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Breast inflammation: Indications for MRI and PET-CT

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Abstract Breast MRI should not be used for differential diagnosis between inflammatory breast cancer and acute mastitis (AM) prior to treatment. When mastitis symptoms persist after 10 to 15 days of well-managed medical treatment, MRI may be performed in addition to an ultrasound examination, a mammogram and to taking histological samples, in order to eliminate inflammatory breast cancer (IBC). For staging, MRI would seem to be useful in looking for a contralateral lesion, PET-CT for finding information about remote metastases and in certain centres, for information about the initial extension to local/regional lymph nodes, which would guide the fields of irradiation (since patients can become lymph node negative after neoadjuvant chemotherapy). MRI and PET-CT seems to be useful for early detection of patients responding poorly to neoadjuvant chemotherapy so that the latter may be rapidly modified.

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The term mastitis is used when the breast is inflamed, for whatever reason, resulting in a breast that is red, hot and possibly painful. Two recent studies report the aetiological diagnoses of patients consulting for breast inflammation in specialised breast centres [1,2]. According to these studies, the number of consultations for breast inflammation is low, estimated to be 0.6% of consultations (22/3762). Infection is the commonest diagnosis for breast inflammation and is said to be found in more than half of the cases (54 to 67%). Non-infectious mastitis is also common, representing about a third of the consultations with many different aetiologies including post-therapeutic sequelae, systemic diseases (lupus, sarcoidosis etc.), and granulomatous or plasma cell mastitis. Finally, inflammatory breast cancer, which must always be borne in mind, is the least common differential diagnosis, representing between 4.5 to 5.6% of consultations for breast inflammation.

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Given the frequency of acute mastitis (AM) relative to inflammatory breast cancer (IBC), it is common practice to give a case of acute mastitis a trial antibiotic treatment for 10 days if it is accompanied by fever, and otherwise to initiate non-steroidal anti-inflammatory drugs (NSAID) treatment. Complete regression of the symptoms is one of the best arguments confirming the diagnosis of AM. If the symptoms do not subside, an inflammatory cancer must be eliminated, even if the incidence of this disease is low, and skin and breast biopsies must be performed rapidly. Inflammatory breast cancer is in fact a therapeutic emergency, and no exploratory examination, in particular a MRI, should delay management of the condition.

Imaging

Diagnosis and characterisation

Diagnosis of infectious mastitis is clinical. Favourable evolution with antibiotic treatment in 15 days confirms this diagnosis. An ultrasound examination can be useful in young women to eliminate an abscess.

MRI should not be used for differential diagnosis between inflammatory breast cancer and acute mastitis prior to any trial treatment (evidence level 1b, recommendation level A) [3]. After well-managed medical treatment of a presumed mastitis, a breast MRI may be performed if there are still doubts about the presence of an underlying cancer (conventional imaging) (evidence level 2b, recommendation level C) [3]. This examination should not delay breast biopsies. Nevertheless, MRI could help locate a target hidden in ultrasound and mammography examinations by oedema, which increases the density of the breast parenchyma (overall attenuation with ultrasound and type III or IV density in a mammogram).

However, differentiating between cancer and acute mastitis remains a challenge even with MRI. Indeed, these two conditions, both, exhibit signs of inflammation [4,5]: skin thickening (83% versus 67% for IBC and AM respectively), an increase in the size of the breasts (69% versus 62%), nipple abnormalities (67% versus 52%), prominent mammary vessels (85% versus 71%), cutaneous oedema in T2 hypersignal (81% versus 67%), and oedema of the breast parenchyma (90% versus 83%). Dynamic criteria do not seem

