

# Quintessential Role of 18Fluorine Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Differentiation of Viable Tumor Tissue and Nondisease Desmoplastic Residue

## Abstract

The authors report a series of cases of treated nodal, solid malignancies showing persisting physical residue after completion of treatment with 18-F fluorodeoxyglucose positron emission tomography-computerized tomography showing non-avid status conjuring a nondisease desmoplastic residue over morphological disease.

**Keywords:** 18F-fluorodeoxyglucose positron emission tomography/computed tomography, desmoplastic residue, non-Hodgkin's lymphoma, seminoma testis

## Introduction

18-F fluorodeoxyglucose positron emission tomography-computerized tomography (18F-FDG PET-CT) has a very important role in staging, restaging, prognostication, therapy response monitoring, and also in early detection of recurrence in a number of malignancies.<sup>[1]</sup> It also provides essential information for planning radiation treatment, helping with critical decisions when delineating tumor volumes and residue.<sup>[2]</sup> Besides, all these, it is the only metabolic imaging testifying the absence of disease in the presence of a residual mass after the standard of care. This case series is intended to highlight the pivotal role of FDG PET-CT in differentiating viable tumor mass from fibrotic/desmoplastic residue to enable precise further management. A meticulous evaluation of PET and CT findings with judicious understanding of limitations is mandatory for the optimal utilization of this technique to differentiate metabolically active disease versus nondisease fibrotic residue and to prevent further downstream unwarranted therapy or investigations.

## Case Reports

### Case 1

A 70-year-old male presented with progressive painless abdominal distention of 6 months duration with no bowel

related symptoms or any systemic B symptoms manifestation such as fever, loss of appetite, or weight. Imaging workup with CT revealed a large mesenteric nodal mass measuring 22 cm × 22 cm × 22 cm, nonobstructively encasing the mesenteric vessels [Figure 1a]. Trucut biopsy revealing Non-Hodgkin's Lymphoma confirmed on immune histochemistry with CD 20, CD 3 markers. Bone marrow biopsy did not show any marrow involvement. The patient was started on R CHOP regime preceded by prephase induction with steroids in view of bulky disease. Post three cycles of R-CHOP, an interval response assessment was done with contrast CT abdomen which showed regression of the mass to 14.1 cm × 7.9 cm × 12.5 cm [Figure 1b]. In view of the morphological response on CT, further three cycles of R CHOP were completed uneventfully with good symptomatic improvement. PET-CT was performed at the end of treatment showed a totally non-FDG avid residual mass 13.6 cm × 7.6 cm × 11.5 cm [Figure 1c], of similar dimensions as were seen in the interim CT. There was thus a complete metabolic regression with morphological residue of sizable dimension which presumably was a desmoplastic residue than the viable disease in view of the metabolic inactivity and nonprogressive static size. However, a multidisciplinary tumor board

**Vatturi Venkata Satya Prabhakar Rao, Vijaya Aditya Yadaraju<sup>1</sup>, Aditya Narayan<sup>1</sup>, Muralidhar Bora<sup>1</sup>, Praveen Adusumalli<sup>2</sup>, Sweta Sinha<sup>3</sup>**

*Departments of Nuclear Medicine and PET-CT, <sup>1</sup>Radiation Oncology, <sup>2</sup>Medical Oncology and <sup>3</sup>Pathology, HCG Cancer Centre, Visakhapatnam, Andhra Pradesh, India*

### Address for correspondence:

*Dr. Vatturi Venkata Satya Prabhakar Rao, Department of Nuclear Medicine and PET-CT, HCG Cancer Centre, Visakhapatnam - 530 045, Andhra Pradesh, India. E-mail: vvs\_prabhakar@yahoo.co.uk*

