Dual PET/CT with F-DOPA and F-FDG in metastatic medullary thyroid carcinoma and rapidly increasing calcitonin levels: Comparison with conventional imaging

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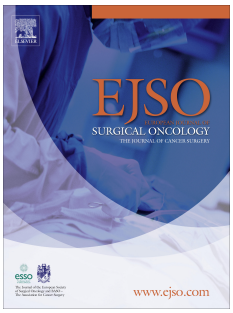

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Dual PET/CT with ^{18}F-DOPA and ^{18}F-FDG in metastatic medullary thyroid carcinoma and rapidly increasing calcitonin levels: comparison with conventional imaging

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Running title: Multi-imaging PET in MTC

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Abstract

Background: To evaluate the role of a multi-imaging PET with ^{18}F-DOPA and ^{18}F-FDG in comparison with conventional imaging (CI) in recurrent medullary thyroid carcinoma (MTC).

Methods: 18 MTC patients who had thyroidectomy were included; they presented with elevated and rapidly increasing calcitonin levels during follow up. CI had revealed metastatic deposits in 9 patients. Patients were referred to us for a PET/CT with ^{18}F-DOPA and ^{18}F-FDG. Histologic/cytologic confirmation of recurrent MTC was obtained in at least one PET-positive lesion in all patients.

Results: Foci of abnormal uptake were observed in 15 patients at ^{18}F-DOPA and in 11 at ^{18}F-FDG; 8 patients showed the same number of positive lesions with both tracers, 2 showed more lesions on ^{18}F-FDG, 1 was positive at ^{18}F-FDG alone and 5 at ^{18}F-DOPA alone. In 3 patients with a DOPA-positive loco-regional relapse a re-operation with curative intent was offered. SUV_{max} values were higher for ^{18}F-FDG compared to ^{18}F-DOPA (mean 12.7 +/- 4.1 vs. 5.5 +/- 2.1, $p<0.05$). Calcitonin was higher in PET positive patients compared to PET negative ones, while no significant differences were observed between ^{18}F-DOPA and ^{18}F-FDG positive patients.

Conclusions: In MTC patients with rapidly increasing calcitonin levels during follow up, ^{18}F-DOPA has a good sensitivity and a complementary role with ^{18}F-FDG PET/CT in detecting metastatic deposits. In our experience, the sensitivity of a multi-imaging ^{18}F-DOPA & ^{18}F-FDG PET/CT approach is greater than that obtained with CI. The higher SUV_{max} values found with ^{18}F-FDG in some patients may reflect more aggressive tumors.

Keywords: medullary thyroid carcinoma; recurrent disease; calcitonin; ^{18}F-FDG PET/CT; ^{18}F-DOPA PET/CT; multi-tracer PET/CT examination

Introduction

Medullary thyroid carcinoma (MTC) is a rare endocrine tumor arising from the parafollicular C cells of the thyroid. It accounts for approximately 3-5% of all thyroid malignancies and can occur in a sporadic form in 70-80% of patients or an hereditary form in 20-30% of patients [1]. Because the C cells produce calcitonin, serum levels of this hormone serve as a reliable and highly sensitive tumor marker for diagnosing MTC recurrence after primary treatment [1]. Another frequently used serum marker is carcinoembryonic antigen (CEA) [2]. Unlike the more common histological type of differentiated carcinoma of the thyroid, MTC cannot be followed up or treated with iodine isotopes, and surgery (total thyroidectomy and loco-regional lymph node dissection) remains the only potentially curative therapeutic approach, particularly in the early stages [3-5].

Surgery is also the treatment of choice for loco-regional recurrent MTC, which is typically suspected on the basis of rising serum calcitonin/CEA levels. Moreover, patients in whom a rapid increase of serum calcitonin levels is observed are usually characterized by a more aggressive behavior of the metastatic spread [1, 6-8]. Patients with recurrent disease to whom re-operation with curative intent should be offered, are those characterized by loco-regional metastatic spread only, while patients with distant metastatic spread may be offered systemic therapy with possible surgery for palliative intent only. Therefore, the early localization of loco-regional deposits plays a mainstay role in planning the subsequent therapeutic strategy. Unfortunately, both morphologic imaging (US, contrast enhanced CT (c.e.CT) and MR) and the traditional scintigraphic imaging (^{123}I/^{131}I-MIBG, ^{99m}Tc(V)-DMSA, ^{111}In-[DTPA]-octreotide, ^{99m}Tc-sestamibi) have demonstrated relatively low to moderate sensitivities in detecting recurrent MTC [7-10].

Recently, some preliminary favourable results have been reported with PET/CT using several positron-emitter radio-tracers such as ^{18}F-FDG, ^{18}F-dopamine, ^{18}F-dihydroxyphenilalanine (^{18}F-DOPA) [11-14] and ^{68}Ga-lebelled peptides [15, 16]. However, the published data on the potential value of PET/CT in detecting deposits of recurrent MTC are still limited.

