

Utility of F-18 Fluorodeoxyglucose Positron Emission Tomography - Computed Tomography in Primary Thyroid Lymphoma

Abstract

Primary thyroid lymphoma (PTL) is an uncommon malignancy. The majority of PTLs are non-Hodgkin's lymphoma. Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET/CT) is the state-of-the-art imaging in lymphoma and plays a pivotal role in staging, follow-up, and treatment decisions. There is good evidence that it performs well in a wide variety of nodal and extranodal lymphomas (ENL). However, the data are scarce on its usefulness in rare ENL. Herein, we describe four cases of PTLs and a brief review of the literature. FDG PET/CT was performed at baseline to assess the disease status and response to treatment. This case series highlights the varied appearance of PTL and response to treatment. It establishes the importance of FDG PET/CT in the personalized management of PTL.

Keywords: Extranodal lymphoma, fluorodeoxyglucose positron emission tomography-computed tomography, follow-up, non-Hodgkin's lymphoma, primary thyroid lymphoma, staging

Introduction

Primary thyroid lymphoma (PTL) is uncommon and accounts for <2%–5% of all thyroid malignancies and 2.5%–7% of all extranodal lymphomas (ENLs).^[1-3] Graff-Baker *et al.* published the most extensive study of PTL. It included 1408 patients from the surveillance, epidemiology, and end results database. NHL accounts for most cases (98%).^[2] More than two-thirds of the patients have diffuse large B-cell lymphoma (DLBCL) histological subtype. Other histological subtypes include follicular (10%), marginal zone or mucosal-associated lymphoid tissue (MALT) (10%), and small lymphocytic lymphoma (3%).^[2] DLBCL is the most aggressive type, with a stringent treatment protocol.^[2,4,5] MALT lymphoma is a benign variant of PTL. It follows an indolent course and is of low grade.^[2-5] MALT lymphoma can lead to DLBCL, and the two are occasionally diagnosed combined as a mixed subtype.^[4,5]

PTL commonly affects 50–80 years' females with a low incidence in young patients.^[2,5] Patients with Hashimoto's thyroiditis have a 67–80-fold higher risk of getting PTL.^[6] Patients usually present with an enlarging

anterior neck mass with or without cervical lymphadenopathy. Some patients have obstructive symptoms.^[7] B-type symptoms such as fever, night sweats, and weight loss are noted in 10% of individuals.^[8] Fine-needle aspiration cytology (FNAC) is unreliable for diagnosing PTL; hence, ultrasound-guided needle biopsy or surgical biopsy is the primary diagnostic modality.^[9]

Positron emission tomography-computed tomography (PET/CT) has become an integral imaging modality for managing lymphomas, including staging, prognostication, response assessment, and treatment planning.^[10] It is more accurate than anatomic imaging CT or magnetic resonance imaging. It distinguishes between viable tumor and necrosis or fibrosis in posttherapy residual mass frequently noted in lymphoma without any clinical or biochemical evidence of disease.^[10] However, due to the rarity of PTL, there is scarce data available for PET/CT utilization in it. The published literature regarding FDG PET/CT for evaluation and treatment response assessment of PTL is limited.^[11-13] We reported four cases of PTL that show varied responses to therapy, highlighting the utility of FDG PET/CT in the entity.

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Case Report

Case 1

For 4 months, a 17-year-old male experienced gradual swelling of his neck. He also had complained of discomfort during swallowing. He had repeated episodes of fever with drenching night sweats. On examination, large hard swelling was noted in the neck, likely arising from the thyroid. It moved with deglutition. His biochemical and hematological parameters were normal except for raised serum LDH (752 U/L). FNAC was suggestive of lymphoid malignancy. Biopsy revealed DLBCL. Immunohistochemistry (IHC) demonstrated that lymphoid cells expressed CD20, PAX5, and Bcl6. It was negative for cytokeratin, TTF1, and CD10. MIB-1 labeling index was ~90%. Pretreatment baseline FDG PET/CT revealed mass arising from the left lobe of the thyroid [Figures 1a and 2a,b]. Mass encased trachea and esophagus with significant airway compromise. FDG-PET/CT was suggestive of stage IE. The patient received four cycles of rituximab, cyclophosphamide, hydroxydaunorubicin, Oncovin, and prednisone (R-CHOP). Interim FDG-PET/CT [Figure 1b] showed a complete metabolic response (CMR) with a significantly decreased mass size. The patient underwent follow-up PET/CT after completing six cycles of R-CHOP chemotherapy. There was complete resolution of the thyroid mass. Mild diffuse FDG uptake was noted in both thyroid lobes [Figures 1c and 2c,d]. He has been in regular follow-up for 1 year and remains asymptomatic. His hematological and biochemical parameters are unremarkable. Follow-up

ultrasonography (USG) of the neck region revealed no abnormality.

