Calculation of Sensitivity and Specificity:

Table 4.4: Sensitivity

Sensitivity:
$\text{Sensitivity} = \text{TP} / (\text{TP} + \text{FN}) \times 100$
$= 28 / (28 + 8) \times 100$
$= 28 / 36 \times 100 = 77.8\%$

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

Table 4.5: Specificity

Specificity:
$\text{Specificity} = \text{TN} / (\text{TN} + \text{FP}) \times 100$
$= 2 / (2 + 1) \times 100$
$= 2 / 3 \times 100 = 66.66\%$

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:
$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{Total Population}} \times 100$
$= \frac{28 + 2}{39} \times 100$
$= \frac{30}{39} \times 100 = 76.9\%$

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):
$\text{PPV} = \frac{\text{TP}}{\text{FP} + \text{TP}} \times 100$
$= \frac{28}{1 + 28} \times 100$
$= \frac{28}{29} \times 100 = 96.6\%$

Table 4.7 show 96.6% Positive predictive value indicate when PET/CT was positive, there was a 100% chance it was truly recurrent PTC.

Table 4.8: Negative Predictive Value (NPV)

Negative Predictive Value (NPV)
$= \frac{\text{TN}}{\text{TN} + \text{FN}}$
$= \frac{2}{2 + 8} \times 100$
$= \frac{2}{10} \times 100 = 20.0\%$

Table 4.8 show 20.0% Negative predictive value indicate a negative PET/CT scan only excluded cancer correctly 20.0% of the time.

Table 4.9: Diagnostic Odd Ratio

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

Table 4.9 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.

Chapter 5

DISCUSSION

Papillary thyroid carcinoma is the most common type of cancer. 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(50). Recurrence of papillary carcinoma is an evident problem which need early diagnosis for better prognosis. We evaluated FDG-18F PET/CT for its ability to diagnose the recurrence of PTC in patients with raised Tg along with negative iodine scans. Histopathological findings were kept as a gold standard for it. The purpose of study was 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 uniform with those described in prior studies. 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(51).

T Haslerud et.al, in 2016, conducted a study based in the US, to assess the function of 18-FDG-PET/CT in thyroid cancer. They calculated a sensitivity of 79% which is close to the above calculated results(52).

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 ailment recurrence when the scan is positive. Zhi Lu et.al, in 2016 conducted a study in China in which they determined convenience of 18-FDG-PET/CT in diagnosing recurrence of thyroid cancer. They calculated a PPV of 91.40% which is close to what we calculated(53). Another study by Ali Razfar et.al, (2010) on clinical convenience of PET-CT in recurrent thyroid carcinoma showed a PPV of 94% further validating the results(54).

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(55).

Similarly, Choi JW, et.al, in 2011, included 115 patients who went through 18-FDG PET/CT for evaluation and diagnosed with PTC by postoperative 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 hard to detect with 18-FDG-PET/CT because 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 lympho-vascular invasion. This also suggested that prognosis in those with negative pre-operative findings is better than those with positive findings. They results determined the absence of peri-thyroidal, lympho-vascular invasion were independent predictors of false-negative results on early ^{18}F -FDG PET/CT in patients with PTCs. Moreover, negative preoperative ^{18}F -FDG PET/CT findings may be indicative of less aggressive tumor behavior in primary PTC. (56) Some studies have reported that results of FDG-18F PET/CT can be affected by serum Tg levels(57,58,59,60).

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, study supports moderate diagnostic value of FDG-18F 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.

Chapter 6

CONCLUSIONS

The study concludes that FDG-18F PET/CT demonstrates high positive predictive power and moderate diagnostic accuracy in identifying recurrent PTC among patients having raised Tg-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.

Limitations

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-18FPET/CT is valuable tool in identifying recurrent PTC, 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, low negative predictive value, the strengths of PET/CT in identifying true positives support its use as a frontline imaging modality in patients with raised thyroglobulin levels, complemented by clinical and laboratory correlation where necessary.

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APPENDICES
APPENDIX - 1
ENGLISH CONSENT FORM

The study you are about to participate is a randomized control trial survey titled as;

“Diagnostic Accuracy of Flourodeoxyglucose-18 Positron Emission Computed Tomography in the evaluation of Recurrent Papillary Thyroid Carcinoma with patient’s raised Thyroglobulin Level in Lahore”

The study has no potential harm to participants. All data collected from you will be coded in order to protect your identity, and should not be disclosed to anyone. Following the study there will be no way to connect your name with your data. Your answers to the questions will not affect the quality of education given to you. Any additional information about the study results will be provided to you at its conclusion, upon your request.

You are free to withdraw from the study at any time. You agree to participate, indicating that you have read and understood the nature of the study, and that all your inquiries concerning the activities have been answered to your satisfaction.