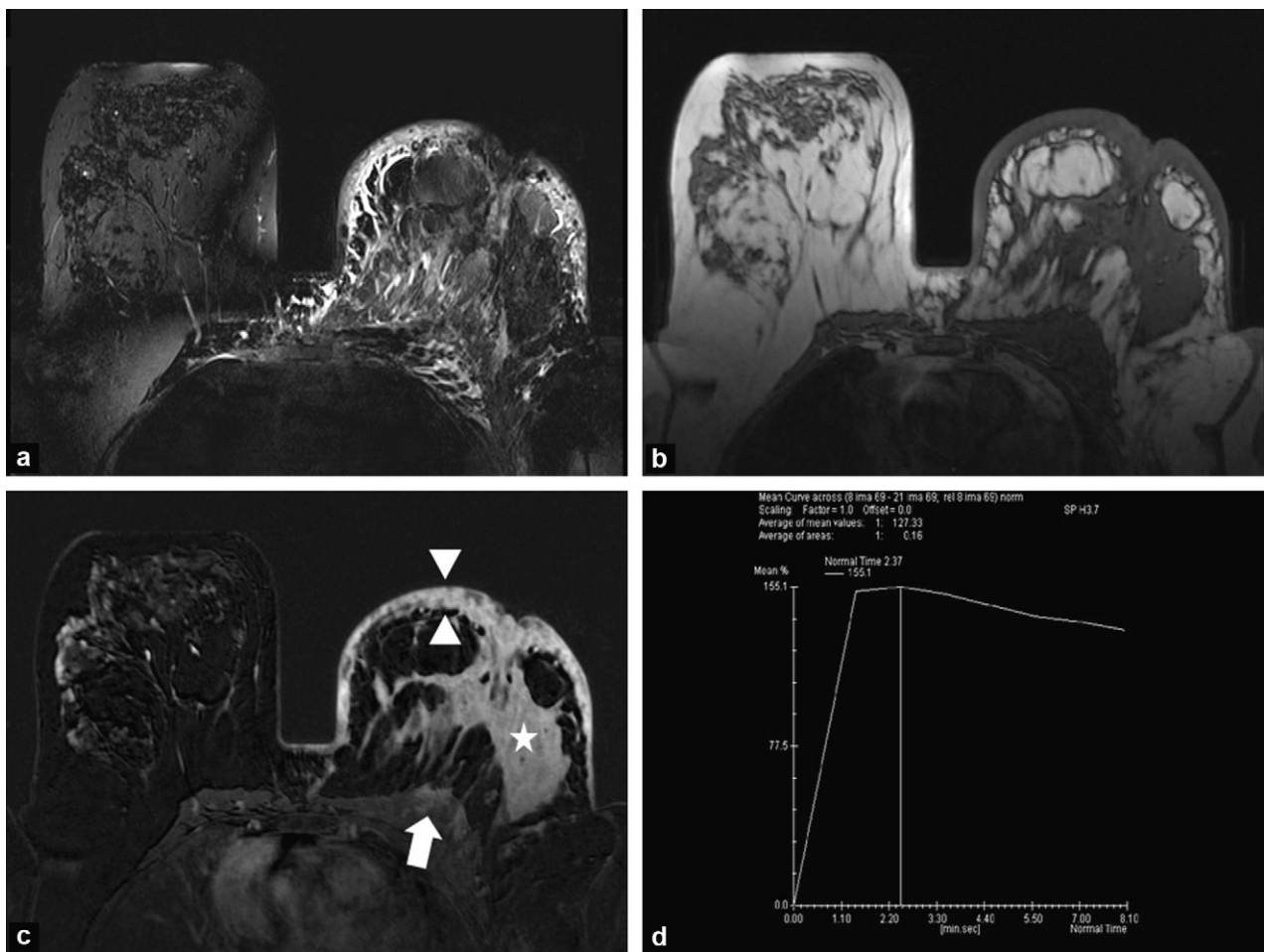


Figure 1. MRI appearance of an infiltrating ductal carcinoma (SBR grade III, triple negative) of the left breast, with clinically cutaneous inflammation and an orange peel skin (PEV 3). The T2 sequence (a) shows inflamed and thickened skin and a pectoralis major muscle hypersignal possibly indicating parietal infiltration. The T1 (b) and subtracted injected T1 sequences (c) show a homogeneous mass (star) of irregular shape with irregular margins, with early intense enhancement (d) followed by washout (type 3). The subtracted injected T1 sequence (c) also shows skin thickening (arrow head) and infiltration of the pectoralis major muscle (arrow).

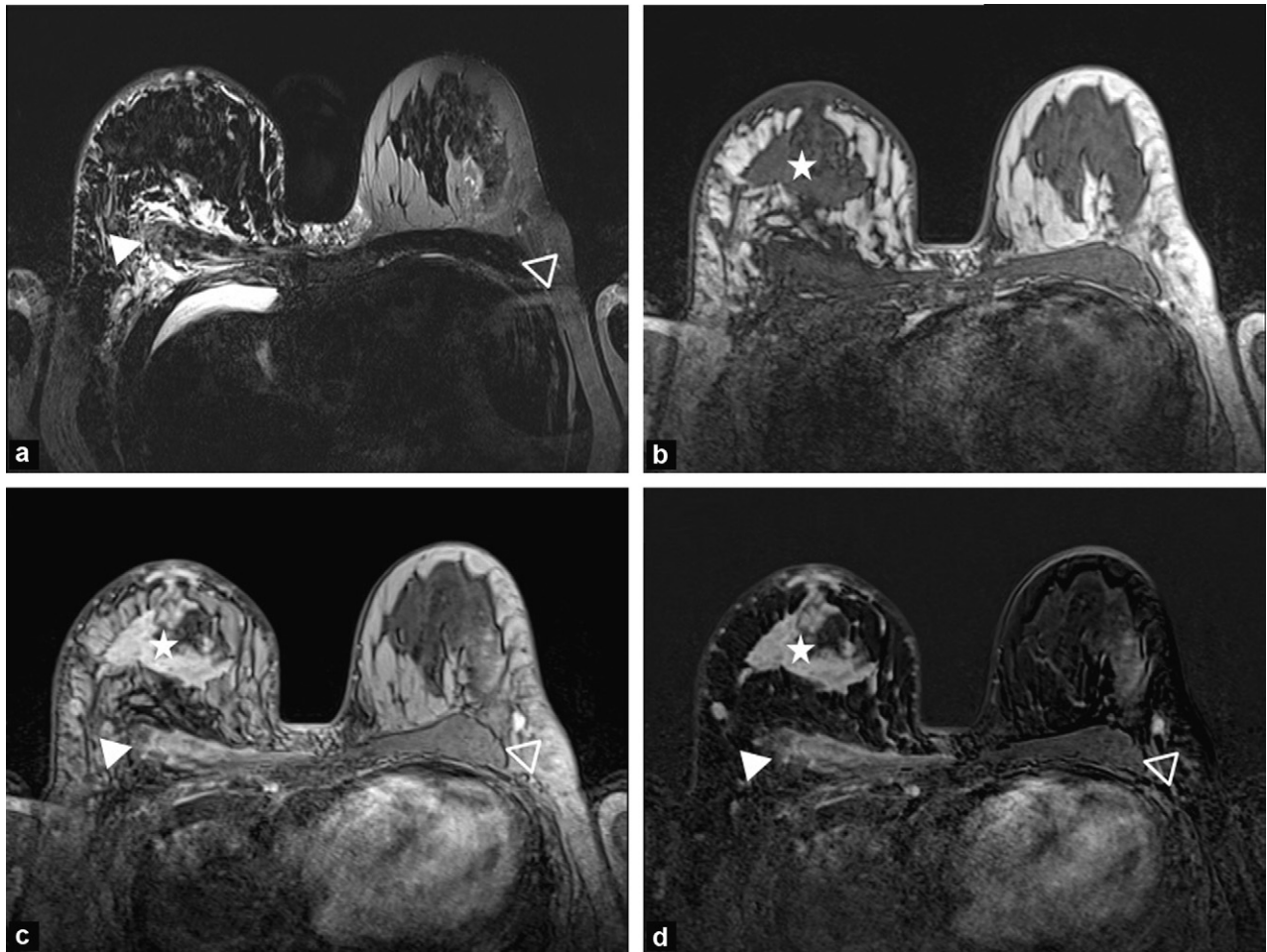


Figure 2. MRI appearance of an infiltrating ductal carcinoma (SBR grade III, triple negative, with P53 mutation) of the right breast, clinically PEV 3. The T2 sequence (a) shows a right pectoralis major muscle hypersignal (solid arrow head), which is asymmetric relative to the left pectoralis major muscle (hollow arrow head). The T1 (b), injected T1 (c) and subtracted injected T1 (d) sequences show enhancement of the pectoralis major muscle which confirms tumour infiltration. These sequences also show the irregularly shaped homogeneous mass with irregular margins (star).

to be really discriminating either. Intense early enhancement (> 100% before 90s) is found in the majority of cases of IBC (80%–90%) but also in nearly half of AM patients (45%–55%). On the other hand, kinetics with a washout (Fig. 1) seem to be more often associated with IBC (69%) than with AM (14%) [4,5]. The enhancement kinetics for IBC and AM are similar because both the tumoural and inflammatory angiogenesis phenomena are caused by VEGF. This cytokine increases the formation of microvessels (responsible for the initial intense enhancement) and modifies the permeability of capillary walls (explaining the washout and oedema) [6].

