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PICTORIAL ESSAY

Pitfalls and artifacts of FDG PET/CT in recurrent breast cancer patients

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Abstract
Purpose FDG PET/CT is often indicated in breast cancer patients for the detection of recurrent disease. However, the differential diagnosis between benign and malignant lesions is sometimes difficult to address, especially in organs that are often a potential site of recurrent disease. The present collection of clinical cases aims to provide some information on these likely sites of false-positive findings at FDG PET/CT in breast cancer patients and to give some physiopathological explanations.
Methods A search of the literature was performed for articles published between 2011 and 2016 that reported data on false-positive findings in patients with suspicious breast recurrence undergoing FDG PET/CT. Moreover, all false-positive findings at FDG PET/CT from a single institutional collection between 2011 and 2016, in the same setting of patients were recovered and singularly described.
Results From a search of the literature using different keywords, 57 articles reporting false-positive findings at FDG PET in recurrent breast cancer were found. However, from a careful analysis, 10 reports were used for the analysis of data. Mediastinal and loco-regional lymph nodes represent the most common site for false-positive findings at FDG PET/CT ($n = 33/74$; 44.6% of subjects with available results) in breast cancer patients linked to different benign conditions. Moreover, from an institutional collection of data, 15 cases were carefully described, including explanations about their physiopathological mechanisms.
Conclusions FDG PET/CT images in recurrent breast cancer patients should be carefully read to avoid over diagnosis of metastatic disease. False-positive findings should be clearly considered, especially in regional lymph nodes. Moreover, correlative CT information and clinical history including recent treatment and procedures are key in avoid false-positive finding.

Keywords Positron emission tomography · Breast cancer · False positive · Recurrences · Physiopathology

Introduction

Breast cancer is the most common tumor in women and shows a heterogeneous biology and prognosis. Based on the European and American guidelines of Nuclear Medicine, FDG PET/CT is indicated in patients with breast cancer for staging (in the case of locally advanced breast cancer) in recurrent setting (i.e., increase in tumor markers or indeterminate conventional imaging findings) and during/after therapy [1, 2]. Despite advances in morphological and metabolic imaging, the differentiation of breast cancer recurrence from benign lesions is occasionally difficult. Morphological findings at imaging (i.e., with computed tomography—CT or magnetic resonance imaging—MRI) are sometimes similar in benign and malignant conditions, resulting in common or inconclusive features. Furthermore, FDG is not specific to neoplastic processes, because it accumulates at sites of physiological tracer biodistribution such as the brain, muscles, salivary glands, myocardium, gastrointestinal tract, urinary tract as a result of benign,

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inflammatory, or granulomatous processes [3, 4]. However, the interpretation of FDG PET/CT can be improved with the assessment of concomitant morphological and metabolic findings and with a careful analysis of the anamnestic data. The many possibilities for false-positive FDG PET/CT in breast cancer support the recommendations in many guidelines to restrict the use of FDG PET/CT to more advanced disease or scenarios where suspicious patient findings or symptoms are not explained by standard imaging. Examples include the NCCN guidelines (www.NCCN.org) and studies demonstrating a preponderance of false positives in patients with early-stage disease imaged by FDG PET [5]. In this article, we discuss and illustrate a variety of specific interpretation issues, including hypermetabolic lesions that can mimic the presence of recurrent disease. In particular, we focused our attention on specific organs that are possible sites of breast recurrence, such as lymph nodes, liver, lung, bone, and other. Finally, some physiopathological explanations are provided at the end of each clinical case.

Materials and methods

Approach to review. From the PubMed database, a search of the literature from 2010 to 2016 was performed. The following keywords were used: "breast cancer" AND "PET", "breast cancer" AND "PET" AND "RECURRENCE", "breast cancer" AND "FDG PET" and "recurrence", and "false positive" AND "PET" AND "breast cancer". The search was carried out with and without the addition of filters (such as English language and human species). Two researchers performed the literature search separately. A first analysis of the literature excluded clinical cases and studies without any data on false-positive findings. Second, all clinical cases were re-analyzed to choose those that met the criteria of the literature search strategy. The quality of the papers was not tested, because it resulted beyond the scope of the present review.

Search results

From the literature search, we found 1273 articles for "Breast cancer" AND "PET", 136 for "breast cancer" AND "PET" AND "RECURRENCE", 94 for "breast cancer" AND "FDG PET" and "recurrence", and finally 57 for "false positive" AND "PET" AND "breast cancer". Ten articles were selected for the final analysis (Table 1). As shown in the Table, the rate of false-positive findings in recurrent breast cancer patients varies from one study to another, and in the majority of cases, it is found to be higher in the lymph nodes or parenchymal organs (i.e., liver or lung). However, mediastinal and loco-regional lymph nodes represent the most common site for false-positive findings ($n = 33/74$; 44.6% of subjects with available results) in breast cancer patients [8, 11–15].

Besides the original articles, clinical cases also discussed the false-positive findings at FDG PET/CT in recurrent breast cancer. For example, some are related to the suspicion of local lymph node recurrence, such as silicone adenitis in axillary and internal mammary chain lymph nodes [16, 17] or benign schwannoma in the supraclavicular lymph nodes [18]. Other studies described cases of an FDG uptake pattern that can mimic the presence of skeletal disease, such as costosternal chondrodynia [19] or a sternal intraosseous schwannoma [20]. Finally, local recurrence could be confounded by a breast silicone implant [21], fat necrosis [22] or a rupture of breast implant [23].

Table 1 Data from collected articles

Authors	Year pub	*N* pts	FP (%)	Site of FP
Dirisamer et al. [5]	2010	52	2 (3.8)	NA
Aukema et al. [6]	2010	56	2 (3.6)	NA
Evangelista et al. [7]	2011	111	38 (34.2)	Adrenal gland; bone; lung; LN
Murakami et al. [8]	2011	53	2 (3.8)	Degenerative vertebral bone; pulmonary pneumonia
Manohar et al. [9]	2012	111	1 (0.009)	NA
Evangelista et al. [10]	2012	190	35 (18.4)	LN, lung, liver, bone
Chang et al. [11]	2014	100	9 (0.09)	Lung TBC, LN, liver, bone
Dong et al. [12]	2015	26	11 (42)	Lung, LN, ribs old fractures
HilDeBrant et al. [13]	2016	121	7 (0.6)	LN, bone
Jung et al. [14]	2016	1161	17 (0.014)	LN, bone, lung TBC, muscles
All	–	1981	124 (0.062)	LN, bone, lung, liver and adrenal glands

FP false positive, *NA* not available, *LN* lymph node, *TBC* tuberculosis

Case histories

Case 1

A 41-year-old woman with breast cancer treated with right mastectomy in November 2011 (pT2N1a; ER: 80%, PR: 40%; ki67: 50% and HER2: 0) (Fig. 1). Due to the unfavorable biological tumor characteristics after surgery, the multidisciplinary team opted for an FDG PET/CT examination that was performed three months after surgery. Current International guidelines, such as those from the European Society of Medical Oncology (ESMO), suggest a PET/CT scan in case of high-risk breast cancer, meaning in patients with suspicion for distant metastases. As illustrated in the figure, PET/CT showed an intense uptake in symmetric bilateral peri-hilar and paratracheal lymph nodes, but no other site of pathological uptake in the residual sites. After a careful analysis of the CT images, the lymph nodes appeared enlarged and showed some punctate calcifications compatible with sarcoidosis. Moreover, the patient underwent histopathological analysis that showed a chronic, non-caseating, granulomatous inflammation, compatible with sarcoidosis. In fact, in the absence of specific symptoms or signs for recurrent breast cancer, sarcoidosis is the most common cause of bilateral lymph node enlargement.