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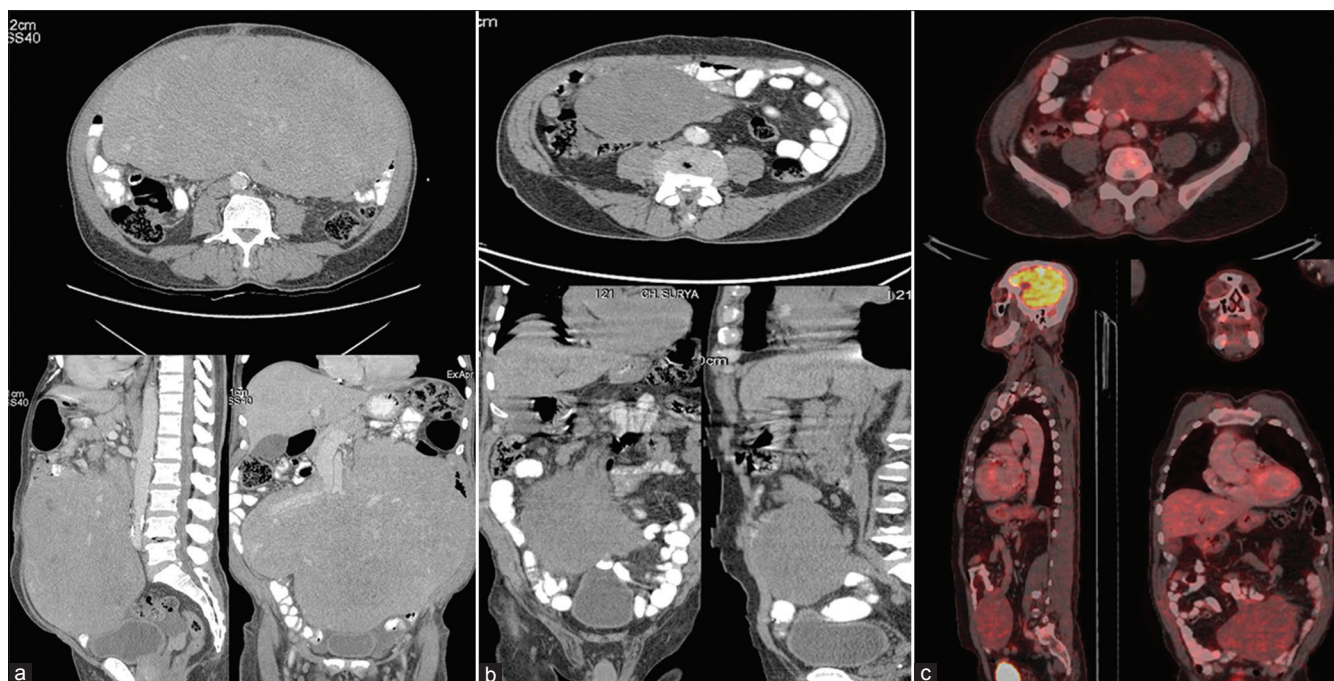
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**Figure 1:** (a) Computerized tomography mesenteric nodal mass 22 cm × 22 cm × 22 cm nonobstructively encasing the mesenteric vessels. (b) Post three cycles chemotherapy interim computerized tomography abdomen showing regression of the mesenteric nodal mass to 14.1 cm × 7.9 cm × 12.5 cm. (c) Positron emission tomography-computerized tomography at end of treatment showing nonfluorodeoxyglucose avid residual mass 13.6 cm × 7.6 cm × 11.5 cm, of similar dimensions as were seen in the interim computerized tomography

deliberation opted for a radiotherapy adjuvant due to the large physical residue and hence radiation therapy of 40 Grey in 20 fractions was also given. Postradiotherapy follow-up with imaging after 6 weeks with a CT-scan abdomen showed the mesenteric mass remaining unchanged in dimensions [Figure 2a], thus substantiating the premise that disease had complete metabolic remission at the end of treatment with PET negativity, and the morphological residue was only a nondisease desmoplastic component which remains unchanged even after radiotherapy. The patient is on clinical follow-up with symptom and disease-free status. Most recent PET-CT done 1 year after the last review continues to show the same metabolic inactivity and static unchanged morphology [Figure 2b].

### Case 2

A 44-year-old male presented with progressive painless right axillary swelling of 6 months duration. Biopsy revealing Non-Hodgkin's lymphoma. Staging PET-CT revealed an intensely metabolically active right axillary nodal mass, with no other station of lymph nodal involvement nor was any abnormal metabolically active focus identified in rest of the body [Figure 3a]. The patient underwent six cycles of chemotherapy followed by 40 Grey radiation therapy in 20 fractions. The patient was symptom-free, and end of treatment PET-CT revealed complete morphological regression of the right axillary nodal mass with a small ill-defined non-FDG avid, nonmetabolic desmoplastic residue [Figure 3b].