Case 2

50-year male presented with a progressively increasing neck mass for 8 months. It was firm to hard in consistency and moved with deglutition. There were multiple bilateral enlarged cervical lymph nodes. Contrast-enhanced CT (CECT) revealed a large, well-defined, heterogeneously enhancing mass in the right thyroid lobe and cervical lymphadenopathy. Serum LDH was elevated (~1872 U/l). Guided FNAC from thyroid mass suggestive of NHL. Biopsy from the mass consistent with high-grade B-cell NHL. IHC reveals atypical lymphoid cells that were positive for CD45, CD20, and PAX5 and were negative for CD3, CD15, and CD30. MIB-1 labeling index was 30%–40%. Baseline FDG PET/CT [Figures 3a and 4a,b] shows FDG avid lesions in both lobes causing mild right side tracheal shift. Apart from mass, there was lymphadenopathy on both sides of the diaphragm. FDG PET/CT findings were suggestive of a stage IIIIE disease. The patient was started on R-CHOP chemotherapy. Interim FDG PET/CT [Figures 3b and 4c,d] after four cycles of chemotherapy revealed nontracer avid residual thyroid mass. Findings were suggestive of excellent metabolic response (Deauville Score II). End of treatment, PET/CT revealed no residual disease (Not shown). The patient remained asymptomatic for 1 year. After that, he developed recurrent thyroid swelling. USG revealed enlarged thyroid with a nodule in the left lobe of the thyroid (TIRAD-5) (Not shown).

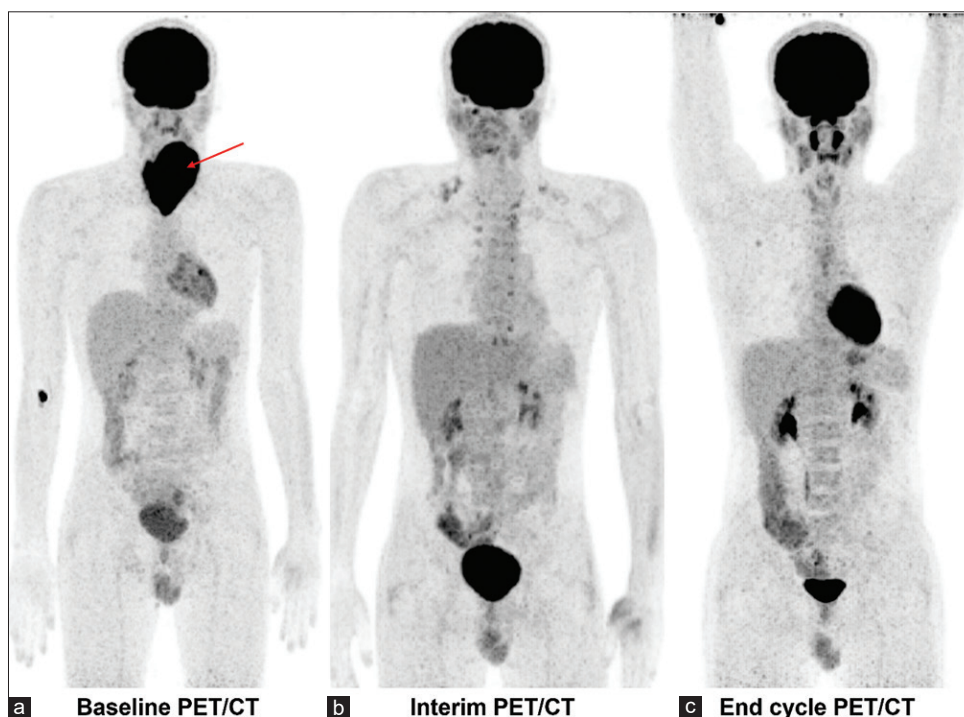


Figure 1: Baseline FDG PET/CT maximum intensity projection (MIP) image (a) revealed increased tracer uptake in the mass lesion in the neck (red arrow), Interim FDG PET/CT MIP image (b) revealed no significant diseases suggestive of Excellent response. End cycle FDG PET/CT MIP image (c) revealed no significant pathological uptake in the body suggestive of Complete response