Case 2

A 40-year-old woman with breast cancer (pT2N2; ER: 90%, PR: 80%, ki67: 34% and c-Erb2: 0%) who received a right mastectomy in December 2011 (Fig. 2). For the positive expression of estrogen receptors, an adjuvant hormonal therapy with Triptorelin (3.27 mg every 28 days) for 5 years was recommended. In January 2012, for suspicion of recurrent breast cancer due to an increase in one of serum tumor markers (CEA: 21 UI/mL), the patient underwent FDG PET/CT (A) that showed the presence of a focal uptake in both the adrenal glands (SUV_{max}: 6.92 and 11.89, respectively, in the right and in the left adrenal gland). (B) To better characterize the adrenal lesions, a ceCT was suggested. On the dynamic enhanced phase image (arterial and portal phase), the left and the right adrenal glands were vigorously enhanced to 85 and 100 Hounsfield Unit (HU). On the 10-min delayed image (late image), the attenuation of the left and right adrenal gland were 29 and 48 HU (lower than that of kidneys, and liver). There is greater than 50% washout between the dynamic phase of contrast enhancement and the 10-min delay, which is diagnostic of an adenoma and confirms the finding on the non-enhanced CT scan. Quantitative region-of-interest measurements (in HU) are important because

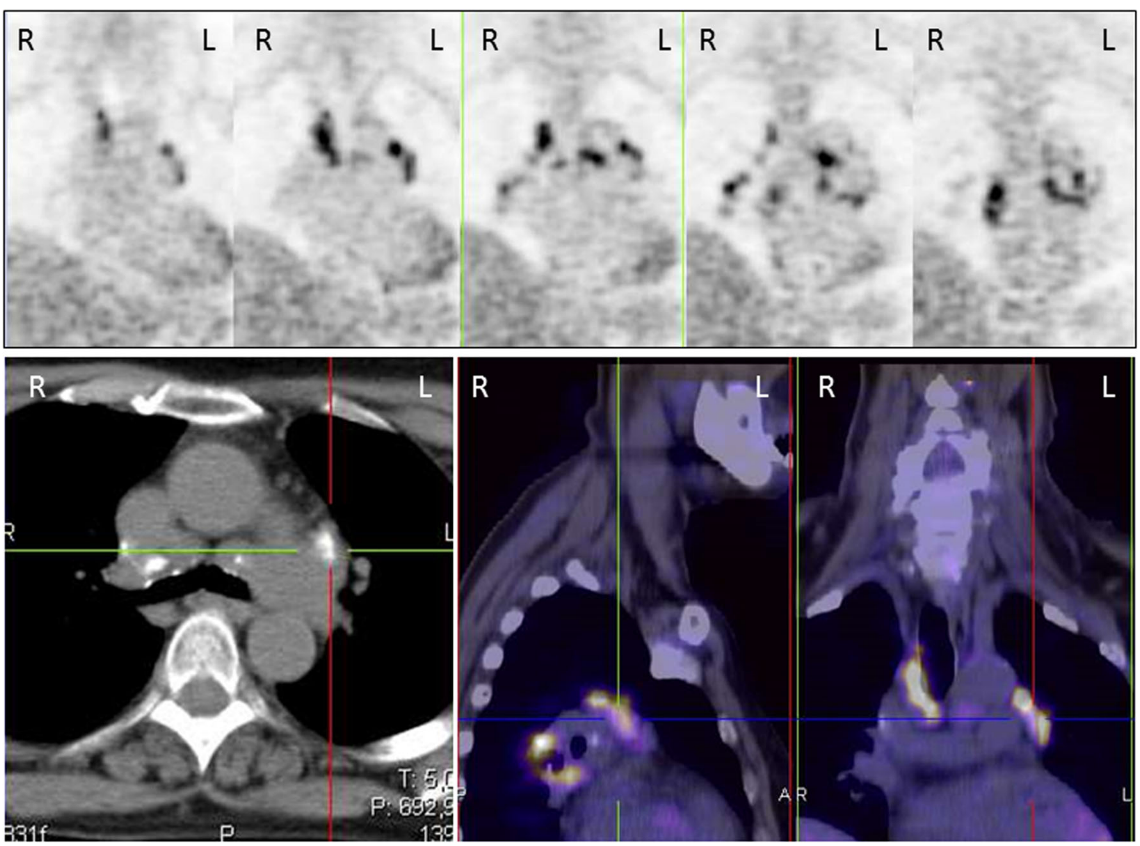

Fig. 1 Suspicion for lymph node involvement

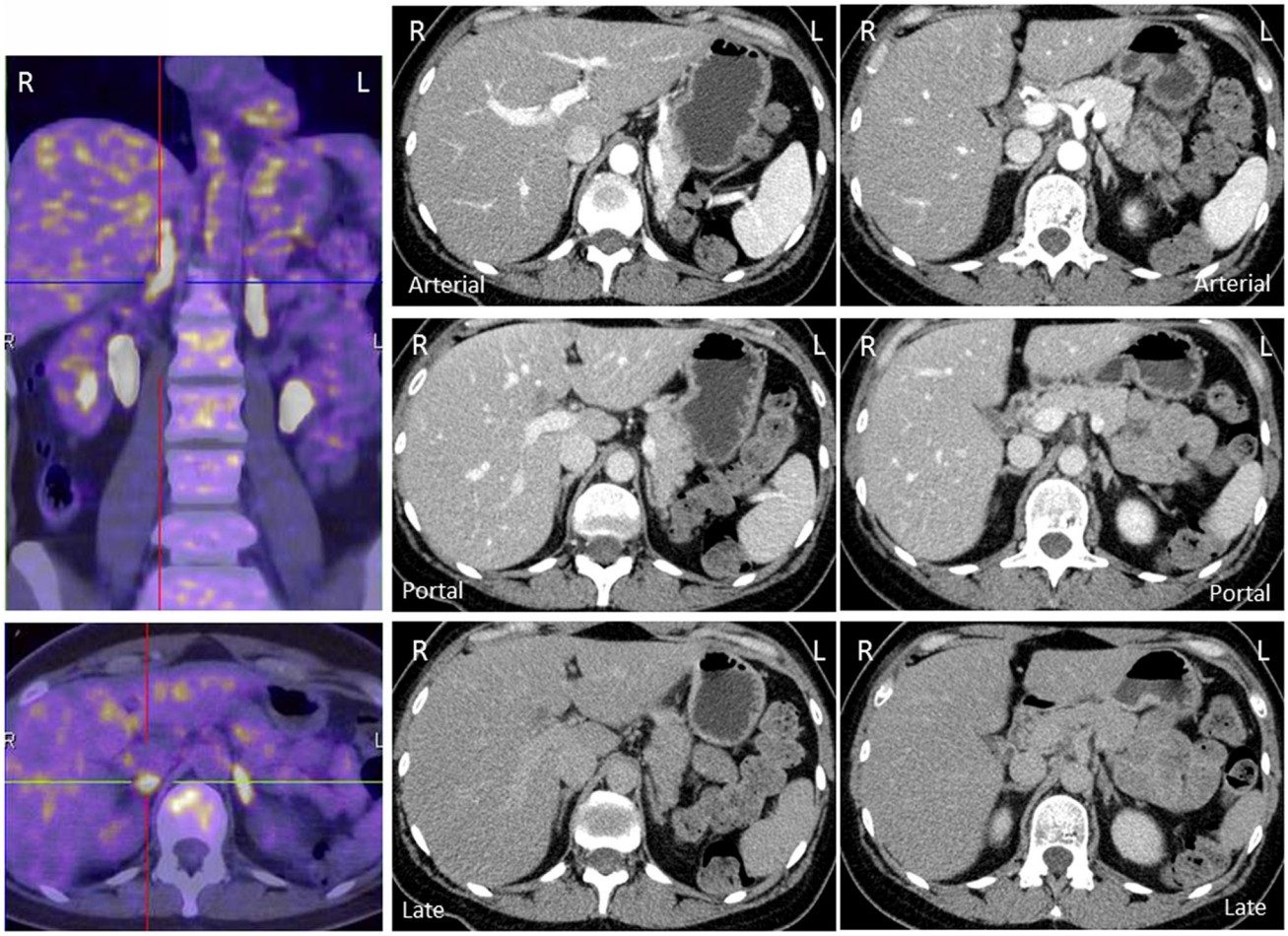

Fig. 2 An uncommon FDG uptake in the adrenal glands

degree of enhancement is difficult to quantify with the human eye.