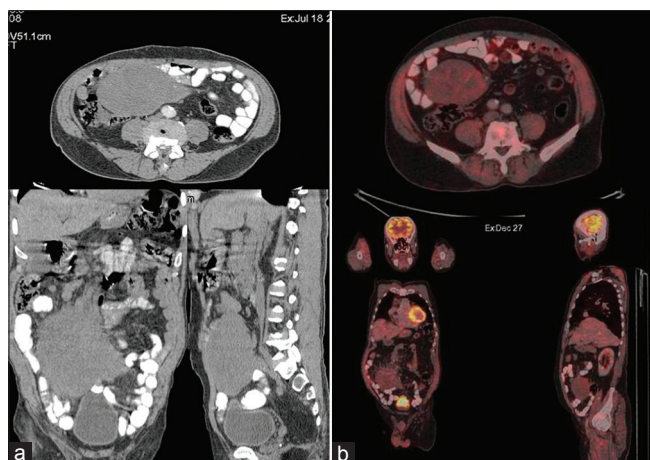
### Case 3

A 44-year-old female with hemoptysis 18 F-FDG PET-CT revealing metabolically active centrally necrotic right upper lobe mass [Figure 4a] diagnosed as small cell carcinoma lung on biopsy underwent concurrent chemoradiation therapy with cisplatin, etoposide and 60 Grey radiation therapy in 30 fractions. End of treatment evaluation with PET-CT revealed complete metabolic regression with a non-FDG avid bland homogeneous residual soft-tissue density in right upper lobe [Figure 4b] with the patient in complete symptomatic relief and disease-free status.

### Case 4

A 29-year-old male who was diagnosed with seminoma right testis underwent high orchidectomy followed by three cycles of chemotherapy comprising of bleomycin, etoposide, and cisplatin. End of the treatment PET-CT revealed no residual disease in the right scrotum, non-FDG avid bulky aortocaval nodes at second lumbar vertebral level [Figure 5a] Alfa Fetoprotein (AFP), lactose dehydrogenase (LDH), and human chorionic gonadotropin (HCG) levels were normal. Having completed the standard of care treatment and the patient being clinically disease-free along with nonelevated marker levels and nonmetabolic PET-CT residue was advised noninterventional surveillance. However, the patient reported only after 4 years for review, and a PET-CT revealed exactly similar findings with metabolically inert and morphologically unchanged



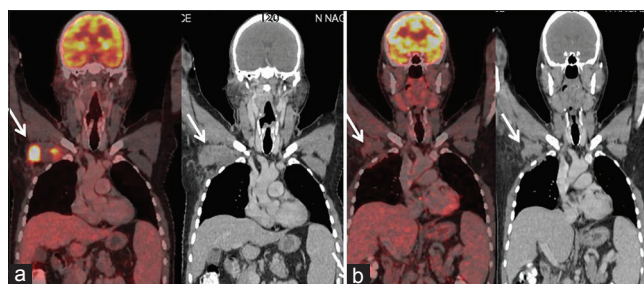


**Figure 2:** (a) Postradiotherapy follow-up computerized tomography scan abdomen showing the mesenteric mass remaining unchanged in dimensions. (b) Positron emission tomography computerized tomography 1 year after last review showing static morphology and metabolic inactivity

aorticaval [Figure 5b] and normal levels of AFP, LDH, and HCG. Two years later, PET-CT continues to show unchanged non-FDG avid aorticaval nodes [Figures 5c] and patient clinically and marker wise free of disease. Thus, an evidence-based 6 years' posttreatment temporal follow-up was recorded with non-FDG avid desmoplastic nodal residue in a clinically disease-free and marker negative status.