In the present study we report the preliminary results of a multi-imaging PET approach with ^{18}F-DOPA and ^{18}F-FDG obtained in a group of patients who had total thyroidectomy for aggressive MTC and presenting with recurrent disease detected by elevated and rapidly increasing serum calcitonin levels.

Materials and Methods

Patients

In the period from Sep. 2008 to Aug. 2009, 18 consecutive patients with recurrent MTC diagnosed on the basis of high and rapidly increasing serum calcitonin levels were referred to our centre for a PET/CT evaluation. There were 10 females and 8 males; mean age 51.3 years, range 34 – 68 years. Sixteen patients had the sporadic form of MTC and two were affected by MEN-2b syndrome. All patients had had total thyroidectomy and cervical lymphadenectomy done 13 to 79 months earlier (median 35 months). At initial pathological staging all patients were diagnosed as pT4N+ suggestive of an aggressive pattern of MTC). During post-surgical follow-up all patients experienced elevated and rapidly increasing serum calcitonin levels that doubled over a period of 6-9 months before PET/CT investigation (latest serum calcitonin values ranged from 1,200 to 137,000 pg/ml, mean 57,458 +/- 14,790 pg/ml). In 6 patients serum CEA levels were also increased (range from 24 to 157 ng/ml, mean 68 +/- 22 ng/ml). Before being referred for

PET, all patients had been investigated with US, c.e.CT and ^{111}In[DTPA]-octreotide scan. In addition, 10/18 patients had MR, and 12/18 had ^{123}I-MIBG scan.

Conventional Imaging

Morphologic imaging (US/CT/MR) had shown metastatic deposits in 7/18 (38.8%) patients: 3 in the neck, 2 in the neck/mediastinum, 2 in the liver. Traditional scintigraphic imaging (^{123}I-MIBG / ^{111}In-[DTPA]-octreotide) revealed metastatic deposits in 9/18 (50%) patients: 4 in the neck, 3 in the neck/mediastinum and 2 in the liver.

PET/CT acquisition

All patients underwent a double-tracer PET/CT examination including both ^{18}F-DOPA PET/CT (IASON, Klagenfurt, Austria) and ^{18}F-FDG PET/CT (GE Healthcare, Ispra, Italy) with an interval of 3-14 days between the 2 tests. These two PET radio-tracers are regularly commercialized in Europe and the combined PET/CT imaging procedure in recurrent MTC patients is a routine practice in our institute. Both ^{18}F-DOPA PET/CT and ^{18}F-FDG PET/CT were performed using the same hybrid tomograph (GE, Discovery STE, Milwaukee, WI, USA) with minimum fasting time of 6 hours. Blood glucose was routinely measured before ^{18}F-FDG PET/CT examination: glucose levels were < 140 mg/dl in all cases. With the purpose to obtain comparable PET examinations the same activity of ^{18}F-DOPA and ^{18}F-FDG (2.2 MBq/Kg) was administered and acquisition started 1 hour after injection using the 3D method. Each patient was scanned from the base of the skull to the mid-thigh, with an acquisition time of 3 minutes per bed position (6 to 7 bed positions). Attenuation correction was obtained by a 16-slice CT integrated in the PET/CT system (CT parameters: 120 kV, 60 mA). OSEM algorithm was used for reconstruction and data processed by a dedicated computer (GE, Xeleris, Milwaukee, WI,

USA). SUV_{max} values were calculated by positioning an automatically-generated ROI of 96 mm^2 in the centre of the lesion(s).

PET/CT evaluation

^{18}F-DOPA PET/CT and ^{18}F-FDG PET/CT were evaluated by two nuclear medicine physicians without prior knowledge of clinical and laboratory data. In cases of discrepancy, agreement was reached by consensus. Any focus of non-physiological uptake was considered as pathologic.

Cytology & histology

Cytological (11 cases) or histological (7 cases) findings were regarded as the gold standard.

Statistical analysis

Statistical analysis was performed by Mann Whitney U test to compare mean values and by Chi square test to compare frequencies. *P* values < 0.05 were considered significant. Data are expressed as mean +/- SD.

Results

Analysis per patient

Fifteen out of 18 patients (83.3%) showed foci of abnormal ^{18}F-DOPA uptake, and 11/18 patients (61%) showed foci of abnormal ^{18}F-FDG uptake. In details, 8/18 patients (44.4%) showed the same number of positive lesions with ^{18}F-DOPA and ^{18}F-FDG (Figure 1) and 2 patients showed a greater number of lesions on ^{18}F-FDG (Figure 2). In 1

patient ^{18}F-FDG was the only positive examination, and in 5 patients ^{18}F-DOPA was the only positive examination (Figure 3). The overall ^{18}F-DOPA plus ^{18}F-FDG PET/CT sensitivity was 88.8% (16/18 patients) against a sensitivity of 50% obtained with conventional morphologic plus scintigraphic imaging (p<0.01).