NAME _____

SIGNATURE _____

DATE _____

APPENDIX - 2

URDU CONSENT FORM

میں ڈاکٹر فہمیدہ انصاری تصدیق کرتی ہوں کہ محترم (لقمان شاہ) نے اپنی اس تحقیق

“Diagnostic Accuracy of Flourodeoxyglucose-18 Positron Emission Computed Tomography in the evaluation of Recurrent Papillary Thyroid Carcinoma with Patient’s Raised Thyroglobulin Level In Lahore”

زیر نگرانی ڈاکٹر فہمیدہ انصاری کے متعلق بتا دیا ہے۔ مجھے اس تحقیق کی نوعیت، مقاصد، احداث، توقعات، فوائد اور خطرات کے متعلق، ساری معلومات فراہم کر دی گئی ہیں۔

اس تحقیق کے دوران ساری معلومات صیغہ راز میں رہیں گی اور مریض کا نام اور دیگر معلومات صرف تحقیق کے لیے استعمال ہوں گی۔ مجھے یہ بھی بتا دیا گیا ہے کہ میں اس تحقیق سے متعلق ہر قسم کے سوال پوچھنے کا مجاز ہوں اور یہ تحقیق صرف ایک شخص کا مفاد میں نہیں ہے بلکہ بحیثیت مجموعی انسانیت کا مفاد اس سے واسطہ ہے۔ تمام تفصیلات جاننے کے بعد میں تحقیق میں شامل ہونے یا نہ ہونے پر کسی کا قائل نہیں ہوں۔ اس تحقیق سے کسی بھی وقت علیحدہ ہونے پر مجھ پر کوئی پابندی نہیں ہوگی۔ میں بذات خود بقائمی حوش و حواس اور رضامندی سے اس تحقیقاتی عمل میں شامل ہوتی/ہوتا ہوں

دستخط محقق-----

دستخط شرکت کار-----

تاریخ-----

APPENDIX - 3

DEMOGRAPHICS FORM & QUESTIONNAIRES

- Serial No:_____
- Age (Years):_____
- Gender (M/F):_____
- Clinical History of Recurrent Papillary Thyroid Carcinoma:_____
- Raised Thyroglobulin Level:_____
- FDG-18-PET/CT Findings: _____
- Histopathological findings:_____

Sr. No	Age (years)	Gender M/F	Raised Thyroglobulin Level	Findings of FDG-18-PET/CT	Histopathological findings
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					

APPENDIX - 4

ETHICS COMMITTEE LETTER



OFFICE OF THE DEAN-FAHS

SUPERIOR UNIVERSITY

Ref.: IRB /FAHS/Allied/04/25/MS/AHS-3754

Date: 18th March 2025

Program: MS Allied Health Sciences

Name: Loqman shah

Registration: SU91-MSAHW-F23-105

Subject: Ethical Approval Letter

The Research Ethical Committee convened on Dated: **17th March, 2025** to discuss your protocol titled **"Diagnostic Accuracy of Flourodeoxyglucose-18 Positron Emission Computed Tomography in the Evaluation of Recurrent Papillary Thyroid Carcinoma with Patient'S Raised Thyroglobulin Level in Lahore"**

No further corrections and recommendations were suggested. The above-mentioned protocol has been approved after considering various research issues including ethical concerns with condition that the researcher will submit completion report at the end of his/her research.

Prof. Dr. Muhammad Naveed Babur
Dean/Convener REC
Faculty of Allied Health Sciences
Superior University, Lahore

- Ethically There is no issue.

Munir Ahmad 21st 4/25
DR. MUNIR AHMAD
Deputy Chief Scientist
INMOL Hospital
New Campus Road Lahore

APPENDIX - 5

PLAGIARISM REPORT

August 25, 2025



PLAGIARISM CERTIFICATE

For MPhil and PhD

This is certified that the thesis entitled: **Diagnostic Accuracy Of Flourodeoxyglucose-18 Positron Emission Computed Tomography In The Evaluation Of Recurrent Papillary Thyroid Carcinoma With Patient's Raised Thyroglobulin Level In Lahore.**

Student Name: Logman Shah

Reg /Roll No: SU91-MSAHW-F23-105

Submitted on date: 25.08.2025

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Supervisor Signature

Research Project / Thesis

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Hassam Khalil
25-08-2025

APPENDIX - 6

PLAGIARISM CERTIFICATE

Report:Diagnostic Accuracy of Flourodeoxyglucose-18
Positron Emission Computed Tomography in the evaluation of
Recurrent Papillary Thyroid Carcinoma with Patient's Raised
Thyroglobulin Level In Lahor

ORIGINALITY REPORT

14%	5%	13%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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2	"Poster Presentations", European Journal of Nuclear Medicine and Molecular Imaging, 2009 Publication	1%
3	Imaging in Clinical Oncology, 2014. Publication	1%
4	"EANM'15", European Journal of Nuclear Medicine and Molecular Imaging, 2015 Publication	1%
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8	Emmanouil Panagiotidis, Jules Tianyu Zhang-Yin. "The Role of Positron Emission	1%

APPENDIX - 7

PUBLICATION

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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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ARTICLE INFO

Keywords: Papillary Thyroid Carcinoma, Serum Thyroglobulin Levels, 18-FDG-PET/CT, Histopathology, Recurrence, Imaging.