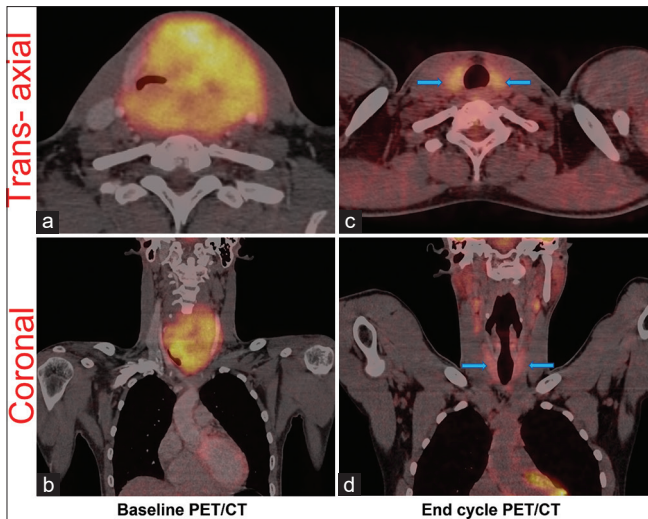


Figure 2: Baseline Fused FDG PET/CT transaxial and coronal images (a and b) revealed a large mass lesion in the bilateral thyroid lobe region (predominantly on the left side) with increased tracer uptake, it is displacing the trachea towards the right side. Fused transaxial and coronal End cycle PET/CT after completion of chemotherapy revealed complete resolution of thyroid mass with diffuse FDG uptake in the bilateral thyroid lobe (c and d)

PET/CT [Figures 3c and 4e,f] revealed metabolically active nodules in both thyroid lobes and lymph nodes in the bilateral axilla. Scan finding was suggestive of disease recurrence. US-Guided FNAC from the thyroid suggested atypical lymphoid cells. USG-guided core biopsy did not show malignancy. The patient was kept on conservative management.

Case 3

A 74-year-old female had complaints of right-sided neck swelling for 3 months. She had dysphagia and multiple episodes of fever. She had significant weight loss over the past 3 months. The swelling was painless and gradually progressive in size. On examination, she had a hard mass in the neck arising from the right thyroid lobe, and it was firm to hard inconsistency. Apart from this, bilateral enlarged cervical lymph nodes were also present. Serum LDH was significantly raised (1326 U/l). CECT neck revealed a mass from the right thyroid lobe and cervical lymph nodes. FNAC from thyroid mass was suggestive of malignant cells in the aspirate. DLBCL diagnosis was established on biopsy. Baseline pretreatment FDG PET/CT [Figures 5a and 6a,b] revealed a large mass in the right lobe of the thyroid. Multiple bilateral cervical and mediastinal lymphadenopathy were also noted. The interim FDG PET/CT after four cycles of R-CHOP chemotherapy [Figures 5b and 6c,d] revealed metabolically active residual soft-tissue lesion in the thyroid. Overall, scan findings suggested a partial treatment response. The patient completed six cycles of chemotherapy and underwent PET/CT [Figures 5c and 6e,f]. It revealed the reappearance of the thyroid mass and lymph nodes. The scan revealed the disease progression with a Deauville

score of V. The patient denied further evaluation and treatment.

Case 4

A 55-year-old female presented with anterior neck swelling for 2 years with recent-onset hoarseness of voice for 2 months. The swelling was progressively increasing in size, there were no B symptoms. On examination, there was a large mass in the anterior neck in the thyroid region, and the lower margin was not palpable. No tenderness was noted, and the overlying skin was normal, there was no palpable cervical lymphadenopathy. On biochemical examination of serum, LDH was found to be 300 U/L. CECT necks revealed homogenous enhancing mass involving the left lobe of thyroid with extension into superior mediastinum. Biopsy from thyroid mass revealed infiltration of lymphoid cells with scattered thyroid follicles overall features suggestive of it being a case of lymphoma. On IHC, lymphoid cells were diffusely immunoreactive for CD20 and largely positive for PAX5. CD3 was positive in the scattered mature lymphocytes. The lymphoid cells are negative for CD10 and cyclin D1. Ki-67 index was 50%–60%. Hence, the diagnosis of DLBCL of the thyroid was made. Baseline FDG PET/CT for staging revealed a large mass on the left side of the neck [Figures 7a and 8a,c] displacing the trachea and esophagus toward the right side. Lobes of the thyroid were not visualized separately. Mass was extending into the superior mediastinum, and it was encasing the left carotid artery. Nonmetabolically active centimetric size multiple cervical lymph nodes were noted. Metabolically active focal soft-tissue thickening was also noted in the fundus of the stomach [Figures 7a and 8b]. Overall features were suggestive of stage IVE disease. The patient was started on RCHOP Chemotherapy. Interim FDG PET/CT after 4 cycles of chemotherapy revealed a faint metabolically active mass lesion on the left side of the neck [Figures 7b and 8d,f] with the disappearance of a focal lesion of the stomach suggestive of residual disease with the partial metabolic response [Figure 8e]. She received 2 more cycles of RCHOP chemotherapy, and an end cycle of FDG PET/CT was performed. End Cycle PET/CT revealed non-metabolically active soft-tissue thickening in the region of the left thyroid lobe (residual thyroid lobe) with no other lesion in the body [Figures 7c and 8g-i] hence CMR status was given. At present, the patient is free of disease and on regular follow-up. No new symptoms were noted.