Analysis per lesion

A total of 102 metastatic lesions were visualized at PET: 40 in cervical lymph nodes, 43 in mediastinal lymph nodes, 12 in the liver, 10 in the lungs and 6 in the skeleton. ^{18}F-DOPA PET/CT revealed a total of 84 lesions, whereas ^{18}F-FDG PET/CT showed a total of 64 lesions. The maximum diameter of the lesion detected at PET examination ranged from 1.2 to 5.5 cm, mean +/- SD = 2.7 +/- 1.8 cm. In 3 patients with limited loco-regional relapse revealed with ^{18}F-DOPA alone, a re-operation with curative intent was offered.

It is worth noting that in patients with positive PET results, SUV_{max} values were higher with ^{18}F-FDG than with ^{18}F-DOPA PET/CT (mean 12.7 +/- 4.1, range 2.7 - 16.7 *vs.* mean 5.5 +/- 2.1, range 1.8 – 8.1, respectively, p<0.05).

Correlation between calcitonin levels and SUV_{max}

Calcitonin levels tended to be higher in PET/CT positive patients than in PET/CT negative ones, while no significant differences in calcitonin levels were noted between ^{18}F-DOPA and ^{18}F-FDG positive patients (mean 56,680 +/- 16,387 vs. 58,244 +/- 17,429 pg/ml, p = N.S.).

Discussion

The likelihood of complete disease remission after surgery in small intrathyroid MTC is very high with a 10-years survival rate greater than 90% [1]. However, in patients with

aggressive tumours with invasion of the thyroid capsule and lymph node metastases at presentation (pT4N+), the prognosis is significantly worst. In this group, biochemical progression and loco-regional recurrences and/or spread to distant site are frequent with a 10-year survival rate < 50% [16-18].

MTC therapeutic management

Patients with aggressive MTC are difficult to manage. Unlike differentiated thyroid cancer, MTC cannot be treated with radioiodine. Moreover, neither chemotherapy nor external beam radiotherapy have been shown to be effective in metastatic MTC. The only potentially curative therapeutic option is surgery, both at initial diagnosis and in recurrence. In this respect, it is extremely important to detect metastatic disease at the early loco-regional stage where re-operation with curative purpose can be planned. Unfortunately, both morphologic (US, c.e.CT, MR) and conventional nuclear medicine imaging (^{111}In-[DTPA]-octreotide, ^{123}I/^{131}I-MIBG, ^{99m}Tc(V)-DMSA, ^{99m}Tc-sestamibi), have a relatively low to moderate sensitivity ranging from 25% to 50% in reported series [6-9].

MTC and ^{18}F-FDG PET/CT

Recently, following the widespread employment of PET/CT for the assessment of numerous types of tumors, great progress has been made in the evaluation of neuroendocrine tumors including MTC. The most common positron–emitter radiopharmaceutical is ^{18}F-FDG which is a glucose-analogue. ^{18}F-FDG PET/CT is highly sensitive in the vast majority of tumors, especially those characterized by high metabolic activity and rapid growth. Conversely, in some tumors characterized by low growth such

as well-differentiated neuroendocrine tumors, ^{18}F-FDG PET/CT has relatively low sensitivity.

A limited number of studies have been reported in the literature about the role of ^{18}F-FDG PET in recurrent MTC. De Groot et al [21] reported a study on 26 patients with MTC in which ^{18}F-FDG PET showed higher sensitivity in localizing metastatic deposits when compared to ^{99m}Tc(V)-DMSA, ^{111}In[DTPA]-octreotide, US, c.e. CT and MRI. In particular, ^{18}F-FDG detected metastases in 50% of patients, with a lesion-based sensitivity of 96%. Similar results were reported by Khan et al. [23] in a group of 26 patients with recurrent MTC. In a recent study by Iagaru et al. [24], the authors evaluated a group of 13 patients with MTC and increased serum calcitonin levels, but negative conventional imaging. They found ^{18}F-FDG PET to have a 54% sensitivity in visualizing metastatic deposits. A study from our group [25] focused on a group of 16 patients with MTC evaluated with ^{111}In[DTPA]-octreotide, c.e.CT CT and ^{18}F-FDG PET/CT. The latter modality was the most sensitive in detecting metastases of recurrent MTC patients with increased serum calcitonin levels and was useful to plan a more accurate re-operation. In contrast, Gotthardt et al. [26] studied 26 patients with recurrent MTC and found a higher sensitivity with c.e.CT. CT scan than with ^{18}F-FDG PET in detecting metastatic lesions.

MTC and 18F-DOPA PET/CT

More recently, other positron-emitter radiopharmaceuticals have been proposed to evaluate neuroendocrine tumors, based on the unique property of these tumors to produce and secrete a large variety of substances that can be radiolabelled. One of these substances is ^{18}F-DOPA, an amino-acid labeled with ^{18}F, originally used for the evaluation of movement disorders (mainly Parkinson's disease) [27]. ^{18}F-DOPA has also

been used more recently to differentiate between diffuse congenital hyperglycemia and insulinomas [28] and the detection of neuroendocrine tumors [29]. MTC is associated with the APUD system, and its cells can take up and decarboxylate amine precursors such as DOPA and therefore can be visualized with ^{18}F-DOPA PET/CT.