The signs more often observed in IBC than in AM on MRI are the existence of masses of more than 10 mm (75% versus 31% respectively) and axillary adenopathy (67% versus 48%, Fig. 1) [4]. The shape of the masses in the MRI does not seem to be a criterion discriminating between the two conditions, since irregular masses are found in 30% of cases of IBC and 27% of AM cases. On the other hand, irregular margins or spicules seem to be more often seen in IBC than in AM (82% versus 53%). Heterogeneous internal enhancement and the “blooming sign” (a progressive increase in the size

of the lesion after injection: 63% versus 32%), would also seem to give weight to malignity [7,8]. Masses seem to be more often hypo-intense in T2 weighting in IBC (78%) than in AM (18%), because of desmoplastic fibrous remodelling [9,10] more often associated with abscesses or granulomas [4,5,11]. Non-mass type enhancement is found in both conditions. The lesions tend to be superficial in infectious AM because of the progression of microorganisms inwards from the nipple, while IBC lesions tend to be central or deep [4]. Early, intense, punctiform enhancement in the cutaneous layer speaks in favour of cancer (56% versus 7%). These lesions are often present (70 to 80%) where there are tumoural emboli of the lymphatic vessels of the skin [12]. The T2 hypersignal indicating prepectoral oedema or oedema in the pectoral muscle tends to indicate IBC (Fig. 1) [4]. This particular appearance seen in IBC is explained by the possible obstruction by tumoural emboli of deep lymphatic vessels linked to the internal thoracic network. Pectoral muscle signal abnormalities tend to be discriminating (Fig. 2), (interruption of the fatty interface: 54% versus 17%; pathological enhancement of the muscle: 33% versus 7%) [13].

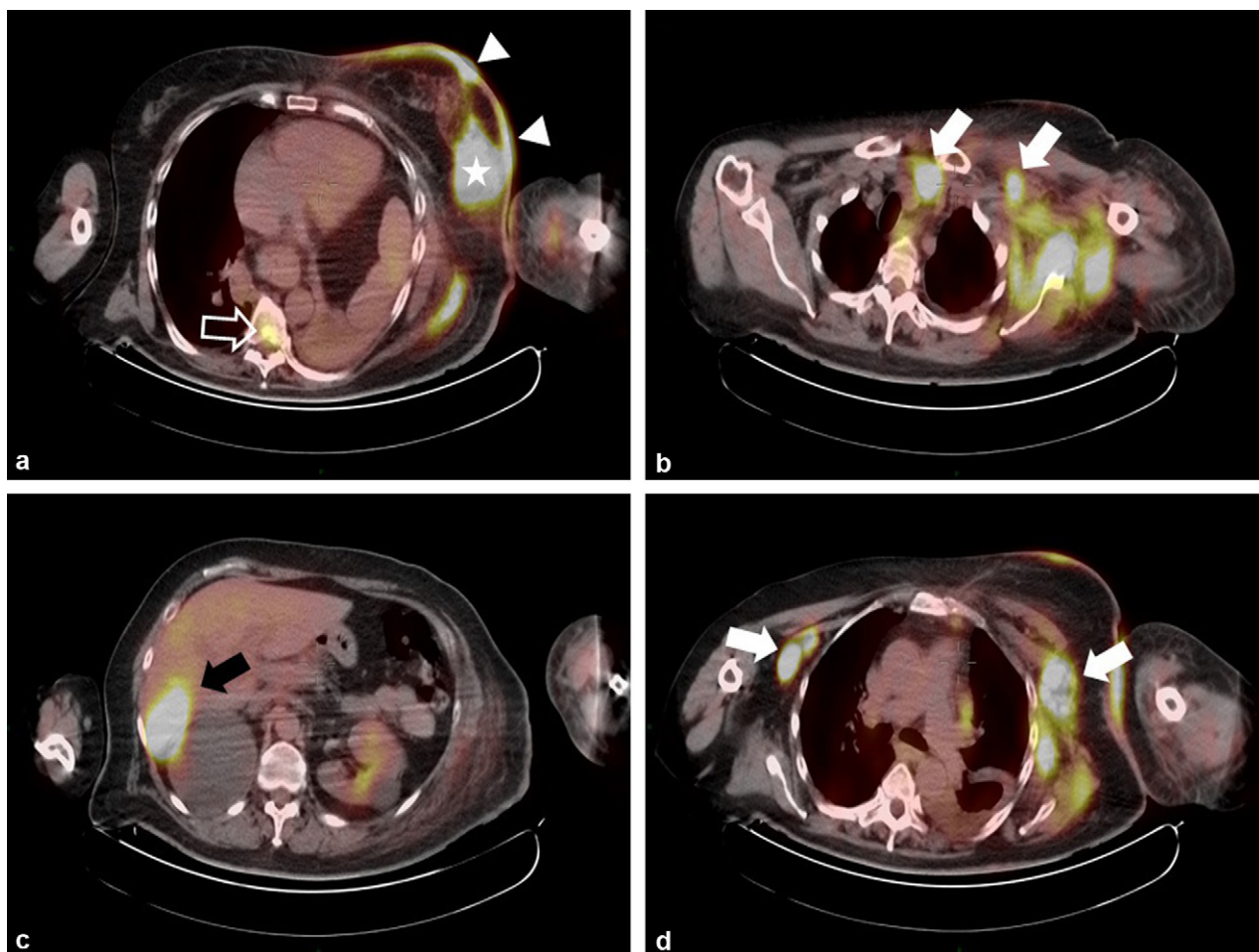


Figure 3. Staging of an infiltrating ductal carcinoma (SBR grade III, triple negative, with P53 mutation) of the left breast, clinically PEV 3 (a). Locally, the PET-CT with ^{18}F FDG shows the tumour (star) of the left breast and skin infiltration (arrow head). Regional staging shows bilateral axillary, left subclavicular and mediastinal adenopathies (arrow) (b, c, d). The PET-CT also shows hepatic (black arrow) and bone (hollow arrow) metastases.