Discussion

Lymphoma comprises a histologically heterogeneous group of cancers derived from the immune system cells, representing approximately 5% of all cancers.^[14] Lymphoma is a malignancy characterized by the swelling and proliferation of lymph nodes or secondary lymphoid tissue. Both NHL and Hodgkin's lymphoma can develop from or affect practically any. ENL is a terminology that has been coined to characterize a neoplastic growth

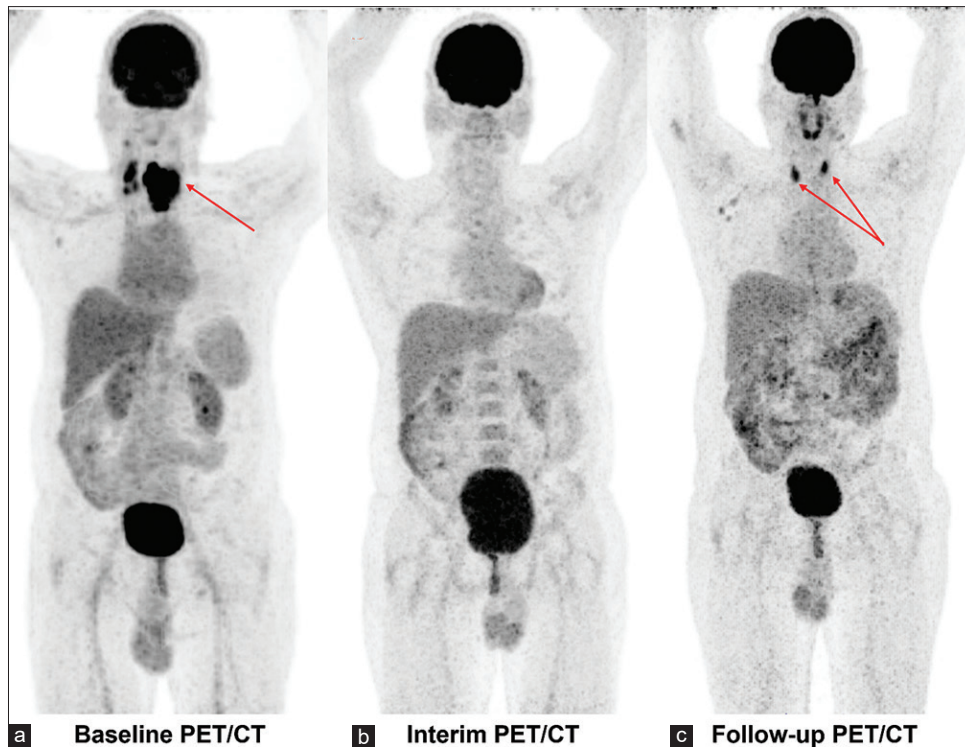


Figure 3: Baseline image (a) revealed increased tracer uptake in a large mass in the thyroid region (red arrow), interim image (b) revealed no significant uptake suggestive of excellent response to chemotherapy. End cycle PET/CT suggestive of excellent response (not shown). The patient developed recurrent thyroid swelling after one year. Follow-up image (c) revealed increased uptake in the bilateral thyroid lobe suggestive of recurrence (red arrow) which turned out to be a false positive on Biopsy