## Discussion

Treatment-related evidence of cure in a solid organ malignancy including lymph nodal disease has historically been objective disappearance of the physical mass on conventional imaging like CT. The persistence of physical form connotes unresolved disease.<sup>[3]</sup> CT and ultrasonography evaluate the size component reliably, and a subcentimetric nodal size in the short axis has been assigned nonpathological status. However, it is noted on many occasions that nodal size <1 cm harbors disease and size more than a centimeter can represent fibrotic nondisease residue, thus conjuring a dilemma of viable disease versus fibrotic response.<sup>[4,5]</sup> <sup>18</sup>F-FDG PET-CT has been able to distinguish between posttreatment fibrosis and viable tumor. <sup>18</sup>F-FDG PET-CT has a higher specificity of 92% versus 17%, and a higher accuracy of 96% versus 63% over CT.<sup>[6]</sup> PET-CT has been able to address the issue by demonstrating that metabolic regression is a reliable parameter in being able to demonstrate the more sensitive and specific metabolic remission of disease despite the persistence of physical mass. As seen in all the three cases, the persisting mass is factually a desmoplastic residue comprising of connective tissue characterized by low cellularity, hyalinized, or sclerotic stroma. This growth called desmoplastic response occurs as a result of tissue injury or neoplasia and is a tissue reaction than disease mass.



**Figure 3:** (a) Positron emission tomography-computerized tomography showing intensely metabolically active right axillary nodal mass (Arrow). (b) End of treatment positron emission tomography-computerized tomography showing complete metabolic regression of the right axillary nodal mass with a small ill-defined nonfluorodeoxyglucose avid desmoplastic residue (Arrow)

The stromal reaction in cancer is similar to the stromal reaction induced by injury or wound repair. The result is an increased extracellular matrix production which spuriously contributes to the total bulk of the tumor. The interaction between cancer cells and surrounding tumor stroma is bidirectional and is contributed both by the tumor and the host tissue.<sup>[7]</sup> The quantum of desmoplastic reaction is variable, however, some malignancies evoke a higher degree of desmoplastic response especially mucin-producing tumors. Desmoplasia has a number of underlying causes. The mechanism of which is mediated through the proliferation of fibroblasts and subsequent secretion of collagen. A desmoplastic response is characterized by larger stromal cells with increased extracellular fibers.<sup>[6]</sup>

Mitotic solid tumor lesions including lymph nodal diseases are sought with this desmoplastic physical component spuriously adding to the gross tumor volume thus posing a clinical and therapeutic challenge. PET-CT assessment of treatment response in these situations addresses this complexity by discriminating the desmoplastic component from the viable tumor component by its bland nonenhancing non-FDG avid nature, while any residual tumor will be showing varying degrees of FDG avidity.<sup>[8]</sup> The first case reaffirms this logic by revealing non-FDG avid nature of a fairly large posttreatment residue persisting even after completion of both chemotherapy and radiotherapy. The last case reveals persisting small retroperitoneal nodal residue in a 6 years' follow-up not changing in the size and PET negativity all through.

PET/CT in the evaluation of treatment response has overcome some of the limiting factors of CT, which include the size criteria for lymph node involvement, the differentiation of unopacified bowel from lesions in the abdomen and pelvis, and the inability to differentiate viable tumor from necrotic/fibrotic lesions after therapy.<sup>[3]</sup>