In a retrospective study, M.D. Anderson's team compared the performance of mammography, ultrasonography, MRI and PET-CT. It appears that MRI was the most precise examination for detecting a cancer in an inflamed breast [14]. In this work, MRI detected all the inflammatory cancers and PET-CT found them in 96% of patients. MRI was decidedly more precise than PET-CT for defining the multifocality and the multicentricity of tumours. FDG-PET is not therefore recommended for characterising breast lesions, whether they are inflammatory or not. It is a standard with a level of evidence A in the SOR system [15,16]. Indeed, the majority of studies have shown its limitations for diagnosing small tumours (<1 cm), for certain histological sub-types (carcinoma in situ and lobular carcinoma) and for well-differentiated and low-grade tumours [17]. Moreover, 18-fluorodeoxyglucose (FDG) is not a specific marker for cancerous lesions, and inflammatory mastitis can intensely fix the tracer; far more exceptionally, certain benign lesions, such as cytotestatonecrosis, and certain fibroadenomas may weakly fix FDG. In IBC, PET-CT shows hypermetabolic, often multiple (multifocal and multicentric) foci associated with thickened skin, which is also hypermetabolic (96% sensitivity). Diffuse, intense, homogeneous fixation or fixation

composed of many diffuse foci in the breast associated with hyperfixing-thickened skin is also possible (Fig. 3) [18,19].

Staging

The place of MRI and PET-CT in the local/regional staging of IBC has not been clearly defined. The potential benefits expected from pre-operative MRI of IBC are not as for other types of cancer (with which healthy margins can be obtained and reduced rates of local recurrence), as almost all the patients will have a mastectomy. The objective of local/regional staging is to look for a contralateral cancer, which is more frequent in IBC (bilateral involvement being found in 4 to 30%, Fig. 4) [20,21], but there is no information in the literature confirming or refuting the usefulness of performing MRI to study the contralateral breast [3]. As for other types of breast cancer, histological evidence is necessary of supernumerary lesions, detected in the contralateral breast by MRI, to plan the best surgery (evidence level 1b, recommendation level A) [3]. MRI and any histological tests must not delay treatment.

Patient management for IBC is generally by neoadjuvant chemotherapy, followed by a mastectomy with axillary

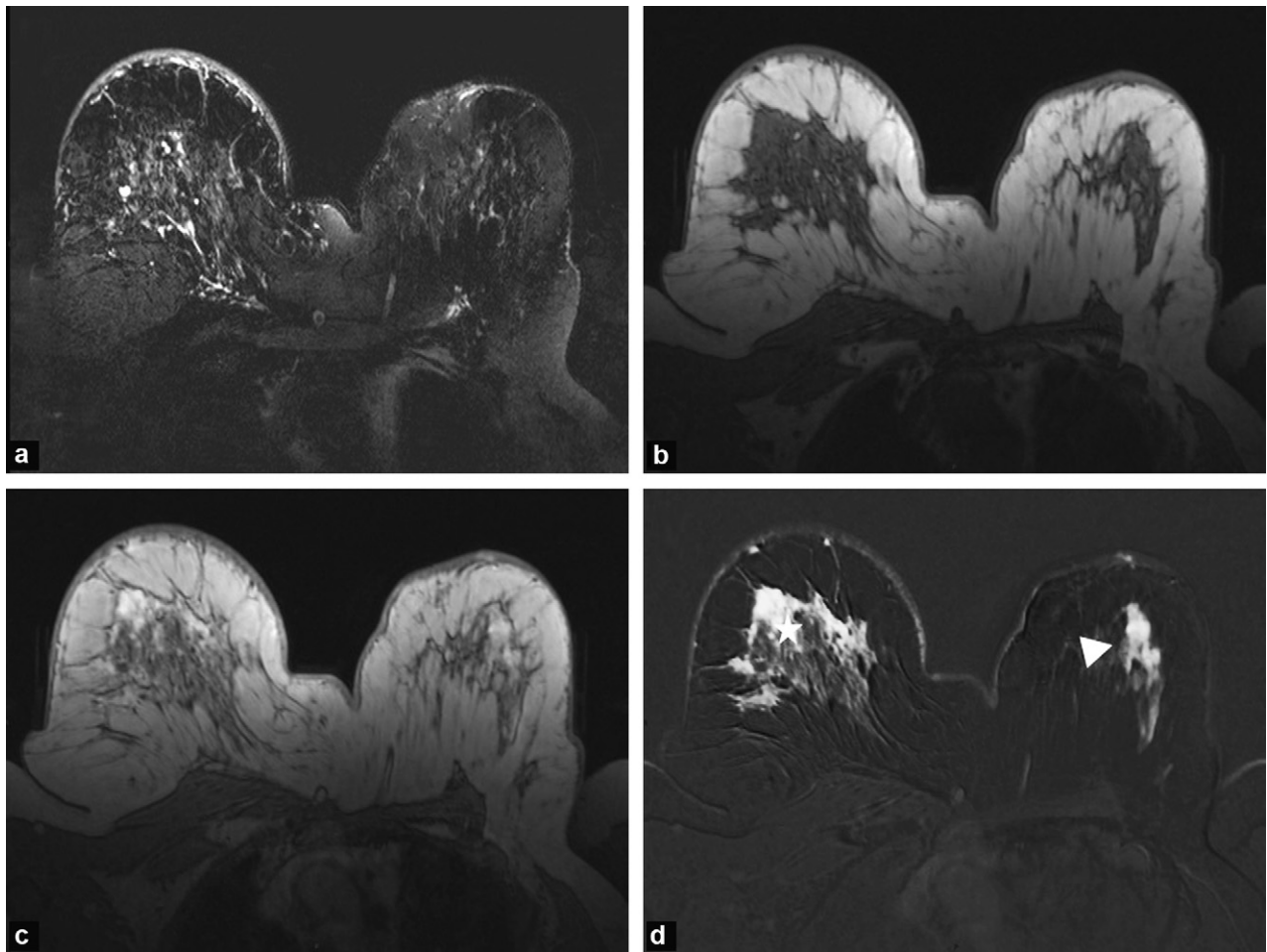


Figure 4. MRI appearance of an infiltrating ductal carcinoma (SBR grade II) of the right breast, clinically PEV 3. The MRI shows a cancer of the right breast in the form of a regional homogeneous non-mass (star) and skin thickening. On the left, the MRI shows homogeneous, segmental enhancement without a mass (ACR 4). A microbiopsy of this lesion of the left breast revealed an infiltrating ductal carcinoma (SBR grade II).

lymph node dissection, radiotherapy and, depending on the case, adjuvant chemotherapy. Axial lymph node dissection performed as a second course of action can prove negative due to the efficacy of the initial chemotherapy, but knowledge of an initial invasion of the axilla can be useful information, particularly for guiding the fields for radiotherapy. Ultrasound is the best examination for removing suspicion from a clinically palpable node and for detecting abnormal non-palpable lymph nodes. However, PET-CT also appears to perform well for lymph node staging, particularly in detecting invasion beyond levels 1 and 2 of the axilla (invasion of the subclavicular, supraclavicular and/or internal thoracic chains) (Fig. 3) [22,23]. On the other hand, the precision of PET-CT or MRI of the breast is not good enough to replace surgical exploration of the axilla [24,25].