Case 3

A 46-year-old woman with a right locally advanced breast cancer (pT2N2; ER: 90%, PR: 90%, ki67: 24% and HER2: ++−) (Fig. 3). For the initial staging of disease and for the high suspicion of distant metastases, the patient was sent to FDG PET/CT exam that demonstrated the presence of a focal uptake in the posterior vertebral body of the 3rd lumbar vertebrae. Patient resulted completely asymptomatic and without any sign of bone metastases. The radiologists confirmed that the CT image was compatible with the presence of calcified Schmorl hernia. Schmorl's nodes are protrusions of the nucleus pulpous of the intervertebral disc through the vertebral body endplate and into the adjacent vertebra. Over time, it can become calcified. This represents a typical false-positive finding, both in terms of osteolytic and osteoblastic lesions.

Case 4

A 49-year-old woman with breast cancer (pT1cN1a; positive ER and PR, c-Erb2: 0%) treated with left mastectomy in 2008 and adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) (Fig. 4). In 2016, for the persistence of pulmonary symptoms and increase in CEA levels, patient underwent PET/CT with FDG. Metabolic imaging showed the presence of an intense FDG uptake in the mediastinal, bilateral peri-hilar and paratracheal lymph node and a slight uptake in some pulmonary sub-solid nodules. CT-coregistered images were analyzed by two radiologists that concluded for lung sarcoidosis. The CT patter of lung sarcoidosis is characterized by enlarged nodules with possible inside calcifications and by a perilymphatic distribution of micronodular lesions in the lung parenchyma. The micronodules are most often found in the subpleural peribronchovascular interstitium and less often in the interlobular septa. Although sarcoid granulomas arise as micronodular lesions, they may

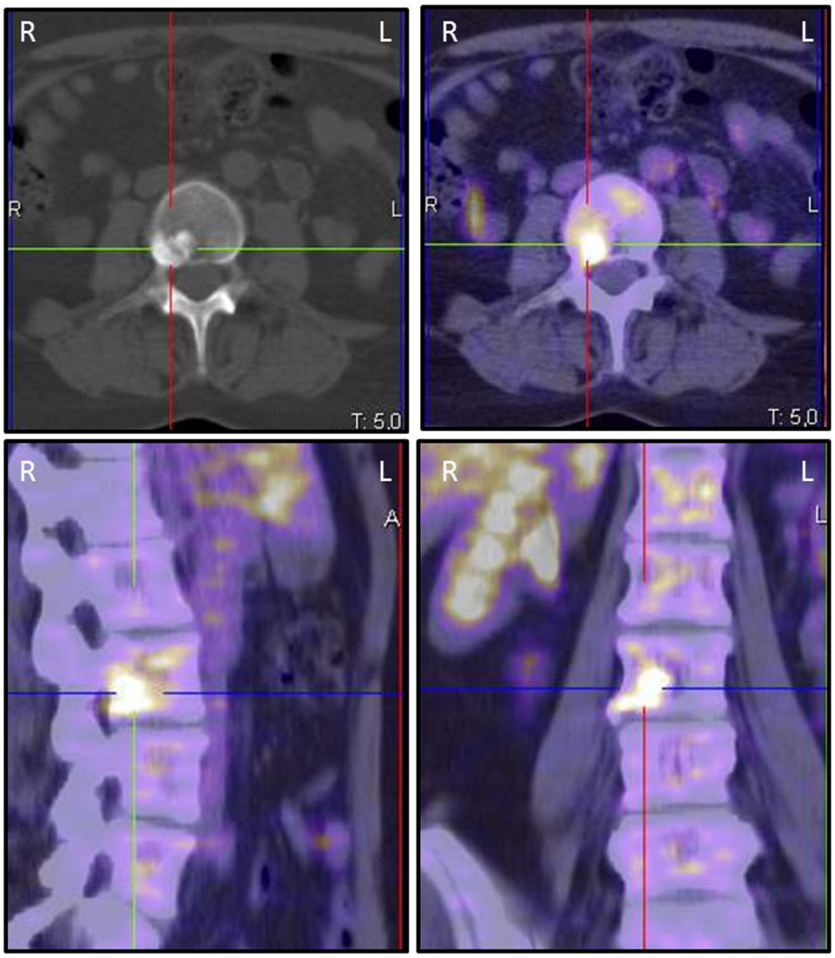

Fig. 3 Focal FDG uptake in the bone mimicking a skeletal metastases

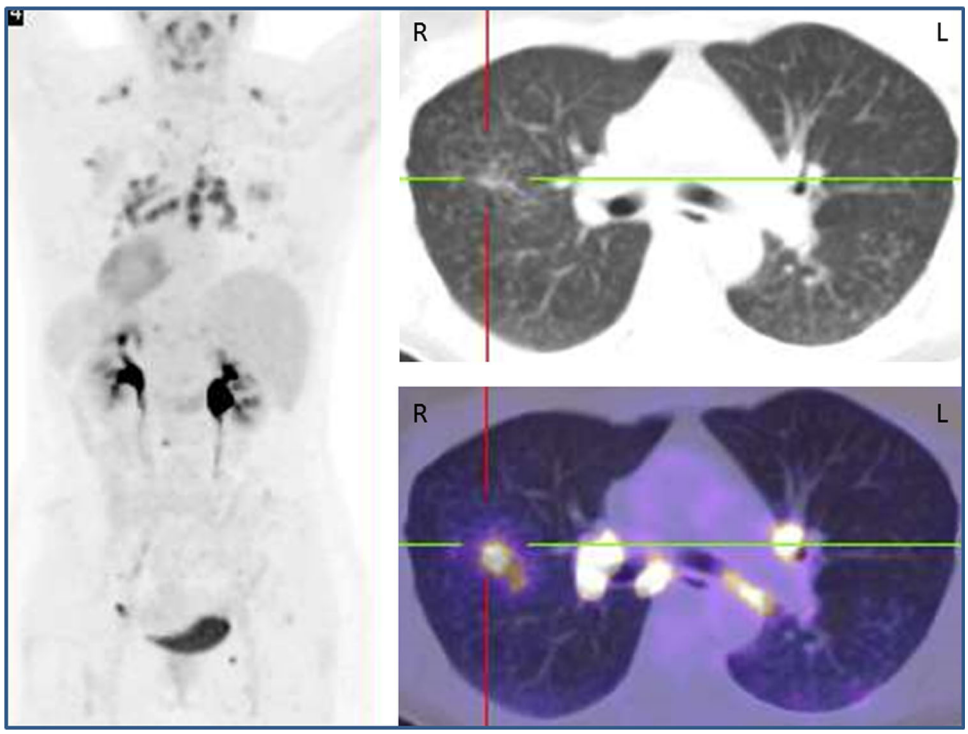

Fig. 4 Bilateral FDG uptake in the lung suggestive of pulmonary involvement

coalesce over time, forming larger lesions (macronodules), similar to the present clinical case.