There are currently scarce data reported in the literature regarding the potential role of ^{18}F-DOPA in MTC patients. Hoegerle et al [26] reported an overall sensitivity of 63% for ^{18}F-DOPA PET in 11 patients with MTC, which was lower than that observed with c.e. CT/MRI (it should be noted that these authors used a stand-alone PET system and not a hybrid PET/CT system), but higher than those observed with ^{18}F-FDG and ^{111}In-[DTPA]-octreotide scan. The authors concluded that ^{18}F-DOPA PET may be a useful supplement to morphological diagnostic imaging that can improve lymph node staging and enable a more specific diagnosis of primary tumor and local recurrence.

In a retrospective analysis by Beuthien-Baumann et al. [14], fifteen patients with MTC were scanned with both ^{18}F-FDG and ^{18}F-DOPA PET. The authors found similar performances for the two methods, suggesting a complementary role of the two imaging modalities. Nonetheless, their observation suggested that ^{18}F-DOPA had more specific uptake than ^{18}F-FDG uptake for metastatic MTC.

Finally, Beheshti et al [11], demonstrated that ^{18}F-DOPA correctly identified 50/53 MTC lesions (81%) compared to 33/53 (58%) detected with ^{18}F-FDG. ^{18}F-DOPA was found to be more accurate than other imaging modalities, in particular for the detection of recurrent disease and nodal involvement in MTC patients. The authors recommended ^{18}F-DOPA PET-CT as a one-step procedure to provide both functional and morphological data in order to select those patients who may benefit from re-operation with curative intent as well as guiding further surgical procedure. On the basis of these results it has

also been suggested that ^{18}F-DOPA PET is more sensitive than ^{18}F-FDG PET because of the MTC is a slow growing tumor.

The preliminary data of our study seems to suggest that in aggressive MTC, ^{18}F-DOPA PET/CT is characterized by moderately higher sensitivity than ^{18}F-FDG. However, in some patients ^{18}F-FDG examination was superior to ^{18}F-DOPA. Furthermore, an interesting observation from our series is that the intensity of uptake, expressed as SUV_{max} value, was significantly higher in ^{18}F-FDG positive lesions than in ^{18}F-DOPA positive ones. This phenomenon could be explained by the fact that the patients we evaluated were characterized by an aggressive pattern of the tumor, and ^{18}F-FDG avidity has been proven to be strictly related to the aggressive nature of tumours as proven in the study by Koopmans et al [13].

Another interesting observation from our study is that in a fraction of our patients the ^{18}F-DOPA PET/CT and the ^{18}F-FDG PET/CT showed a complementary role, and, as a consequence the combined sensitivity of the two modalities was higher than that of a single modality.

A methodological strength of our study is that all the patients had both ^{18}F-DOPA and ^{18}F-FDG PET/CT examinations using the same PET/CT scanner and receiving the same activity per patient based on body weight. Moreover, both PET/CT examinations were closely performed within a short time-interval.

Conclusions

On the basis of the preliminary results of this study, it can be concluded that in aggressive metastatic MTC patients with elevated and rapidly increasing calcitonin levels, ^{18}F-DOPA PET/CT has a good sensitivity and a complementary role to that of ^{18}F-FDG PET/CT. Therefore, it seems reasonable to recommend the performance of both

examinations to improve the global sensitivity in these patients. The higher SUVmax found at ^{18}F-FDG PET/CT in some patients could be related to a higher aggressiveness of the tumor and potentially to a worse prognosis. Further studies involving a greater number of patients and a longer follow up period are necessary to better understand these preliminary observations.

Conflict interest

Dr. M..C. Marzola, Prof. M.R. Pelizzo, Prof. M. Ferdeghini, Dr. A. Toniato, Dr. A. Massaro, Dr. V. Ambrosini, Prof. S. Fanti, Prof. M.D. Gross, Prof. A. Al-Nahhas and D. Rubello stated that they had no relationship with other persons or organizations, both financial and personal that could potentially bias the present work.

Figures legend

Figure 1a. Patient with recurrent MTC in the thyroid bed, in the upper mediastinum and in the right infraclavicular foss. Axial ^{18}F-FDG images indicate the biggest tumoral deposit in the right thyroid bed showing a moderate tracer uptake (SUV_{max} = 4.3)

Upper left, axial CT image of the thyroid region

Upper right, axial ^{18}F-FDG PET image of the thyroid region

Down left, axial fusion image

Down right, MIP image in anterior view

Figure 1b. Axial images indicate the biggest tumoral deposit in the right thyroid bed characterized by very high ^{18}F-DOPA uptake (SUV_{max} = 12.6)

Upper left, axial CT image of the thyroid region

Upper right, axial ^{18}F-DOPA PET image of the thyroid region

Down left, axial fusion image

Down right, MIP image in anterior view

Figure 2a. Coronal ^{18}F-FDG PET images of a patient with recurrent MTC with metastatic deposits in the mid-upper mediastinum, in the left lung and in two areas in the liver.