IBC is an aggressive cancer with a strong tendency towards early metastasis [26]. The place of PET-CT in the management of IBC is therefore essentially in staging remote metastases [22]. PET-CT allows metastatic staging with excellent diagnostic precision (sensitivity 100%, specificity 93%, positive predictive value 100% and negative predictive value 90%). PET-CT with FDG is indeed more sensitive than so-called conventional imaging for staging remote

metastases, particularly in the mediastinal lymph nodes, liver, abdomen and bone (Fig. 3) [27]. Several studies have reported the superiority of PET-CT over bone scintigraphy for detecting bone metastases, but with poorer performance for blastic lesions, underlining the importance of simultaneously reading CT images, or even of an additional bone scintigraphy examination. The other PET-CT false negatives are essentially small-size lesions, particularly in pulmonary and hepatic parenchyma. As far as false positive foci are concerned, they are essentially the prerogative of infectious or inflammatory phenomena.

Therapeutic monitoring

The therapeutic sequence for IBC consists of neoadjuvant chemotherapy followed by treatment combining mastectomy and local/regional irradiation. The place for conservative treatment is extremely limited considering the risk of recurrence and the catastrophic prognosis accompanying it.

Many studies have shown that MRI is a better technique for evaluating the effect of neoadjuvant treatment compared with clinical examination, mammography and

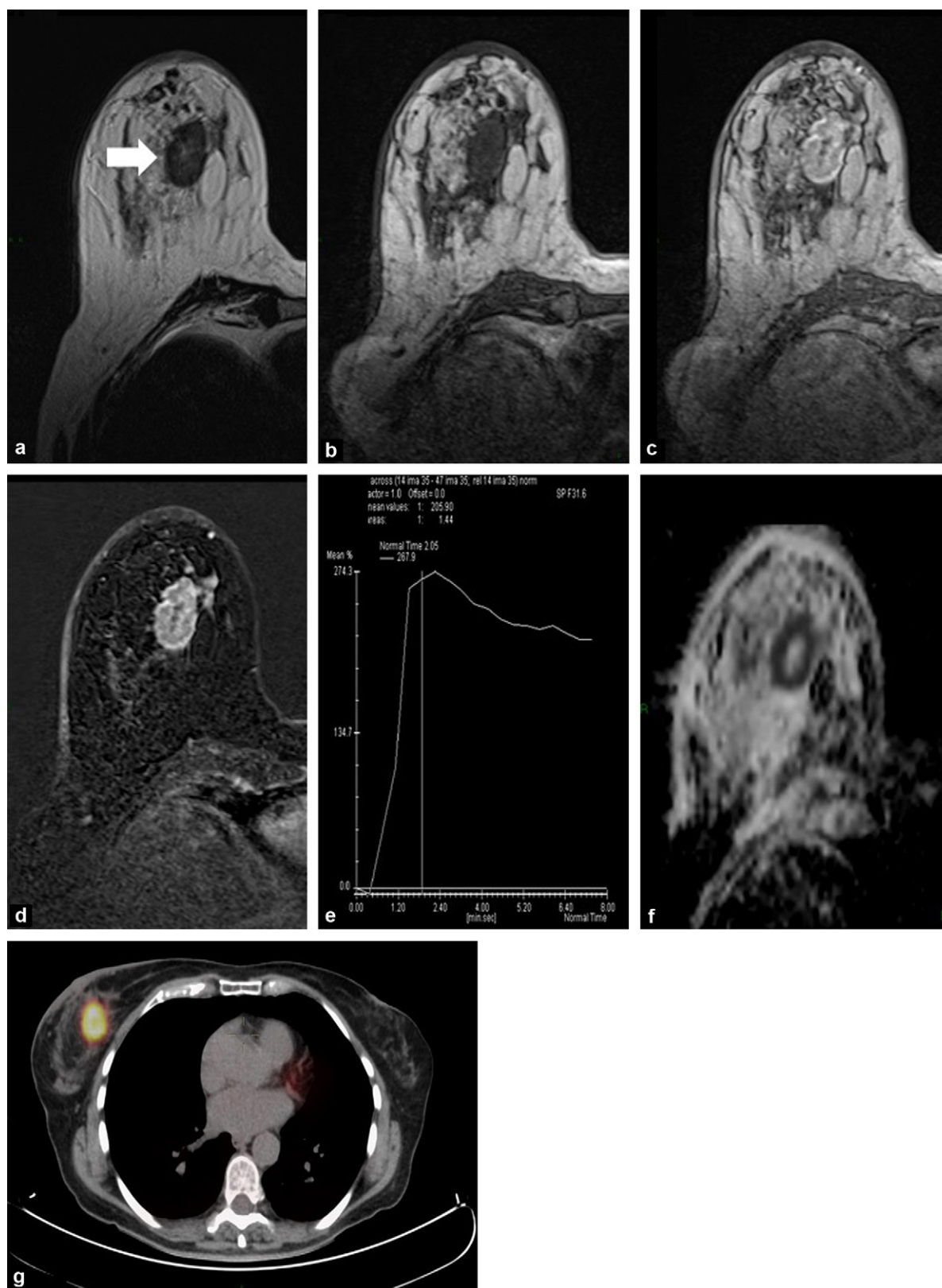


Figure 5. MRI and PET-CT monitoring of a patient treated for infiltrating ductal carcinoma (SBR grade III, HER2 3+, RE negative, Rp negative) of the right breast, clinically PEV 3, treated by neoadjuvant chemotherapy. Before treatment, the MRI morphological analysis showed an oval, circumscribed mass (arrow), with annular enhancement and central necrosis (a: T2, b: T1, c: injected T1, and d: subtracted injected T1). Still before treatment, the tumoural enhancement kinetics show early, intense contrast uptake (267% at 2 minutes) followed by a washout (type 3) (e). The diffusion sequence (f) shows restriction of the diffusion with an ADC measured at $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$. In PET-CT with ^{18}F FDG (g), hypermetabolism is seen in the tumour with an SUV measured as 12.