Case 5

A 62-year-old woman with breast cancer (pT2N1a; positive ER and PR, ki67: 28%, c-Erb2: 0%) treated with left mastectomy in 2009, adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) and hormonal therapy (Letrozole) (Fig. 5). In 2015, for suspicion of recurrent breast cancer in the liver (increase in CEA, transaminase and in CA 19.9), patient was sent to FDG PET/CT that revealed the presence of multiple areas of intense FDG uptake in the liver. At histopathological analysis, the lesions were compatible with liver sarcoidosis. In particular, the pathologist described the presence of aggregated epithelioid histiocytes, fibrin deposits and a central necrosis. Moreover, an additional intrahepatic cholestasis was found, probably due to inflammatory infiltration of basement membranes and portal granuloma formation. This represents an uncommon condition, but it can be falsely interpreted as recurrent breast cancer with a widespread of disease in the liver. Breast cancer is rarely associated with sarcoidosis or sarcoidosis-like reaction. However, many cases of the association between sarcoidosis and breast cancer are described in the literature [24–26]. Often, the final differential diagnosis was made by histopathological examination [24, 25] or by other imaging modalities, such as CT [26]. In the present report, the differential diagnosis between recurrence of breast cancer and sarcoidosis was reported in three cases, involving lymph nodes, lung and liver.

Case 6

A 53-year-old woman with breast cancer treated with lumpectomy in 2013 and adjuvant hormonal therapy for 5 years (Fig. 6). During the follow-up period, a serial Ca 15.3 increase in serum levels, suspicious for recurrent disease, was reported. Conventional imaging (liver ultrasonography and chest X-ray) resulted non-conclusive. For this reason, the patient was a candidate for PET/CT examination with FDG. At PET/CT, a diffuse uptake in the thyroid gland and a focal uptake in a lymph node in the left

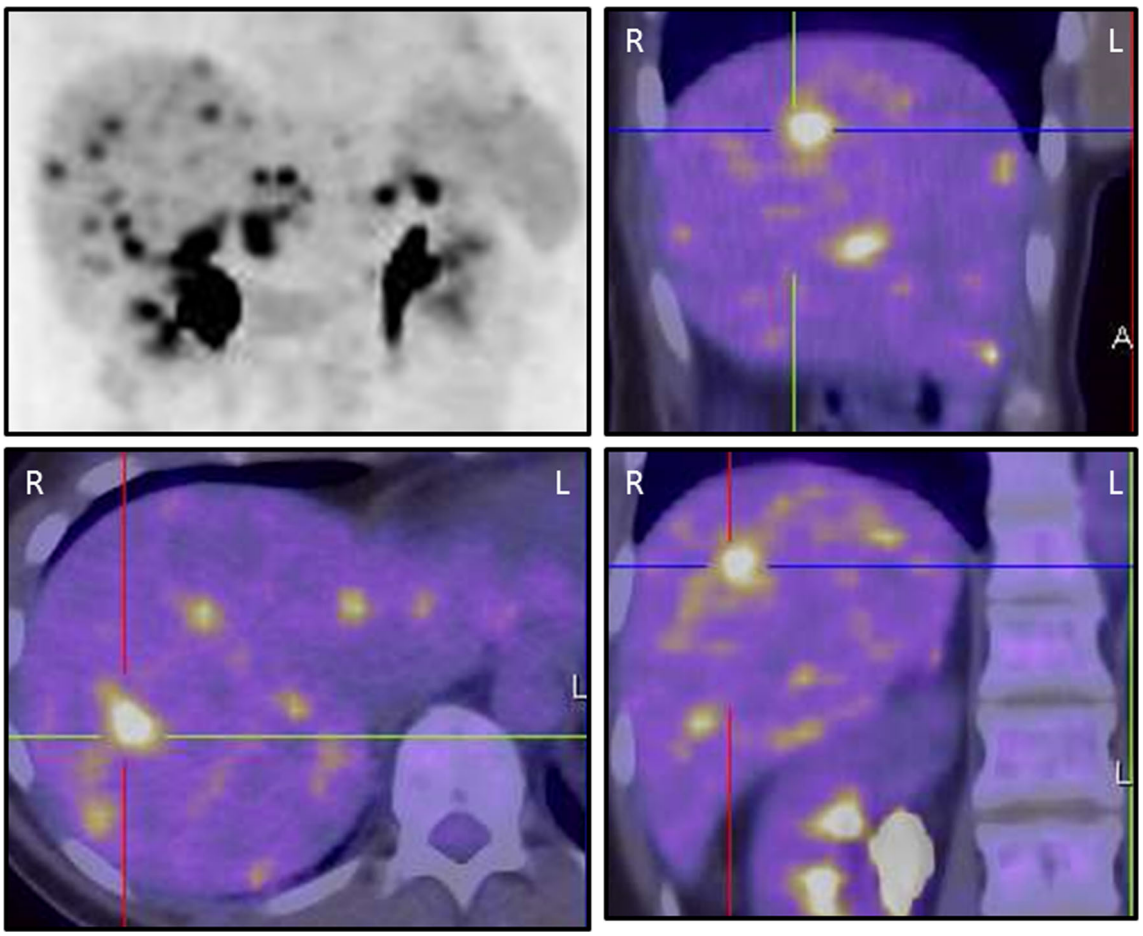

Fig. 5 Multiple focal FDG uptake in the liver

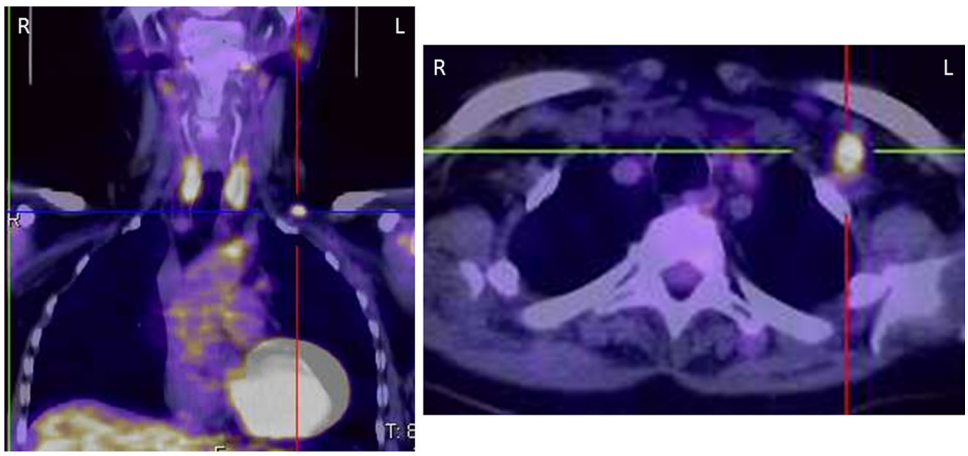

Fig. 6 Focal uptake of FDG in the thyroid and in the sentinel node region

supraclavicular region were documented. Ultrasonography examination and biochemical data were compatible with an inflammatory pattern of the thyroid gland similar to Riedel's thyroiditis. As extensively known, FDG is not a cancer-specific radiopharmaceutical agent and, therefore, as in the example of Figs. 1, 3, 4, and 5, it can be accumulated in the inflammatory tissues. In this case, complementary information was used for the final diagnosis. However, 6 months after the previous PET/CT exam, clinicians suggested a further PET/CT scan, which resulted completely negative; thus reinforcing the diagnosis of a benign condition.

Case 7

(A) A 44-year-old woman with breast cancer treated with surgery and adjuvant hormonal therapy (Fig. 7). For inconclusive findings at CT images, the patient was sent to PET/CT with FDG. No significant uptake was reported anywhere in the body, except for the presence of a significant uptake in the right ovary. (B) A 48-year-old woman with breast cancer (cT2N1a; ER negative, PR negative and HER2 negative) treated with neoadjuvant therapy and surgery (lumpectomy) in 2013. For the suspicion of residual disease, the patient was studied with mammography, chest-X ray and liver ultrasonography. Due to doubtful results, the patient was a candidate for FDG PET/CT scan. The images demonstrated a significant uptake in the right ovary. Both these cases were studied by a further ultrasonographic examination of the pelvis that showed a negative finding. The functional follicle of the ovaries can show a moderate-to-high uptake of FDG at the ovulatory phase of the normal cycle. False-positive findings in the ovary should always be resolved by ultrasonographic imaging, considering the higher association of ovary cancer and breast cancer, particularly in patients with a BRCA gene mutation.