Figure 2b. Coronal ^{18}F-DOPA PET images of the liver metastasis characterized by a moderate tracer uptake (SUV^{max} = 3.8).

Figure 3. Patient with two small foci of MTC recurrence in the left thyroid bed visualized at ^{18}F-DOPA PET/CT. All the other examinations resulted negative.

Upper left, axial CT image of the neck; Upper right, axial ^{18}F-DOPA PET image of the neck; Down left, axial fusion image; Down right, MIP image in anterior view

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Figure(s)

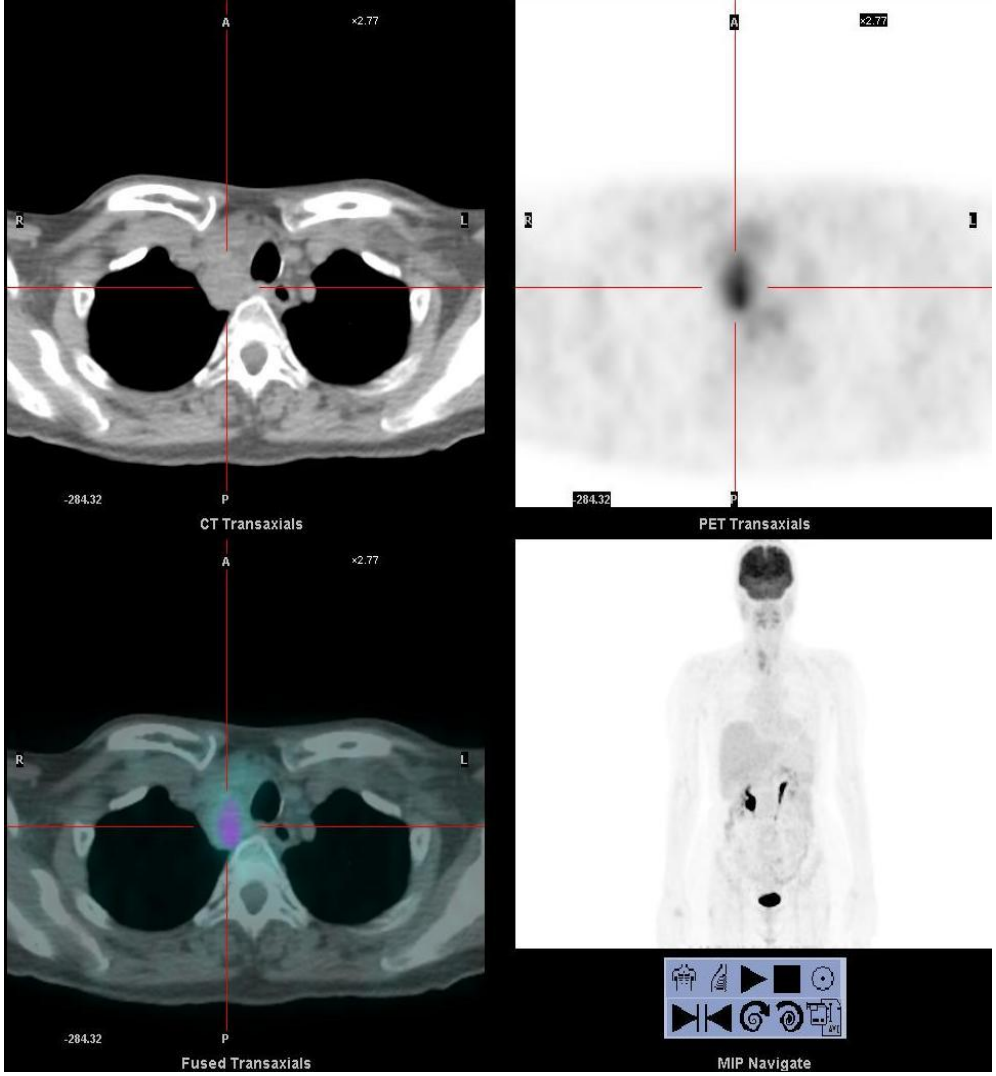

Figure 1a

Figure(s)