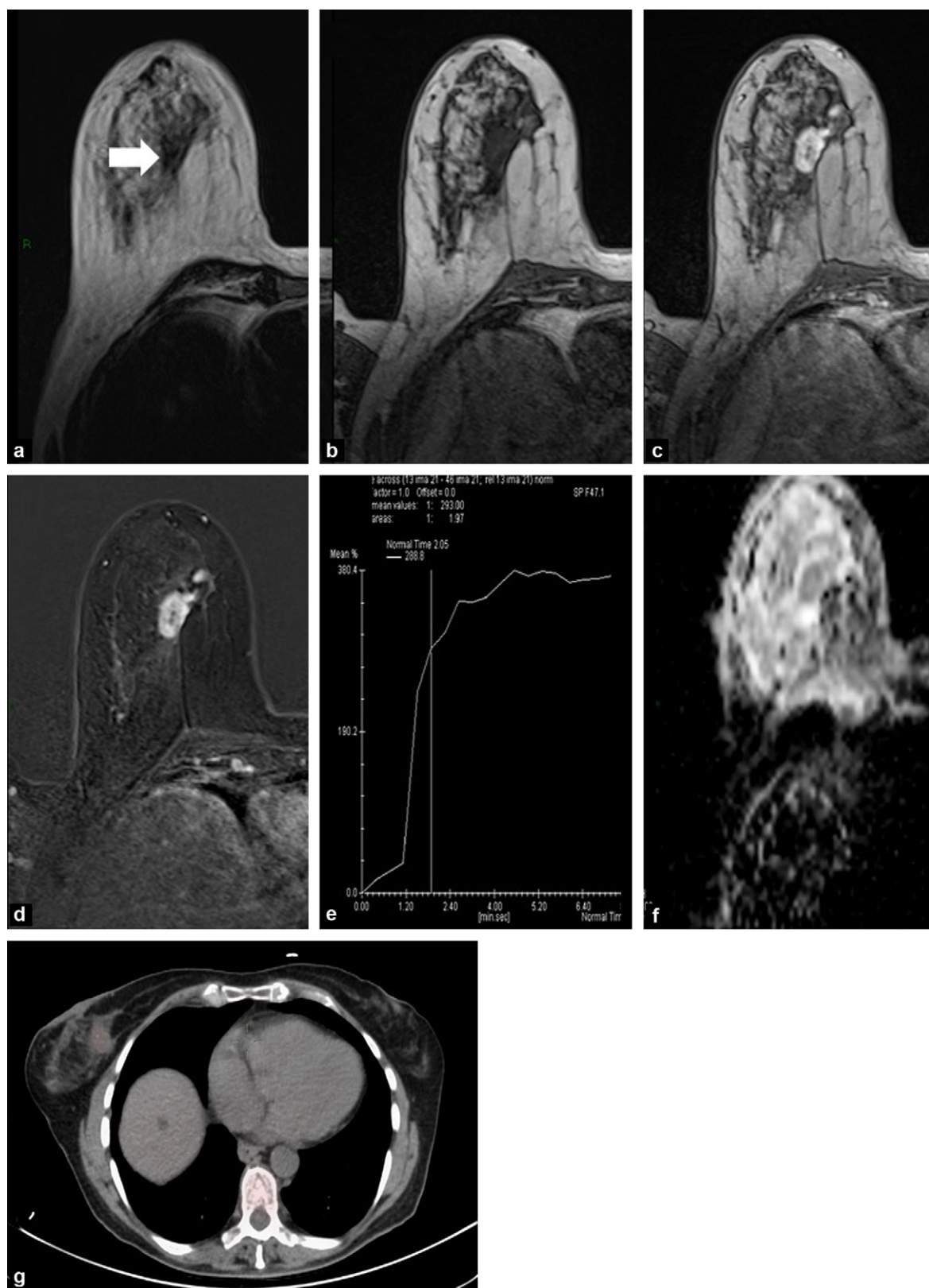


Figure 6. MRI and PET-CT monitoring after two courses of chemotherapy (same patient as Fig. 5). After two courses, the MRI morphological analysis shows an approx. Fifty percent reduction in volume of the mass (arrow) (a). Functional analysis shows less pejorative, intense (288% at 2 minutes) but progressive (type 1) tumoural enhancement kinetics (b, c, d, e). The diffusion sequence (f) shows an increase in the diffusion with an ADC measured at $1.5 \times 10^{-3} \text{ mm}^2/\text{s}$. In PET-CT with ^{18}F FDG (g), a clear reduction in hypermetabolism is seen in the tumour with an SUV measured as 3.9. These morphological and functional data after two courses predict a good final response.