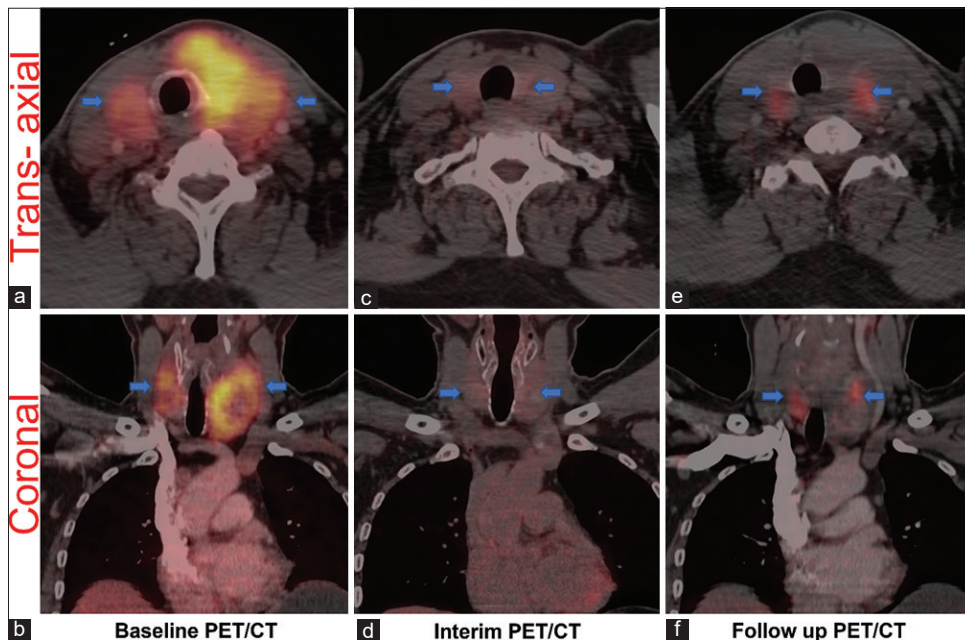


Figure 4: Baseline images (a and b) revealed increased uptake in the large mass in the thyroid region (blue arrow). Interim images (c and d) revealed complete disappearance of FDG uptake and resolution of mass suggestive of excellent response. End cycle PET/CT revealed a complete response (not shown). Patient noticed recurrent thyroid swelling 1 year later, follow up Images revealed increased uptake in bilateral thyroid bed suggestive of recurrence (e and f, blue arrow) which turned out to be false positive on Biopsy

that occurs outside of the expected native lymph nodes or lymphoid tissues. Among the non-lymphoid tissues, the gastrointestinal tract, head, neck (Waldeyer's ring),

skin, orbit, central nervous system, lung, and bone have more predilection. The prevalence and distribution vary significantly depending on the histologic type and stage

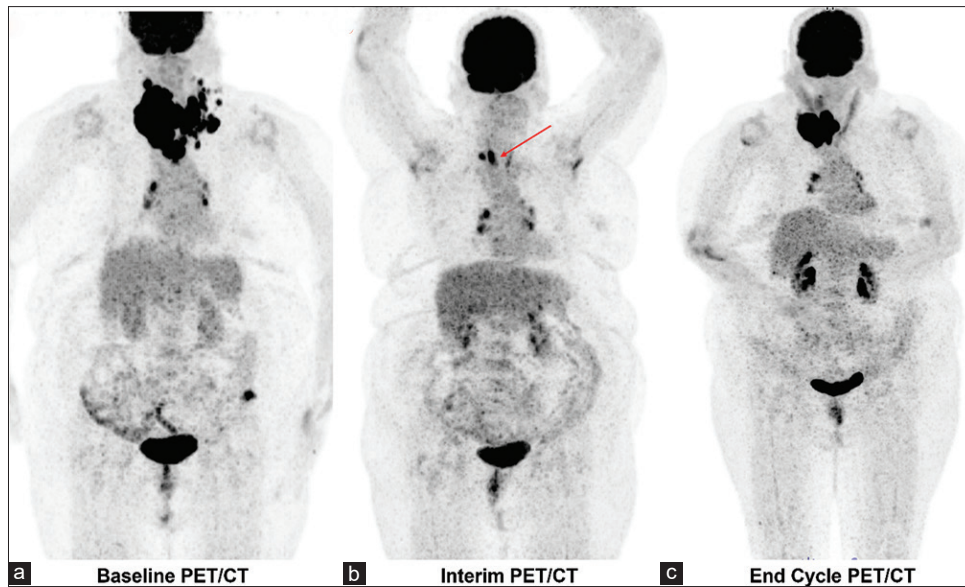


Figure 5: Baseline FDG PET/CT MIP image (a) revealed increased tracer uptake in enlarged thyroid mass with multiple cervical and mediastinal lymphadenopathy, interim FDG PET/CT MIP image (b) after chemotherapy revealed a significant decrease in thyroid mass with decreased uptake suggestive of partial response to chemotherapy. End cycle FDG PET/CT (c) revealed a further increase in thyroid mass with increased uptake suggestive of Disease recurrence