Case 8

A 44-year-old woman with breast cancer (pT2N1a; ER: 90%, PR: 90%, MIB 1: 45%, c-Erb2: 1+) was treated with lumpectomy in 2013, adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) and additional hormonal therapy (tamoxifen for 5 years) (Fig. 8). FDG PET/CT was performed in August 2013 for suspicion of bone metastases (symptoms suggested widespread disease in the bone). FDG PET/CT showed multiple merging areas of FDG uptake in the uterus. Ultrasound examination revealed one hypoechoic lesion measuring 6.4 × 5.0 cm, suggestive of fibromyomas in the posterior myometrium. The reason for the accumulation of FDG in the leiomyoma is not known. It may be explained by the existence of higher levels of growth factors, including basic fibroblast growth factor, transforming growth beta factor, granulocyte macrophage colony-stimulating factors and receptors, and proliferation of smooth muscle cells in leiomyomatous uterus [27]. In breast cancer patients, particularly in those undergoing tamoxifen therapy, the risk for a gynecological cancer (i.e., endometrial cancer) is higher than untreated patients. There cognition of abnormal FDG pattern in the uterus should always be assessed by additional imaging modalities or by a specialist.

Case 9

A 53-year-old woman with breast cancer (pT1cN2; ER: 90%, PR: 90%, MIB 1: 20%, c-Erb2: 1+) treated with lumpectomy in 2015 (Fig. 9). The patient underwent adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel; 6 cycles) and was recommended hormonal therapy (inhibitor of aromatase) for 5 years. In July 2016, for the increase in Ca 15.3 (41 UI/mL and later 124 UI/mL) and CEA (66 UI/mL) levels, the

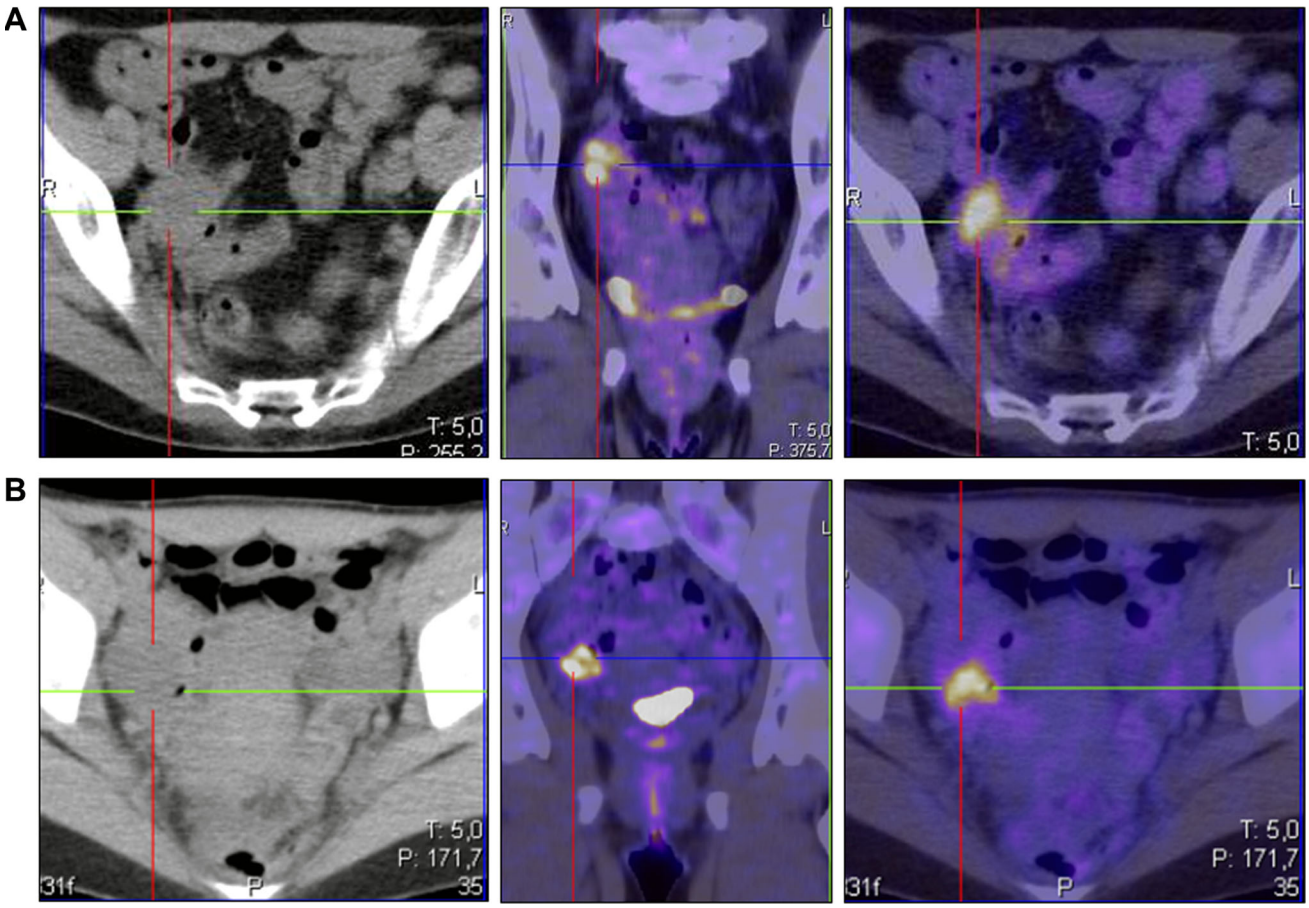

Fig. 7 A focal FDG uptake in the right ovary

patient was sent to FDG PET/CT. Metabolic images showed a high and diffuse FDG uptake in the right pleural cavity, particularly in the basal region. The histological analysis was positive for acute pleuritis, compatible with talcosis. FDG PET/CT seems useful for the differentiation between malignant and benign pleural lesions [28], although in this clinical case, additional information was useful for the final diagnosis. Among benign conditions, asymptomatic primary tuberculosis pleurisy and mycobacterial infections are the most common in patients undergoing FDG PET/CT.

Case 10

A 65-year-old woman with breast cancer (pT2N2a; ER: 80%, PR: %, MIB 1: 18%, c-Erb2: +−−) sent to left mastectomy in 2012 and adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel; 4 cycles) (Fig. 10). In February 2013, due to suspicion of recurrence (doubtful conventional imaging for liver metastases), an FDG PET/CT was recommended. Metabolic imaging showed a focal uptake in the spleen (A). For the characterization of the spleen lesion, an MRI was suggested, being able to better characterize the spleen lesions. However, MRI resulted completely negative (B). For the final interpretation, PET/CT scan was considering suggestive of a hypervascularity of the spleen, as already described by Park in a patient with anal cancer [29].

Case 11

A focal bilateral laterocervical and supraclavicular FDG uptake, without any correspondence to CT-coregistered images (Fig. 11). Hypermetabolic brown fat in cold-induced thermogenesis shows moderate-to-high FDG uptake in the brown adipose tissues that often appears in the supraclavicular region, mid-axillary line, and paraspinal regions of the posterior mediastinum. This pattern can be confounded with the presence of recurrent breast cancer, if the coregistered CT images are not evaluated.