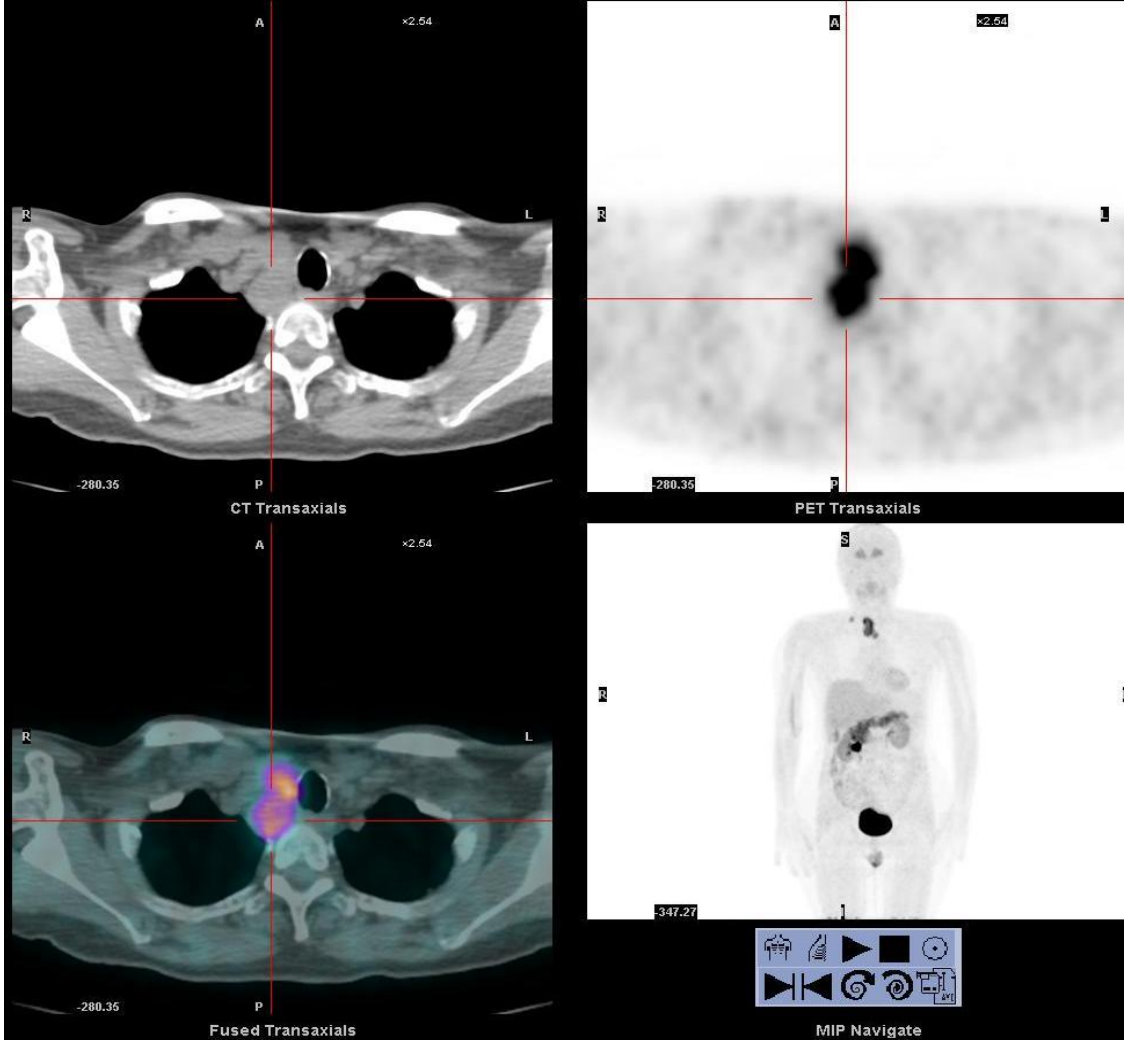

Figure 1b

Figure(s)