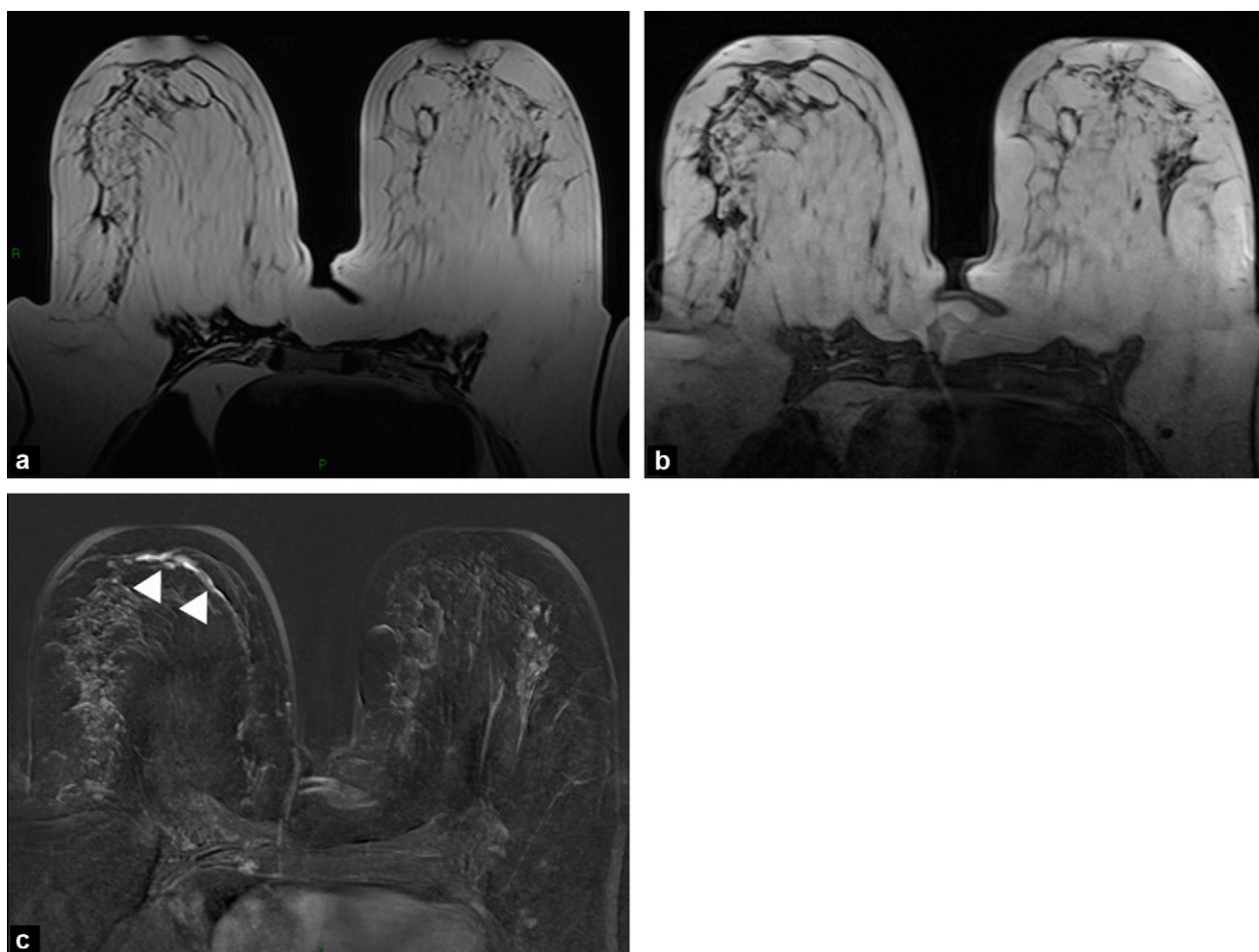


Figure 7. Breast MRI: axial T2-weighted (a), T1 (b), T1 injected with subtraction (c).

ultrasound examination, even if over- and underestimates of the residual condition may be produced, particularly for non-mass lesions and tumours fragmented after the neoadjuvant chemotherapy. The prime objective of breast MRI is moreover based on its ability to show the real extent of the lesion after treatment, in order to guide the choice of lumpectomy or mastectomy. As mastectomy is generally recommended in the case of IBC, the usefulness of MRI can be understood to be limited to evaluating the efficacy of neoadjuvant chemotherapies on the IBC. As for PET-CT, it has no place in the evaluation of the residual condition at the end of neoadjuvant chemotherapy: PET sensitivity is low for this indication, partly because of the limited spatial resolution of the PET detectors and partly because of post-chemotherapy “metabolic stunning” phenomena [28].

MRI and FDG-PET could nevertheless play a major role in assisting in early identification of non-responding patients right from the first course of chemotherapy, so that treatment could be modified without having to wait for the results of conventional evaluation examinations (Figs. 5 and 6) [29,30].

The usefulness of new functional imaging techniques, such as spectroscopy and diffusion, for making an early assessment of the efficacy of neoadjuvant treatments, has also been evaluated in several studies (which included

patients being managed for a locally advanced tumour and patients with IBC). No specific results are available for IBC to date. It is to be noted that an early decrease in choline concentration, from the 24th hour after treatment, is an indicator of a good response [31]. Several studies have also shown that the restriction of diffusion decreases in good responder patients, indicating a reduction in intratumoural cell density (Figs. 5 and 6) [32–35]. Restriction in initial diffusion before treatment may have prognostic value [36].

In practice

When faced with breast inflammation, the most common diagnosis is simple infectious mastitis. Ultrasound may be useful to eliminate an abscess. Most cases of infectious mastitis regress rapidly after beginning anti-infective treatment. Non-infectious mastitis generally has a clinically suspect appearance. A series of examinations including mammography, ultrasonography and biopsy is thus recommended to eliminate a cancer or an infection before beginning corticosteroid treatment. MRI of the breast is not indicated in the treatment of acute or subacute mastitis and should not be used for differential diagnosis between inflammatory breast cancer and acute mastitis prior to

treatment (level of evidence 1b, recommendation level A) [3].

When the symptoms of presumed mastitis do not subside after 10 to 15 days of well-managed medical treatment, another series of ultrasound and mammography examinations plus cutaneous, mammary and lymph node biopsies must be envisaged, to eliminate inflammatory breast cancer. A breast MRI can also be performed if doubt persists concerning the presence of an underlying cancer (level of evidence 2b, recommendation level C) [3]. MRI must not delay histological biopsies or initiating treatment in the case of inflammatory cancer.

MRI may play a role in local/regional staging in inflammatory cancer, in looking for contralateral lesions. PET-CT could be useful in local/regional lymph node and remote metastatic staging. MRI and PET-CT could also be used for early detection of non-responding patients so that an ineffective neoadjuvant chemotherapy can be rapidly modified. This indication is, however, not as yet recommended.

TAKE-HOME MESSAGES

Diagnosis and characterisation

- After well managed medical treatment of suspected mastitis, a breast MRI may be performed if there are still doubts regarding the presence of an underlying cancer.
- The following criteria do not discriminate between IBC and AM: the morphology of masses and non-masses, increase in breast size, diffuse skin thickening, abnormal nipple configuration, hypervascularisation, and cutaneous or subcutaneous oedema.
- The following criteria are seen more frequently in IBC: a T2 hyposignal mass of more than 10mm, type III enhancement, a "blooming sign", infiltration of the pectoralis major muscle, oedema (peri-focal, prepectoral and intramuscular). The main location of AM is generally subareolar, that of IBC, central and posterior.
- PET-CT is not indicated for characterisation.

Staging

- Breast MRI: would be useful when searching for a contralateral lesion.
- PET-CT: would be useful for local/regional lymph node staging before neoadjuvant chemotherapy, for guidance regarding the fields to be irradiated after mastectomy.
- PET-CT: performs well for remote staging.

Monitoring neoadjuvant chemotherapies

- MRI and PET-CT seem to perform well for early evaluation of responders and non-responders, which can allow an ineffective treatment to be changed.
- MRI performs well for evaluating residual tumour volume at the end of treatment, to guide surgery. Nevertheless, the expected benefit of this monitoring is relative, since all patients have a mastectomy.

Clinical case

Question 1

A 50-year-old patient has made an emergency consultation for pain in the right breast, which has evolved over the last 8 months; the breast has been inflamed for 5 days with fever. The mammogram, taken 8 months ago (not available), showed cysts. On clinical examination, the following is noted: tachycardia, a sub-febrile state, no signs of shock, eupnoea, clear symmetrical auscultation, supple, painless abdomen.

The right breast is inflamed with peri-nipple plaque, a subjacent mass, nipple invagination. No axillary adenopathy. What imaging examination(s) would you ask for?

1. None;
2. Ultrasonography;
3. Mammography;
4. MRI.

Answers

1. Yes: the recommendation is to start antibiotic and anti-inflammatory treatment and reassess the situation after 2 weeks;
2. Yes: it is reasonable to ask for an ultrasound examination to eliminate an abscess;
3. Yes: since the patient is more than 35 years old, it is reasonable to ask for a mammogram;
4. No: MRI should not be used for differential diagnosis between acute mastitis and inflammatory breast cancer before a trial treatment lasting 10 to 15 days.