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Declaration

Authors' Contribution

All authors equally contributed to the study and approved the final manuscript

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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.

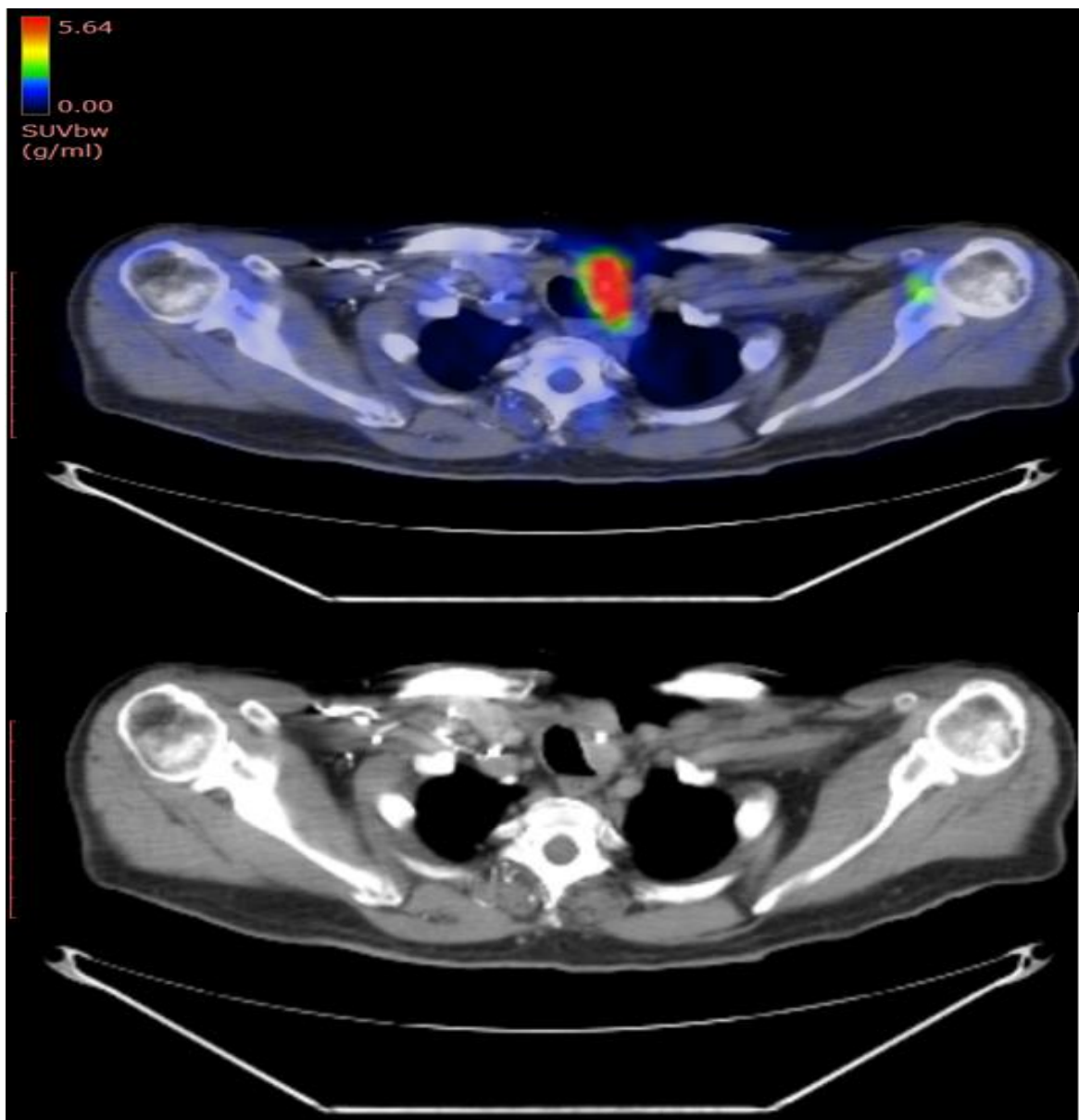


IMAGES

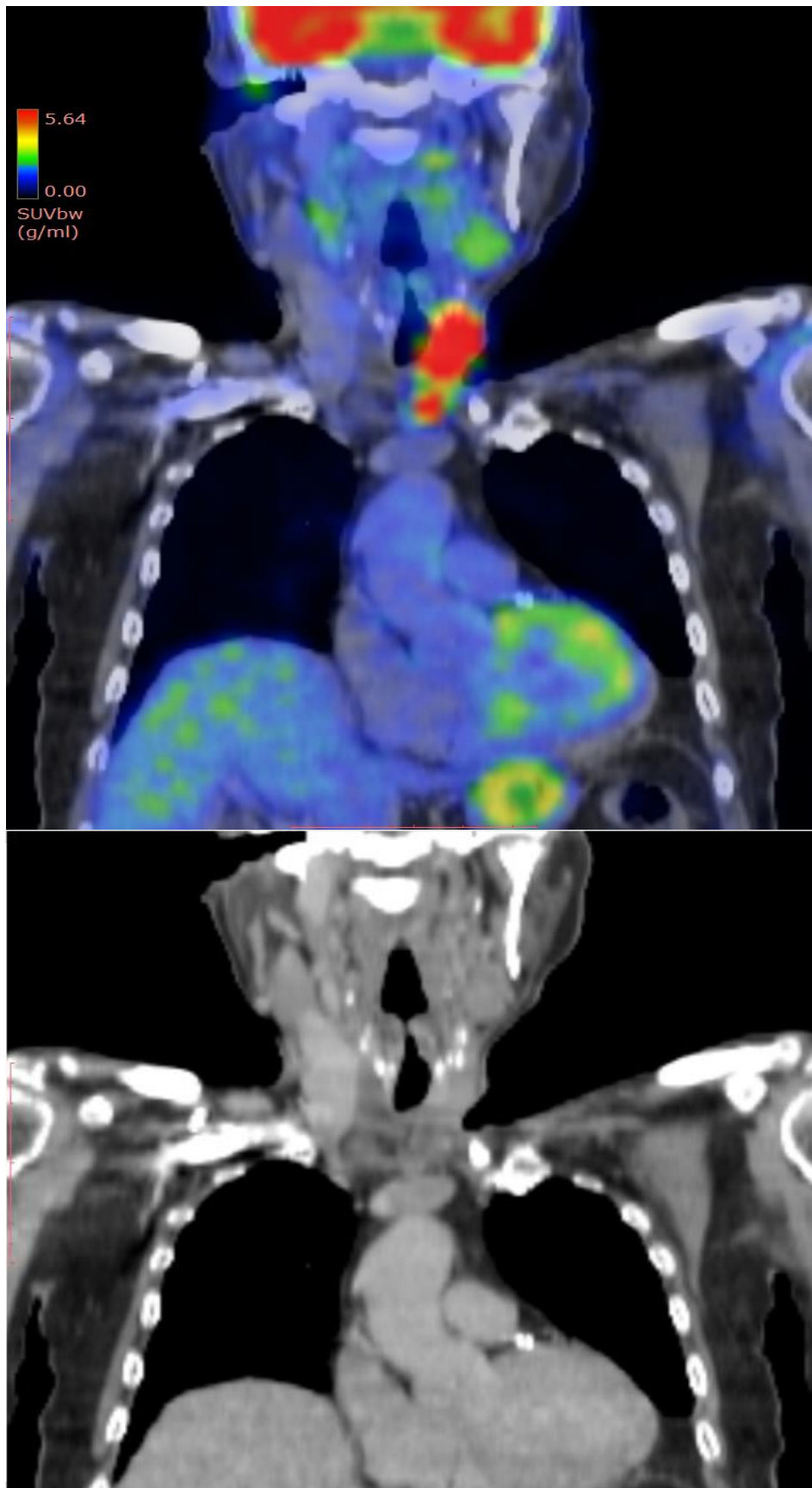
CA THYROID FDG-PET-CT

Case 1:

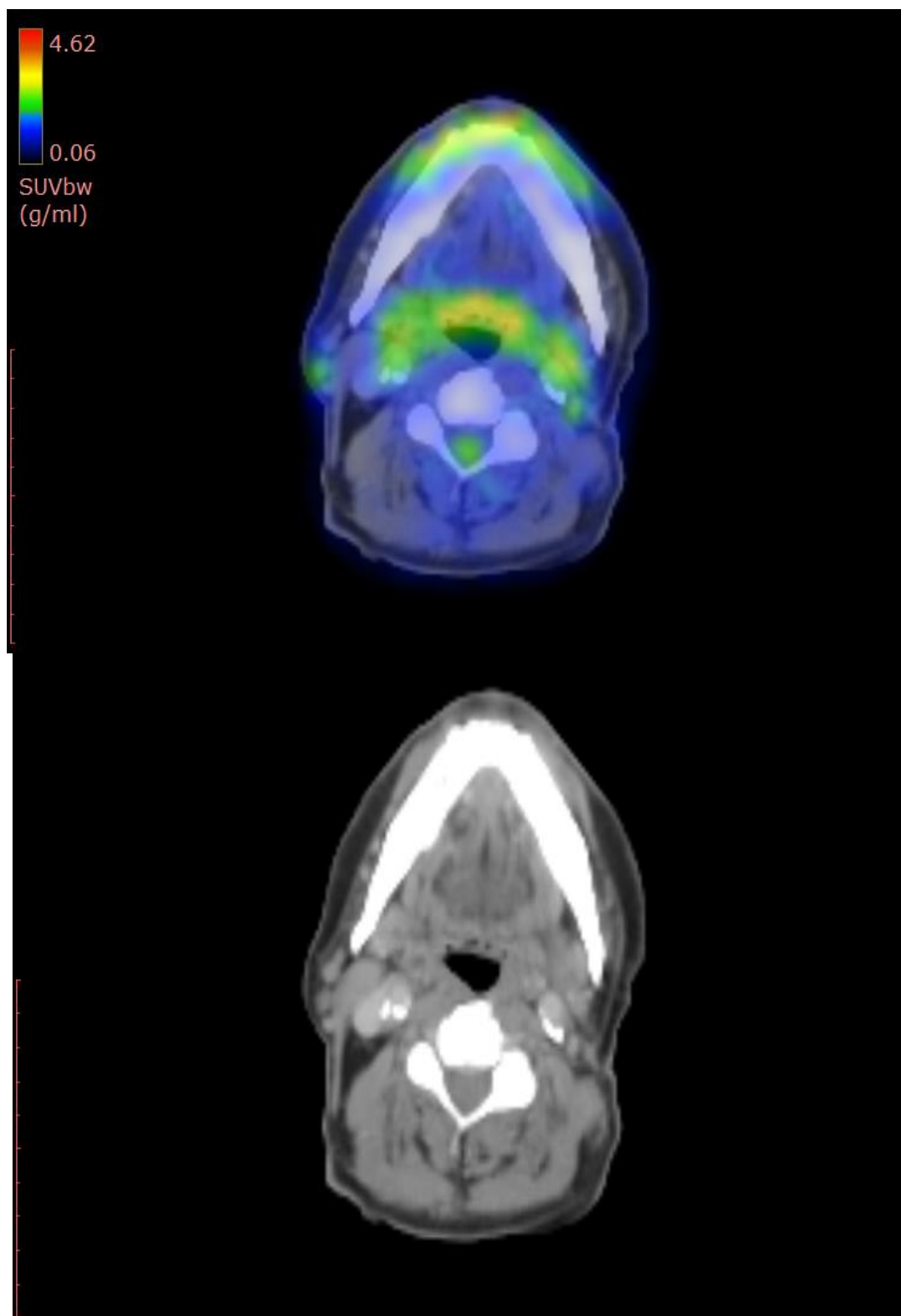
- Diagnosed case of Papillary Ca Thyroid April 2020, Status Post left lobectomy, Isthmectomy and left neck dissection & 2 times Radioactive iodine ablation first in 2020 and second in 2021. Rising Tg. PET Imaging for Suspected recurrence.
- **Hypermetabolic left neck mass – known primary**
- **Hypermetabolic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