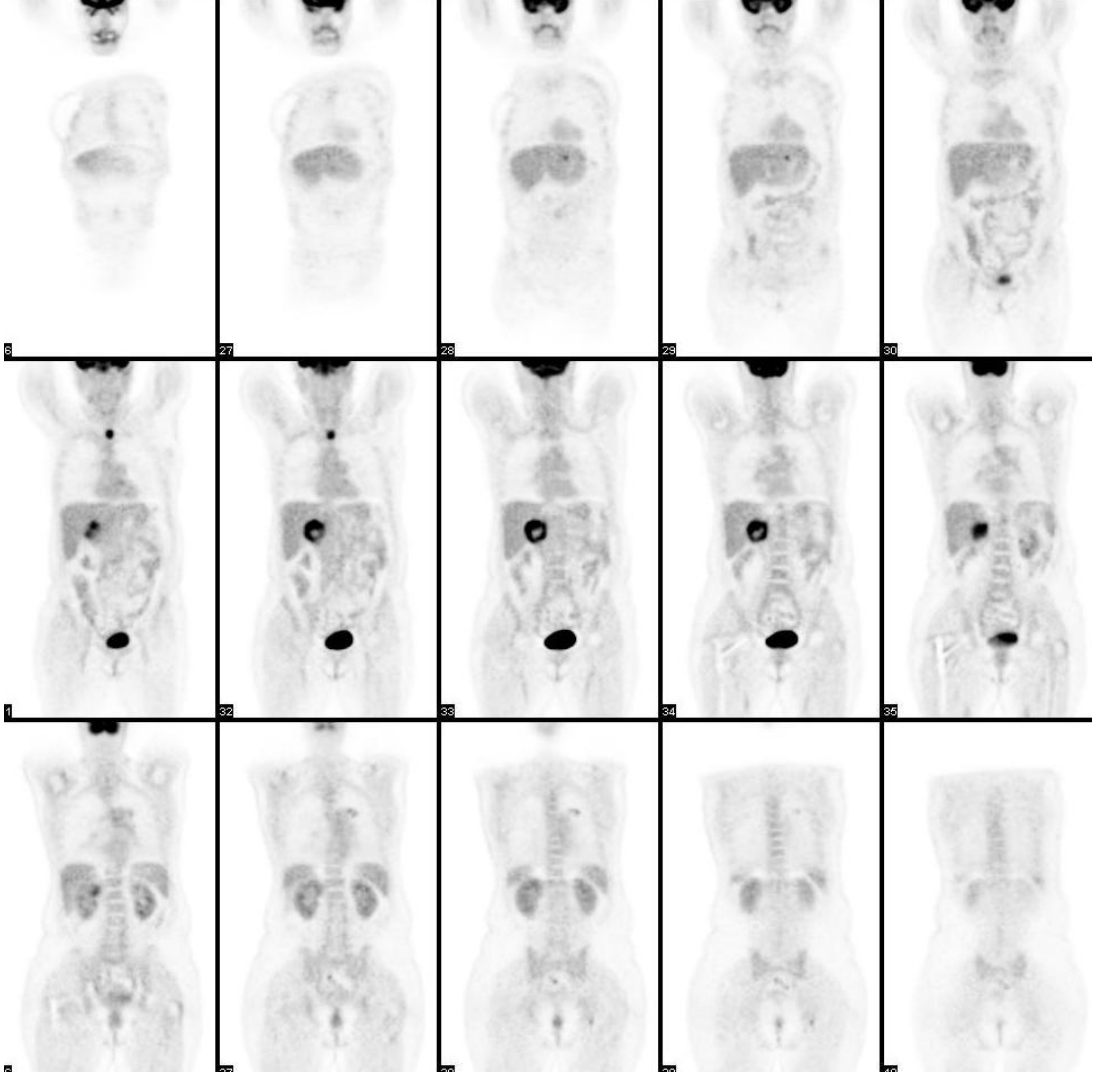

Figure 2a

Figure(s)