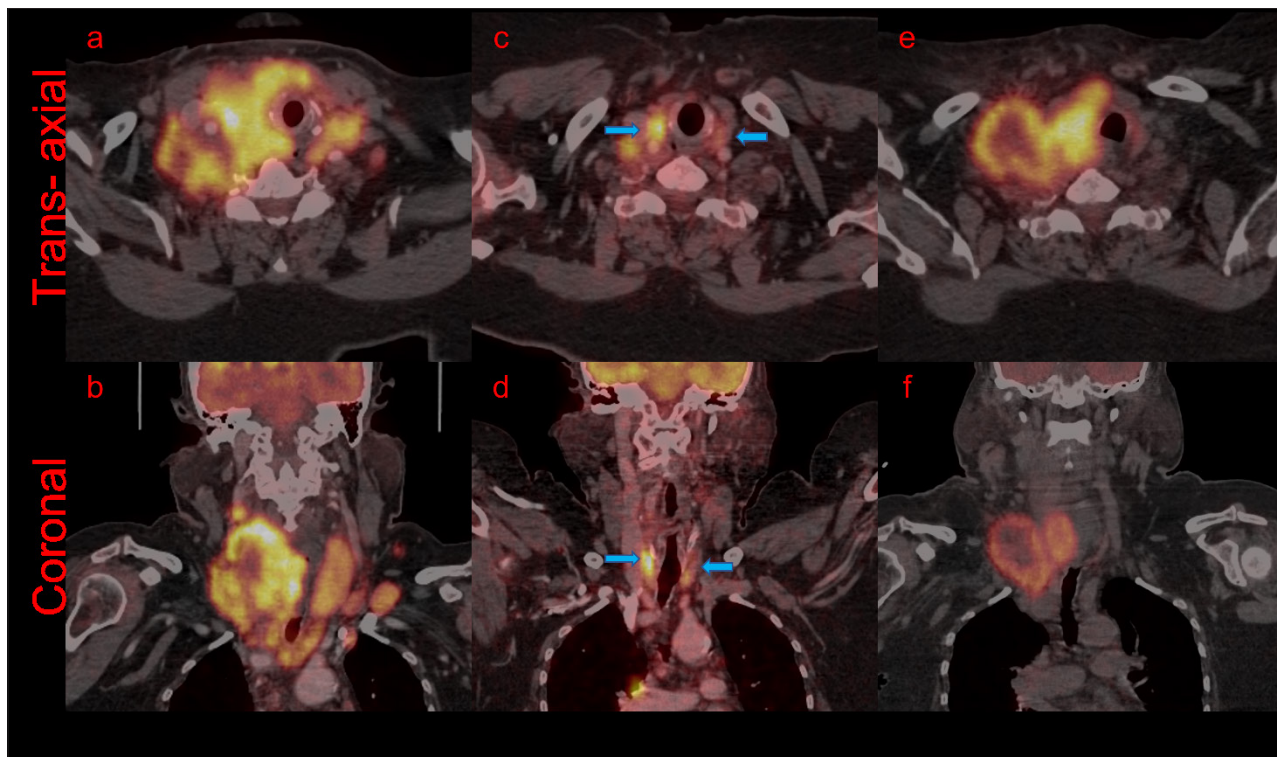


Figure 6: Baseline FDG PET/CT images (a and b) revealed increased tracer uptake in enlarged thyroid mass encasing internal carotid and jugular vein with multiple cervical lymphadenopathies, interim FDG PET/CT images (c and d) after chemotherapy revealed a significant decrease in thyroid mass with decreased uptake suggestive of partial response to chemotherapy. End cycle FDG PET/CT images (e and f) revealed an increase in thyroid mass with increased FDG uptake suggestive of Disease recurrence

of the disease. The reported incidence of ENL is between 25% and 40% of all NHL, depending on geography.^[15] The skin is the most frequent extranodal location, followed by the head and neck. Primary ENL tends to be localized and has more often extranodal relapses than the nodal

form of the disease.^[16] Histologically, DLBCL is the most common variant, followed by follicular lymphomas. Other lymphoma subtypes, such as mucosa-associated lymphoid tissue (MALT) lymphomas and mantle cell lymphomas, are less common lymphoma subtypes but are linked with

Table 1: Clinicopathological features of cases of lymphoma involving the thyroid gland