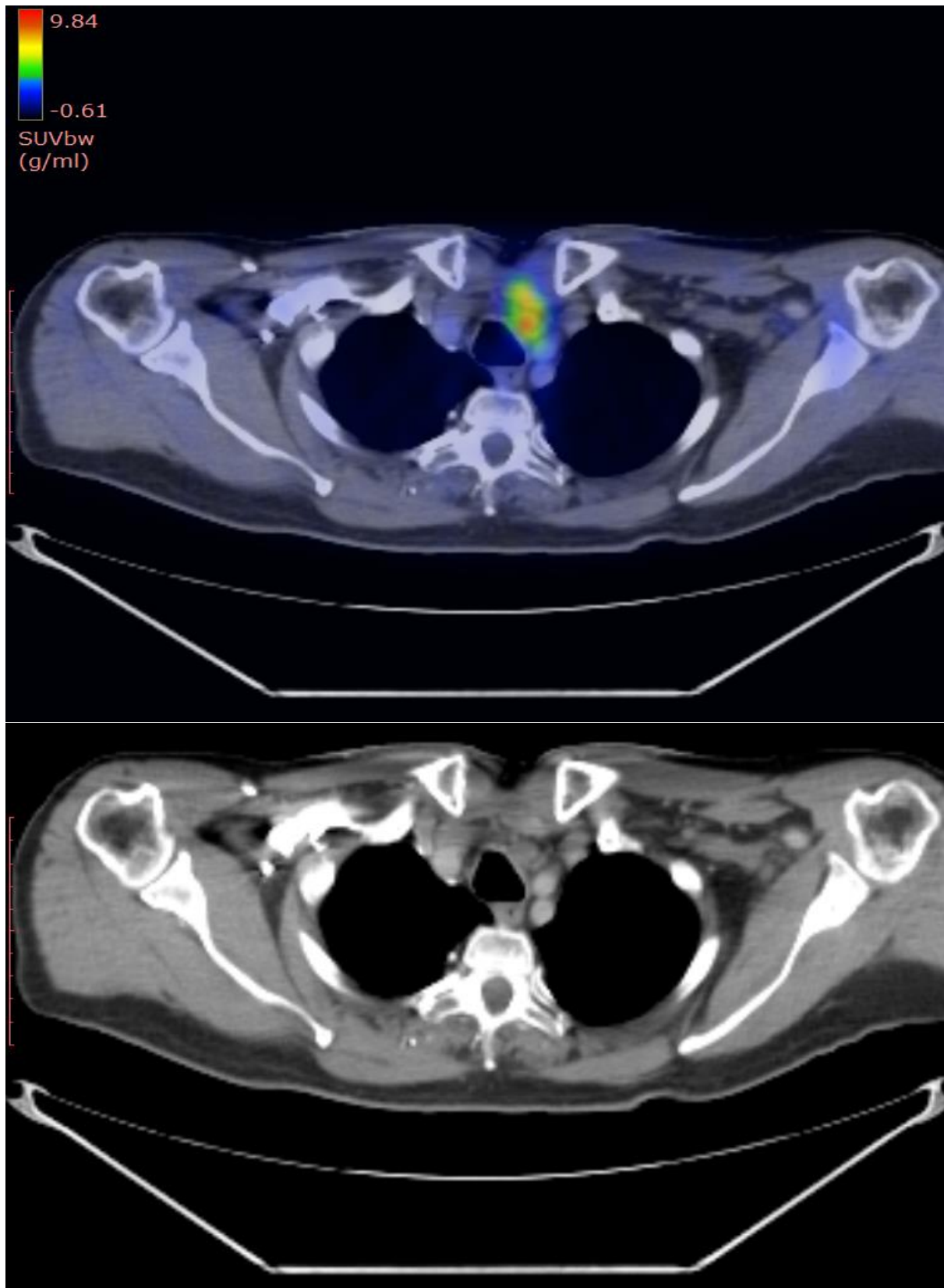
PET-CT & CT Chest (Axial Plane)



PET-CT & CT Chest (Coronal Plane)



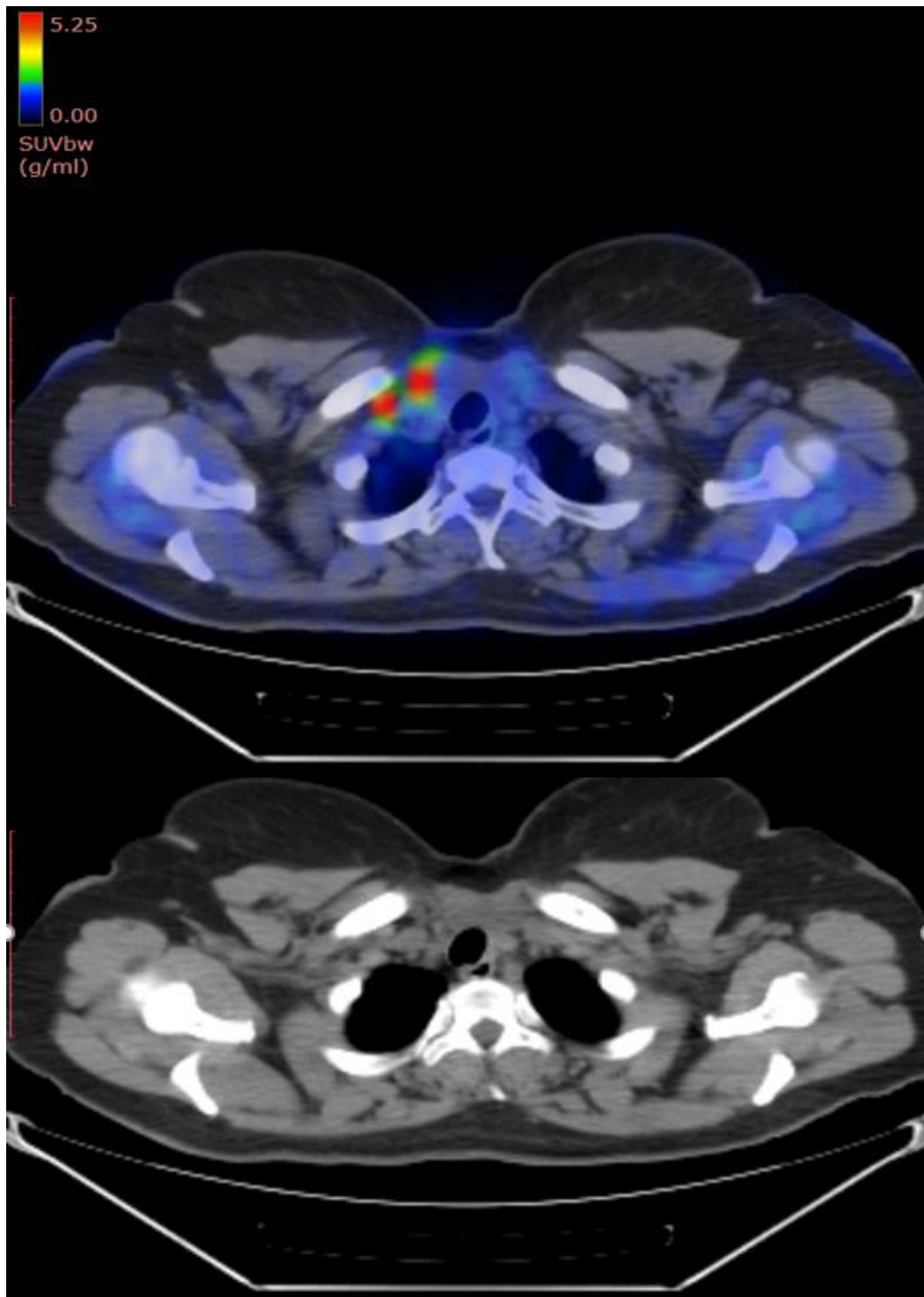
PET-CT & CT Neck (Axial Plane)