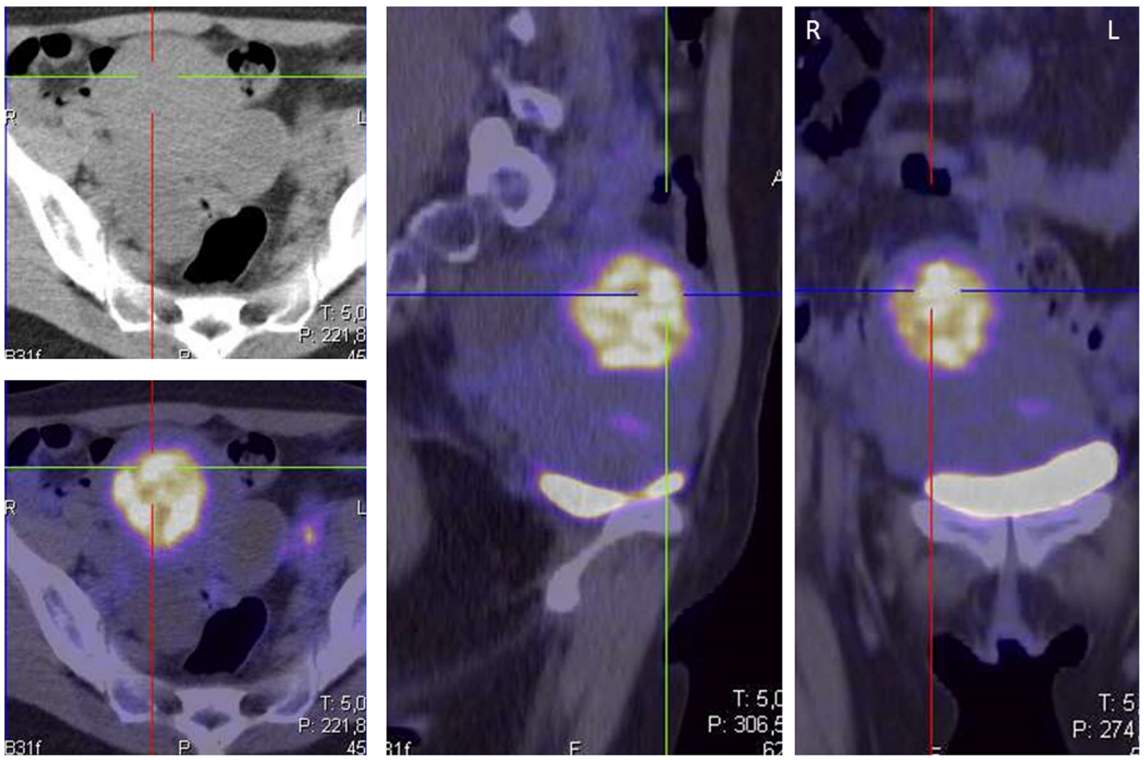

Fig. 8 Intense FDG uptake in the uterus

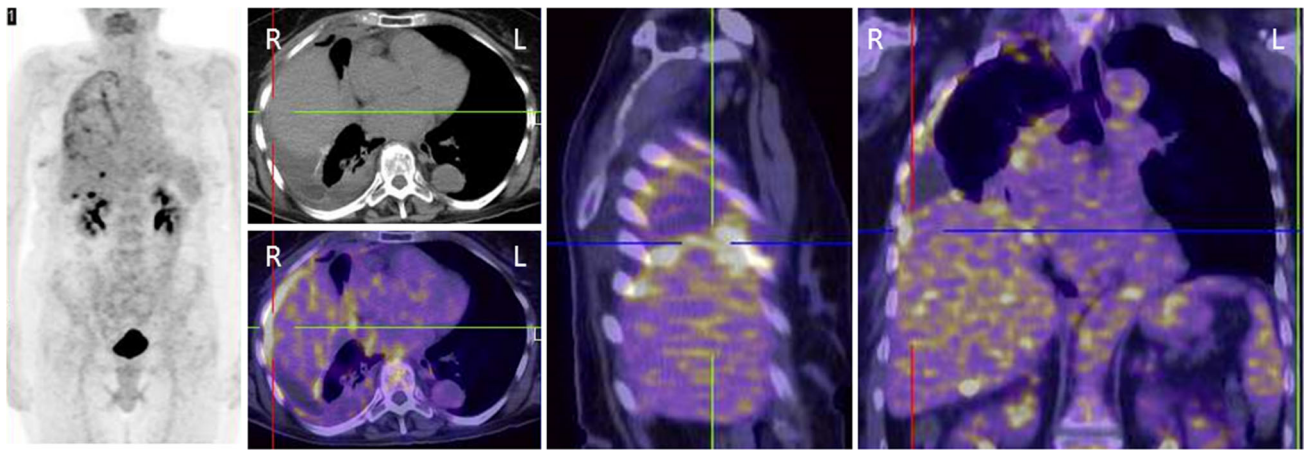

Fig. 9 Diffuse FDG uptake in pleural cavity

Case 12

A 56-year-old patient with left breast cancer (pT2N2; ER+; PR+ and HER2−) who underwent radical mastectomy in 2014 (Fig. 12). For a doubtful mammographic finding after surgical approach, multidisciplinary team proposed an FDG PET/CT scan for a complete assessment of disease status. At FDG PET/CT, a diffuse uptake of tracer was reported superior to the left breast prosthesis. Due to the recent radiotherapy, the uptake of FDG was considered compatible with the presence of post-radiation treatment inflammation. As already mentioned above, FDG uptake can be enhanced by inflammation-induced changes, which include postoperative healing scars and post-radiation therapy. It is important to wait at least 8–12 weeks after the last radiotherapy cycle to avoid a false local recurrence of breast cancer.