Authors (year)	n	Age/sex	Symptoms	Stage	PET	Treatment received	Outcome
Hardoff et al. (1995) ^[20]	2	18-20/all females	1 year history of solitary thyroid nodule f/b cervical lymphadenopathy Painless throat fullness, dysphagia, fever	IIE (n=2)	N	CT, RT (n=2)	NED at 1 year NED at 1.5 years
Wang et al. (2005) ^[21]	5	From 29-59/all females	Hoarseness and stridor Rapidly growing neck mass Dysphagia (n=2) History of HL 14 years ago. Painless thyroid nodule	IIIE (n=4) IE (n=1)	Y	Partial thyroidectomy f/b CT (n=2) Complete thyroidectomy f/b CT (n=1) CT (n=1) Complete thyroidectomy. Recurred year later in cervical LN, treated with CT (n=1)	NED (n=3) CR at last follow-up (n=2)
Basu et al. (2009) ^[22]	6	16-83 all females	Neck swelling (n=5) Neck swelling, Hashimoto's thyroiditis (n=1)	IE (n=3) IIE (n=2) IIIE (n=1)	Y (n=6)	CT (n=6)	CR (n=1) Recurrence (n=2) Not described (n=3)
Kakkar et al. (2019) ^[23]	11	65-76/female (n=8) 60-65/male (n=3)	Neck mass (n=11) Dysphagia (n=3) Dyspnea (n=1) Change in voice (n=1) Fever (n=1)	IE (n=4) IIE (n=3) IVE (n=1) NA (n=3)	Not given	CT (n=9) NA (n=2)	CR (n=5) PD (n=1) LFU (n=3) Dead (n=1) PR (n=1)
Acar et al. (2019) ^[24]	4	51-64 Female (n=2) Male (n=2)	Neck mass (n=4) Fever respiratory discomfort (n=2)	IE (n=1) IIIE (n=3)	N	Total thyroidectomy f/b CT, RT (n=2) CT, RT (n=2)	NED at 5 years (n=3) Dead (n=1)
Present cases	4	17-74 Female (n=2) Male (n=2)	Gradually increasing neck swelling (n=4) Hoarseness (n=1) Discomfort during swallowing (n=2) B symptoms (n=2)	IE (n=1) IIE (n=2) IVE (n=1)	Y (n=4)	CT (n=4)	NED at 1 year (n=2) Disease Progression at last follow-up (n=2)

N: Not done, Y: Done, CT: Chemotherapy, RT: Radiotherapy, NED: No evidence of disease, CR: Complete remission, NA: Not available, PD: Progressive disease, LFU: Lost to follow-up, PR: Partial response, PET: Positron emission tomography, HL: Hodgkin's lymphoma, f/b: Followed by

a high rate of extranodal involvement.^[17] ENL is infrequent in Hodgkin's disease. It commonly spreads by direct extension from adjacent nodal disease; the hematogenous spread is rare in only 5%–10% of patients.^[17]

PTL is uncommon and primarily affects older women. It accounts for <5% of all thyroid malignancy and 1%–2.5% of all lymphomas.^[2,3] Most PTLs present with an enlarging neck mass. A rapidly enlarging neck mass should trigger concern for PTL. DLBCL is the most common subtype.^[5,9] Symptoms may last from a few days to years before being diagnosed, with DLBCL patients reporting a shorter time frame.^[5] Compressive symptoms such as dyspnea, dysphagia, stridor, and hoarseness affect one-third of patients. Pain over the mass is not common (12%).^[5,18,19] Weight loss, fever, and night sweats are infrequent (10%).^[19]

Here reported all four cases presented with enlarging neck mass. Two patients had obstructive and B symptoms. One patient had a complaint of hoarseness of voice. We reviewed the English literature on PTL [Table 1].

Only larger studies were taken in this review. PTL has a female predominance, with only six male patients among 31 cases. Age ranged from 16 years to 83 years. Most of the patients were presented with enlarging neck mass. Compressive symptoms such as dysphagia, dyspnea, and stridor were reported in 11/31 cases (35.4%), while infiltration of adjacent organs was seen in two cases. B symptoms are found in 4/31 (13%) patients. The staging was available in 28 patients. Ten patients presented with stage IE. Stage IIE, IIIE, and IVE were noted in 9 (29.9%), 10 patients (32.2%), and one, respectively.