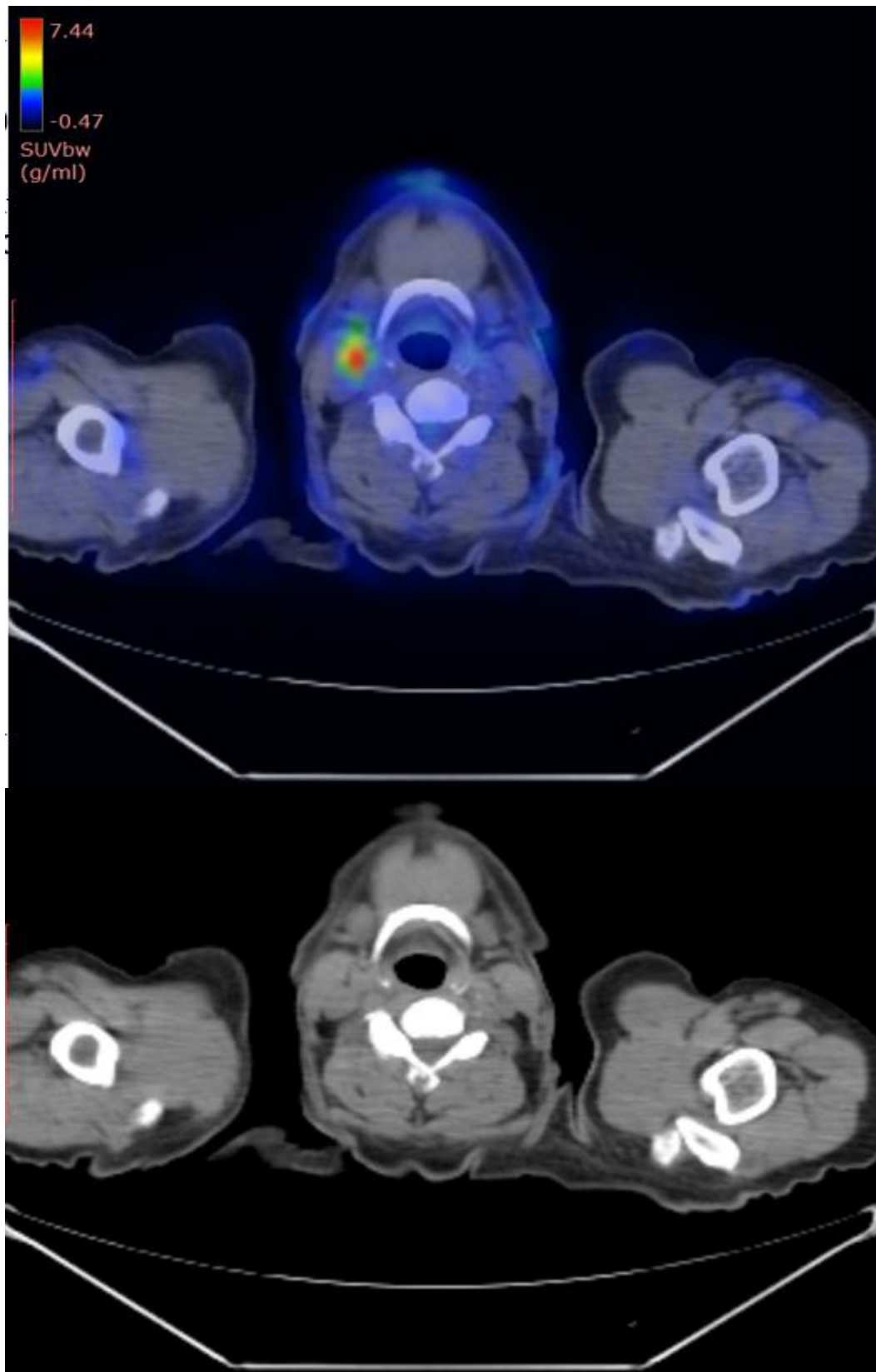
PET-CT & CT Neck (Axial Plane)