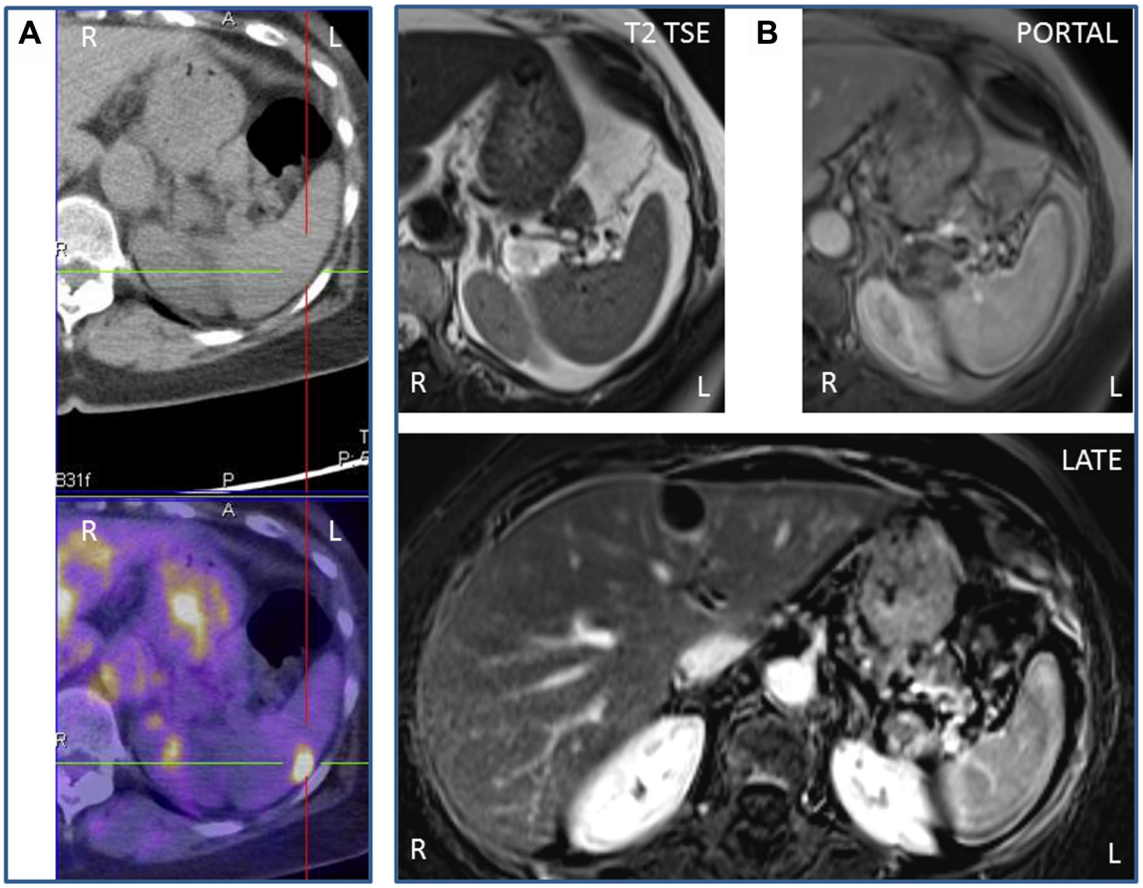

Fig. 10 Focal uptake in the spleen

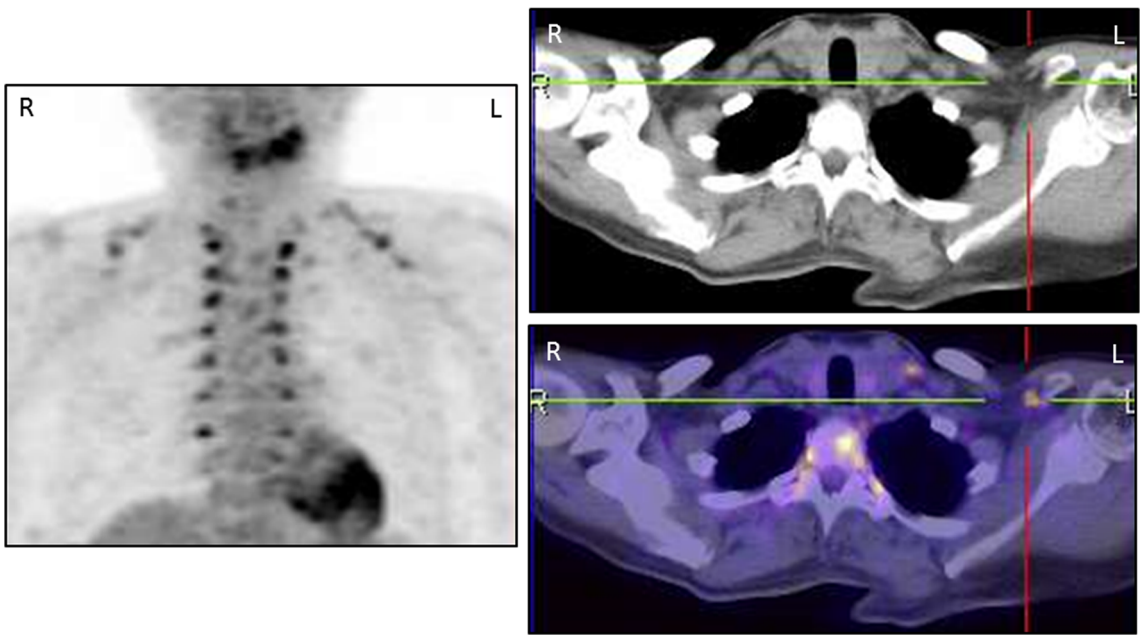

Fig. 11 Brown fat uptake in breast recurrent patient can be falsely interpreted as a diffuse lymph node disease

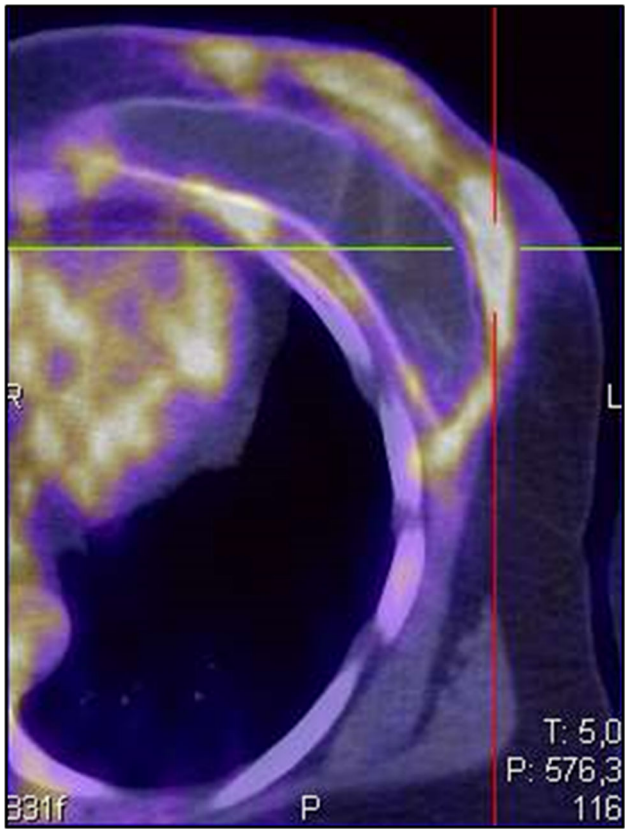

Fig. 12 Diffuse uptake in peri-prothesis region, after mastectomy: residual, recurrence or other?

Case 13

A 56-year-old woman with breast cancer (pT1cN1; ER: 90%, PR: 90%, MIB 1: 35%, c-Erb2: 0%) treated by lumpectomy in 2003 and adjuvant hormonal therapy for 5 years (Fig. 13). The patient developed bone metastases 10 years after the primary treatment and about 5 years after the withdrawal of hormonal therapy. Serial FDG PET/CT scans during therapy with zoledronic acid (ZA) were performed to evaluate the response to therapy (Fig. 13a). In the first image (left), a significant uptake in the sternum and in the ribs was demonstrated. In the second scan (middle), an increase in FDG uptake was registered in the same regions. In the third scan (right) a significant reduction of radiotracer uptake was reported. For each scan, the clinical conditions of the patient were stable, without the appearance of new symptoms suggestive of progressive disease. However, the time between zoledronic acid administration and FDG PET/CT scan was 21, 5 and 27 days for the 1st, 2nd and 3rd images, respectively. Due to the short time interval of the second scan, a flare phenomenon was supposed. Figure 13b shows fused FDG PET/CT and CT images in the vertebral body and in the sternum. As shown, only some differences in the FDG uptake among the scans were reported, while no differences in the morphological pattern were found. A paradoxical flare phenomenon represents rapid bone repair around the responding lesion and may be predictive of successful systemic therapy. It has been reported that up to 75% of patients with breast cancer with responding bony metastases show increased activity or new lesions due to bone repairs, with a subsequent decrease in activity 6 months later [30].

Case 14

A 50-year-old woman with a triple-negative breast cancer treated in 2009 with left radical mastectomy (Fig. 14). FDG PET/CT was performed in November 2015 for the evaluation of recurrent breast cancer and revealed multiple radiotracer uptake in the mediastinal lymph nodes, in the right adrenal mass and in the sternum. A 18F-DOPA PET/CT was performed, later, in June 2016 for the characterization of right adrenal mass, because a suspicion for pheochromocytoma was reported (increase in urinary metanephrines). Between FDG PET/CT and DOPA PET/CT, the patient underwent chemotherapy and radiation therapy in the sternum. 18F-DOPA PET/CT reported a significant uptake in the sternum, in the liver and in the right adrenal mass. Histological analysis of the liver lesion revealed the presence of a metastatic breast cancer recurrence and the adrenal gland was compatible with pheochromocytoma (the patient underwent right adrenalectomy), while the uptake in the sternum was interpreted as progressive disease after radiotherapy treatment (later confirmed by 99mTc-diphosphonate bone scan). To date, no data are available on the role of DOPA PET/CT in breast cancer; however, recently published data about the role of another aminoacid radiopharmaceutical agent, 18F-FACBC, have demonstrated a potential role of PET in patients affected by breast cancer [31]. In our opinion, alternative radiopharmaceutical agents would be useful in case of false-positive/false-negative findings at FDG PET/CT in this setting of patients.