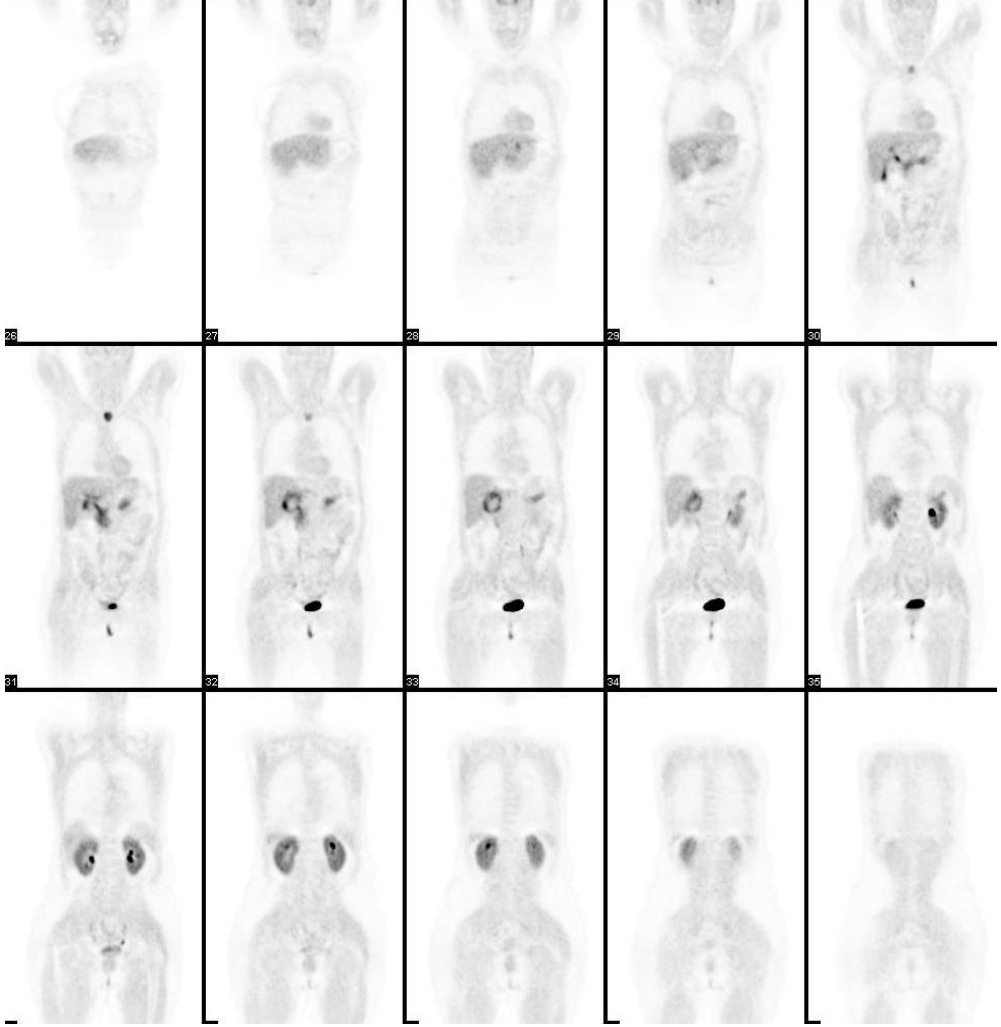

Figure 2b

Figure(s)

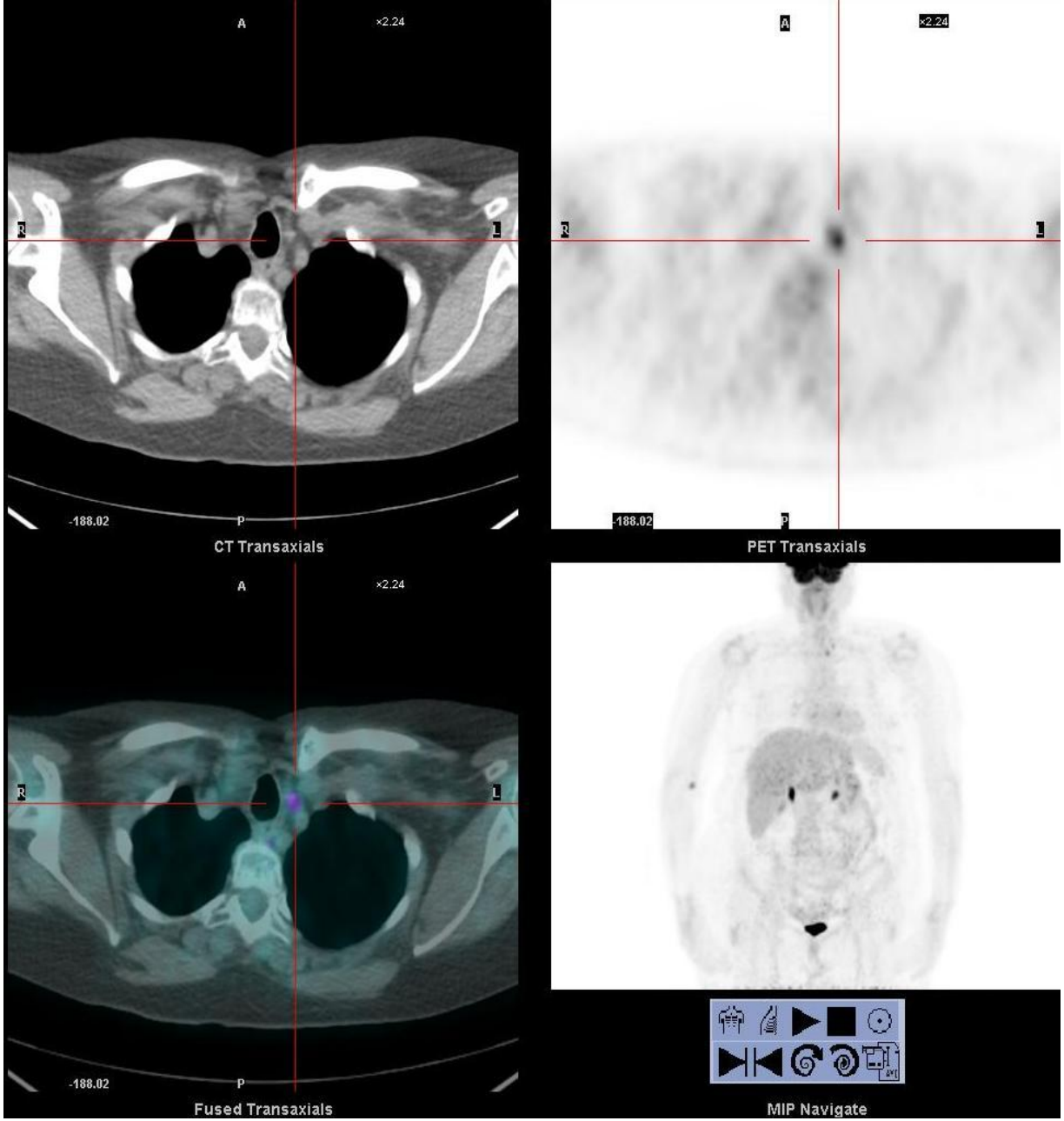

Figure 3