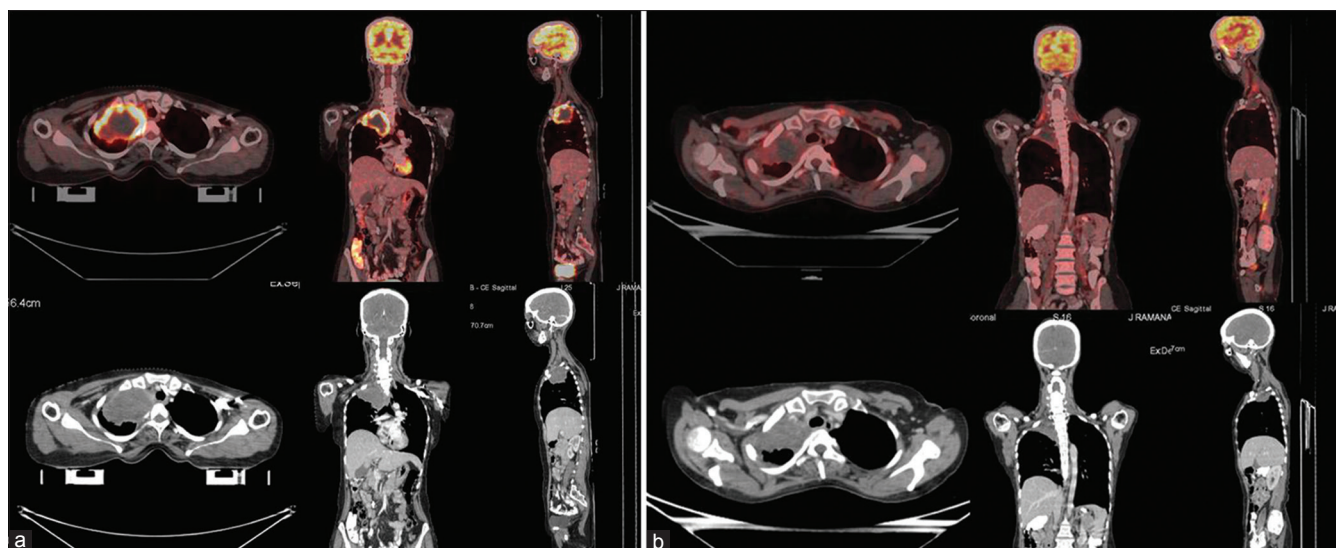


Figure 4: (a) Positron emission tomography-computerized tomography revealing an intensely peripherally metabolically active centrally necrotic right upper lobe lung mass. (b) End of treatment positron emission tomography computerized tomography showing complete metabolic regression and a hypodense homogeneous soft-tissue desmoplastic residue in the right upper lobe

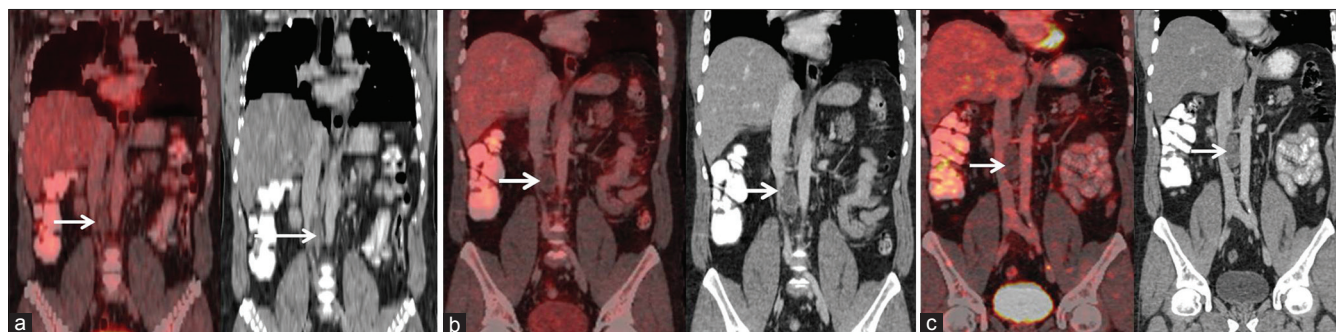


Figure 5: (a) End of treatment positron emission tomography-computerized tomography revealing nonfluorodeoxyglucose avid bulky aortocaval nodes at second lumbar vertebral level (Arrow). (b) Positron emission tomography-computerized tomography 4 years after treatment showing exactly similar metabolically inert and morphologically unchanged aortocaval nodes (Arrow). (c) Positron emission tomography-computerized tomography 6 years after treatment continues to show unchanged nonfluorodeoxyglucose avid aortocaval nodes (Arrow)

The consensus recommendations of the International Harmonization Project 2007 assign a complete response to all patients with a negative PET scan regardless of the presence of a residual mass on CT.<sup>[9]</sup> In seminomatous germ cell tumors, PET-CT is the best predictor of viable disease in residual masses with a sensitivity of 80% and specificity of 100%, in comparison to CT which has a sensitivity of 70% and specificity of 74%.<sup>[10]</sup>

### Conclusion

The recognition of persistence or absence of viable disease in a residual mass especially after the completion of therapy is often intricate. PET-CT by its higher specificity answers this intricate perplexity. Further studies, especially in randomized manner with larger numbers, are required before coming to definitive conclusion of establishing this as a standard of care. However, the findings in these series can be considered as possible guidelines in assigning disease-free status on PET-negative residue.

### 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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