Case No: 02

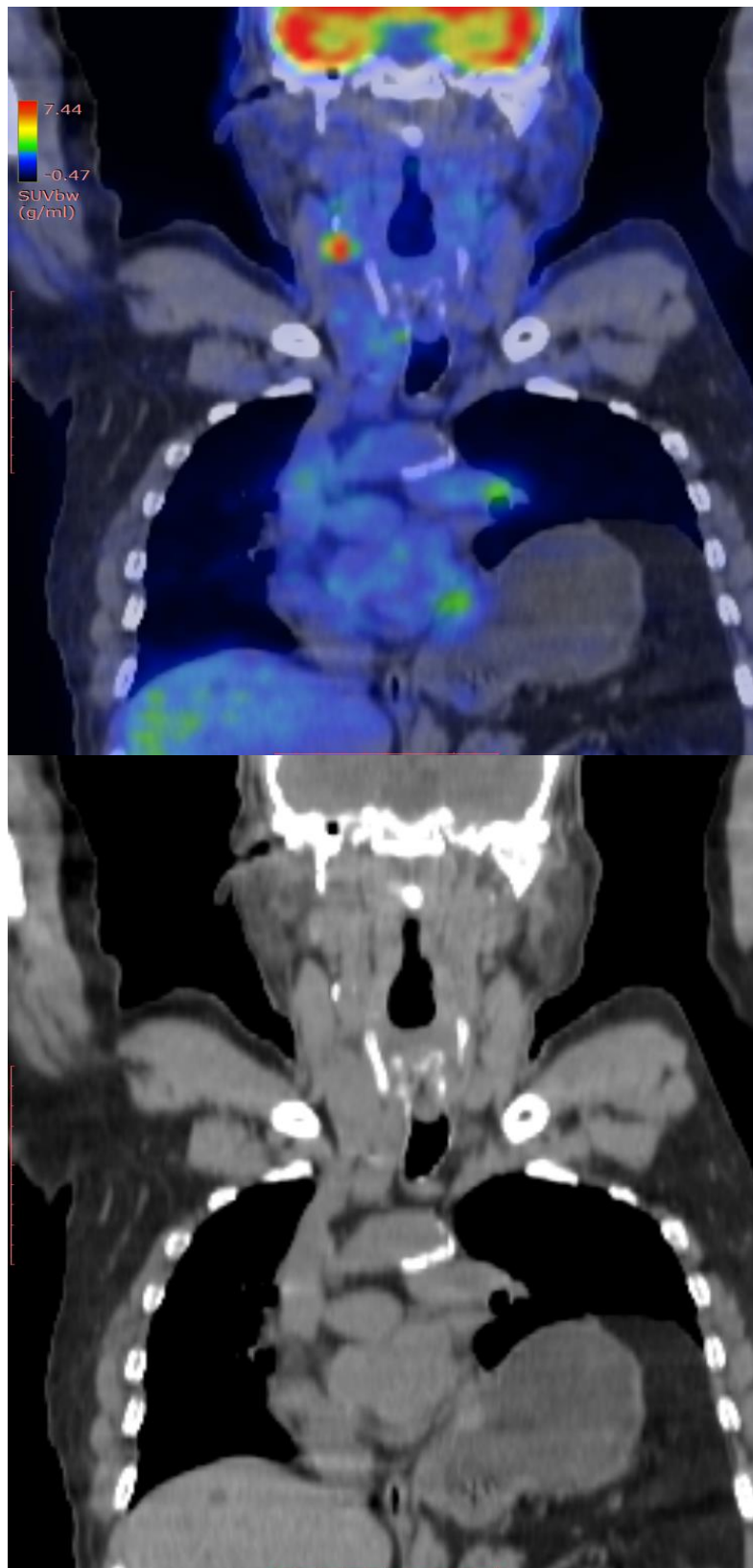
- Very small sized lymph nodes on right side showing metabolic activity which were not significant on CT however PET positive.



PET-CT & CT Chest (Axial Planes)



PET-CT & CT Neck (Axial Planes)



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