Discussion

The correlative interpretation and consideration of clinical data—including treatment—in interpreting FDG PET/CT for breast cancer is necessary to avoid a false interpretation. This was recognized in early studies of FDG PET for staging advanced breast cancer [32]. A simple exchange of information between the clinician, radiologist, and PET physician could solve at least some of

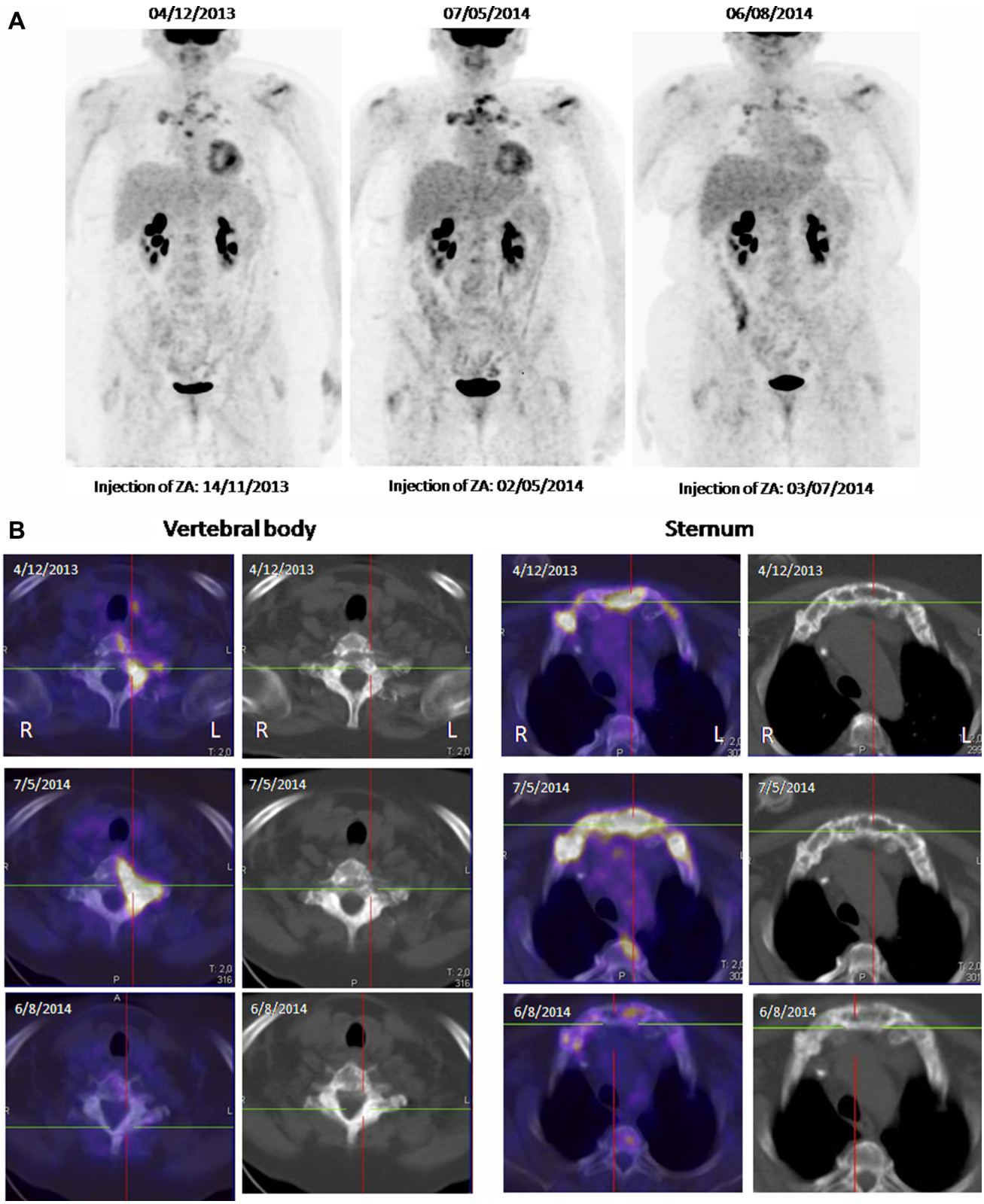

Fig. 13 **a** and **b** False positive FDG uptake in the bone during zoledronic acid (ZA) therapy

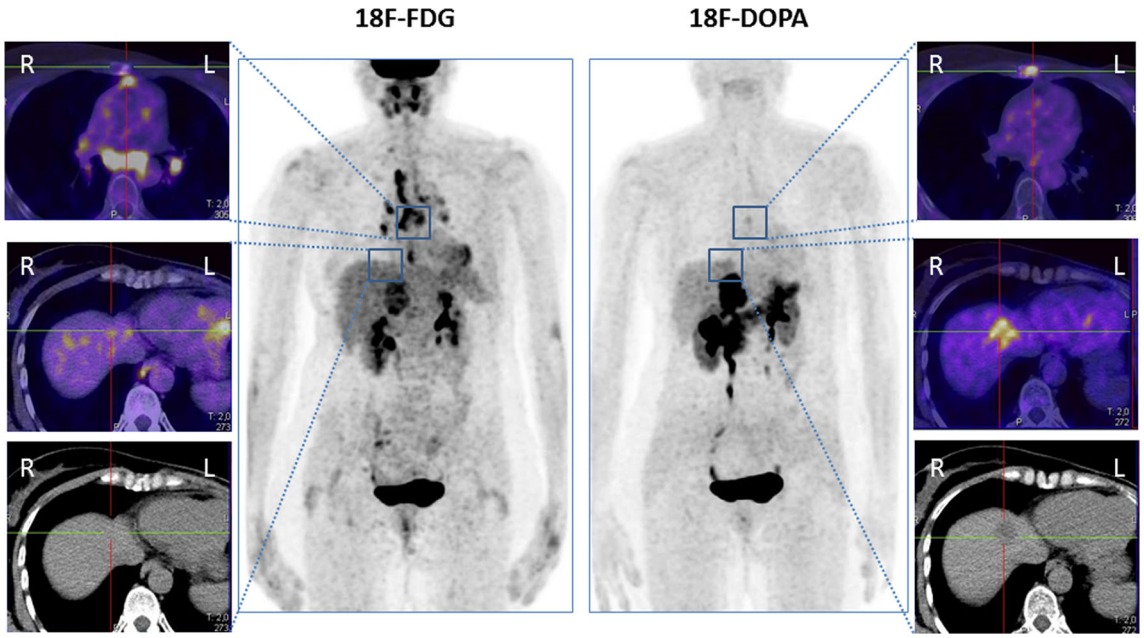

Fig. 14 DOPA and FDG PET results in recurrent breast cancer

undeterminate/doubtful findings [32]. As reported in the clinical cases, many physiological, paraphysiological and benign conditions can be falsely interpreted as recurrent breast cancer. The correct interpretation can avoid unnecessary treatments and directly correlated potential side effects.

By summarizing the abovementioned clinical cases, we can suggest that:

1. the most common site of false-positive findings at FDG PET/CT in patients with breast cancer during restaging phase is lymph nodes;
2. paraphysiological conditions can be associated with a positive FDG PET/CT, but the knowledge of patient clinical conditions and potential differential diagnoses is mandatory;
3. after surgery, breast silicone and radiotherapy can be associated with a false-positive finding at FDG PET/CT. It is useful to respect the temporal window between treatment and FDG PET/CT.
4. similarly, the knowledge of time between systemic treatments and FDG PET/CT is necessary to avoid false-positive findings.
5. alternative radiopharmaceutical agents for breast cancer are still under-evaluated. Future research is required to fill this gap.

In conclusion, false-positive findings should be clearly considered, especially in regional lymph nodes. Moreover, correlative CT information and clinical history including recent treatment and procedures are key in avoiding false-positive finding.

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Compliance with ethical standards

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Conflict of interest The authors declared that they have no conflict of interests.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

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