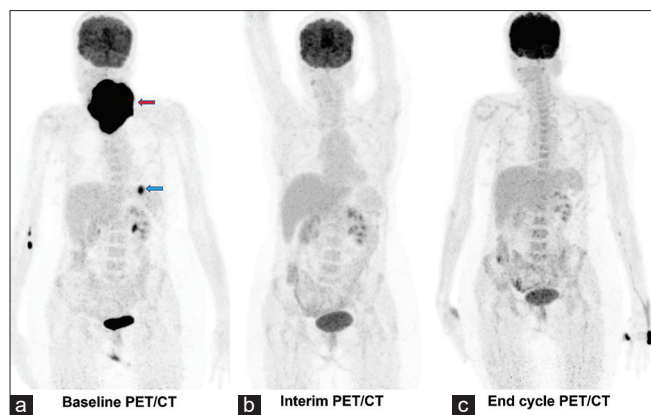


Figure 7: Baseline MIP image (a) revealed increased tracer uptake in the neck (predominantly left) region (a, red arrow) with a focal area of increased uptake in the fundus of stomach (a, blue arrow). Interim MIP image (b) after chemotherapy revealed a significant decrease in thyroid mass with the disappearance of fundus uptake suggestive of excellent response. End cycle MIP image (c) revealed complete disappearance of thyroid mass with absent FDG uptake suggestive of CMR. FDG-PET-CT: Fluorodeoxyglucose positron emission tomography computed tomography, MIP: Maximum intensity projection

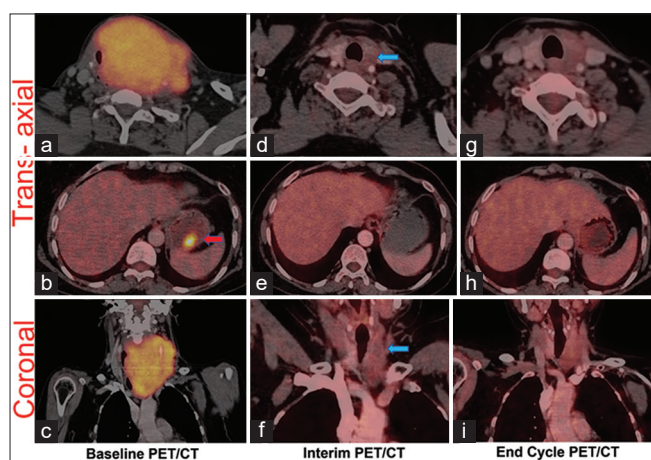


Figure 8: Baseline images (a and c) revealed increased uptake in the neck region (predominantly left), and increased tracer uptake in the stomach suggestive of gastric involvement (b, red arrow). Interim images (d and f) after chemotherapy revealed a hypodense lesion in left thyroid lobe region with faint FDG uptake (blue arrow) and disappearance of fundus uptake (e). End cycle images revealed complete disappearance of thyroid mass lesion (g and i) with absent uptake in the stomach (h) suggestive of CMR

Six patients (19.3%) underwent surgery followed by chemoradiotherapy. Twenty-three patients (74%) were treated with chemoradiotherapy. FDG PET/CT was available in 14 patients. No evidence of disease is noted on the last follow-up in 17/31 (54.8%) patients.

FDG PET/CT is a hybrid functional modality. It improves the depiction of lymphomatous involvement in normal-sized organs. It has become the standard imaging tool for initial staging, follow-up, and therapy response assessment.^[25,26] Several studies have found that F-18 FDG PET/CT is superior to standard CT for assessing extranodal involvement.^[17,27] PET/CT has 88% and 100% sensitivity and specificity for extranodal involvement, respectively,

compared to 50% and 90% for CECT.^[28] In our patients, PET/CT helped in the initial staging. In case number 1, no additional lesions were noted on PET/CT apart from thyroid mass. In the rest of the cases, extra-thyroidal involvement was seen. The available literature is insufficient regarding the exact role of FDG PET/CT for PTL.^[11,12,29] Normal thyroid has no or minimal FDG uptake.^[30] PTL usually presents diffuse uptake in the enlarged gland or focal lesions on FDG PET/CT. Focal thyroid FDG uptake has been associated more with other primary thyroid malignancies.^[31] However, low-grade lymphomas, such as those caused by MALT, have limited sensitivity with 18F-FDG PET/CT. Mikosch *et al.* suggested intense 18F-FDG uptake in the MALT lymphoma with coexisting Hashimoto's thyroiditis. It may be due to the inflammatory component of lymphocytic thyroiditis rather than lymphoma.^[32]

FDG PET/CT is frequently used to evaluate therapy response in lymphoma. Interim PET/CT can detect the patients who have disease resistance to chemotherapy early in the disease. This could lead to a change in management.^[12,33] In the first and fourth cases, the interim PET/CT showed a CMR and disease-free status in follow-up. In the second case, the PET/CT was suggestive of disease relapse, which turned out to be a false positive. There was residual disease in the interim PET/CT in the third case, and the patient relapsed in follow-up. These cases provide insight into the rare PTL. PTL has a varied appearance and clinical presentations. Interim PET/CT helps detect the residual disease and predict a treatment failure. A long-term clinical follow-up is needed as the disease may relapse even after a successful treatment response on PET/CT.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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