Question 2

The patient returns to the breast clinic 17 days later. The volume of the right breast has increased and there is cutaneous erythema, particularly affecting the central region with slight nipple retraction. Palpation is painful. No perceptible mass; no nipple discharge caused. Examination of the contralateral breast is normal. Homolateral and contralateral axillary and supraclavicular lymph nodes are free. What imaging examination(s) would you ask for?

1. None;
2. Ultrasound and mammogram;
3. Biopsies;
4. MRI.

Answers

1. No: symptoms persist despite 17 days of well-managed treatment. An underlying cancer must be eliminated by asking for a mammogram, an ultrasound examination, and skin and mammary biopsies. An MRI could also be requested to look for a tumour which might be poorly visible by mammography and ultrasonography because of oedema;

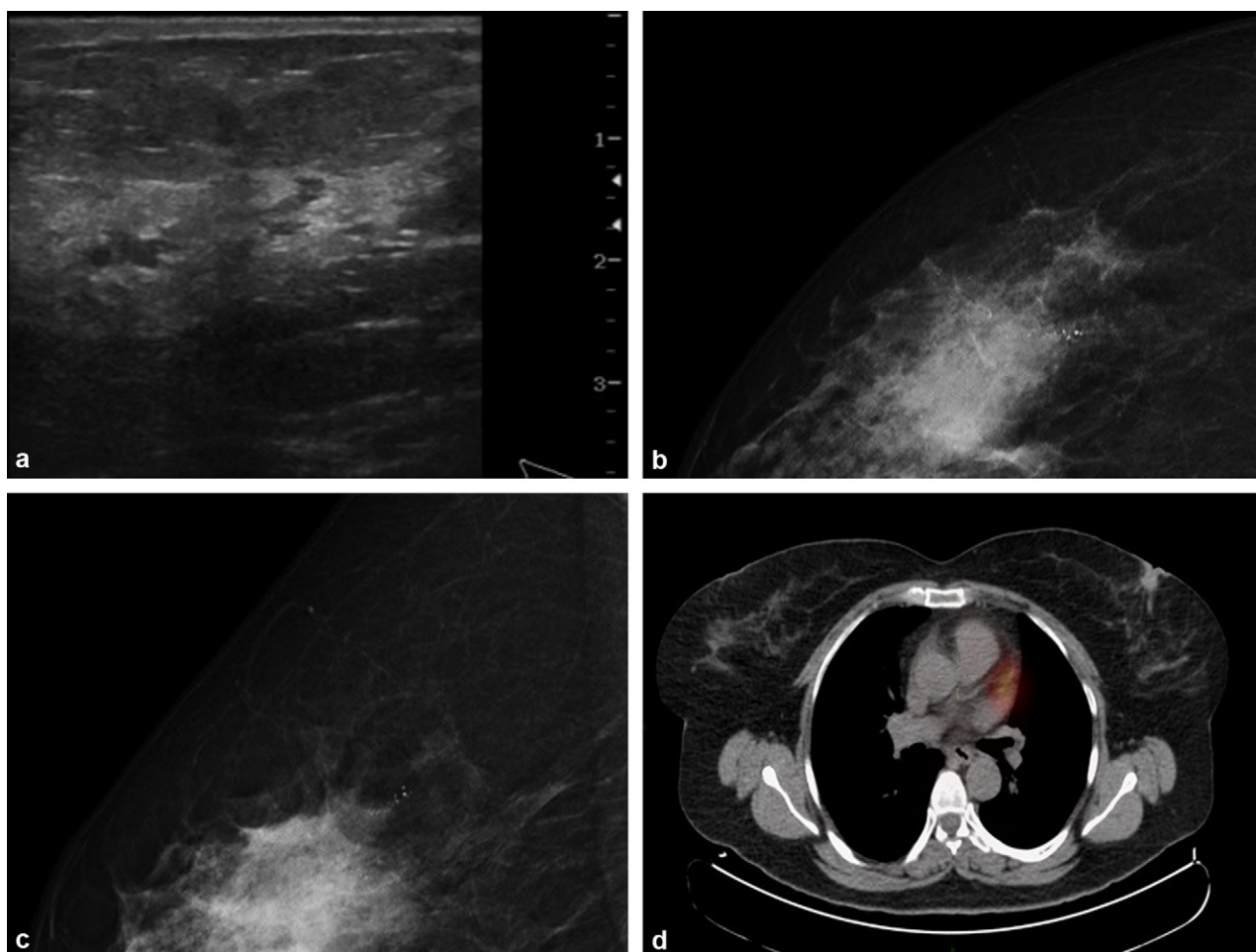


Figure 8. Ultrasound: retroareolar region of the right breast (a), right breast mammogram: enlargement is focused on the external side compartments (b); right breast mammogram: enlargement is focused on the upper compartments in oblique (c) PET-CT performed in the staging (d).

2. Yes;
3. Yes;
4. Yes.

Question 3

MRI is performed (Fig. 7) and shows enhancement without a ductal mass in the superior medial quadrant of the right breast. Ultrasound examination (Fig. 8a) shows duct ectasias, and the mammogram (Fig. 8b: CC, and 8c: MLO) shows a few diffuse heterogeneous large micro-calcifications (ACR 3) in the superior medial quadrant of the right breast. A stereotactically guided macrobiopsy of the micro-calcifications of the right breast is performed and shows dystrophy without atypia. A PET-CT is performed for staging and shows no hypermetabolic foci (Fig. 8d). What would you do?

1. A biopsy under MRI;
2. A new stereotactically guided macrobiopsy;
3. Mammographic, ultrasonographic and MRI monitoring;
4. Nothing, because the PET-CT is negative.

Answers

1. Yes: the stereotactic macrobiopsy does not formally eliminate a cancer;
2. No: sampling was performed under good conditions but this (the micro-calcifications) was not the right target;
3. No: there is an ACR 4a-type lesion in an inflamed breast: cancer must be rapidly eliminated;
4. No: PET-CT is not sufficiently sensitive in the breast to formally eliminate a small cancer.

The patient refuses another macrobiopsy and is monitored by MRI after 4 months (Fig. 9a) and 8 months (Fig. 9b). Compared with the initial MRI (Fig. 9c and d), these two examinations show that the non-mass enhancement has disappeared from the superior medial quadrant of the right breast. A year later, the patient is doing well.

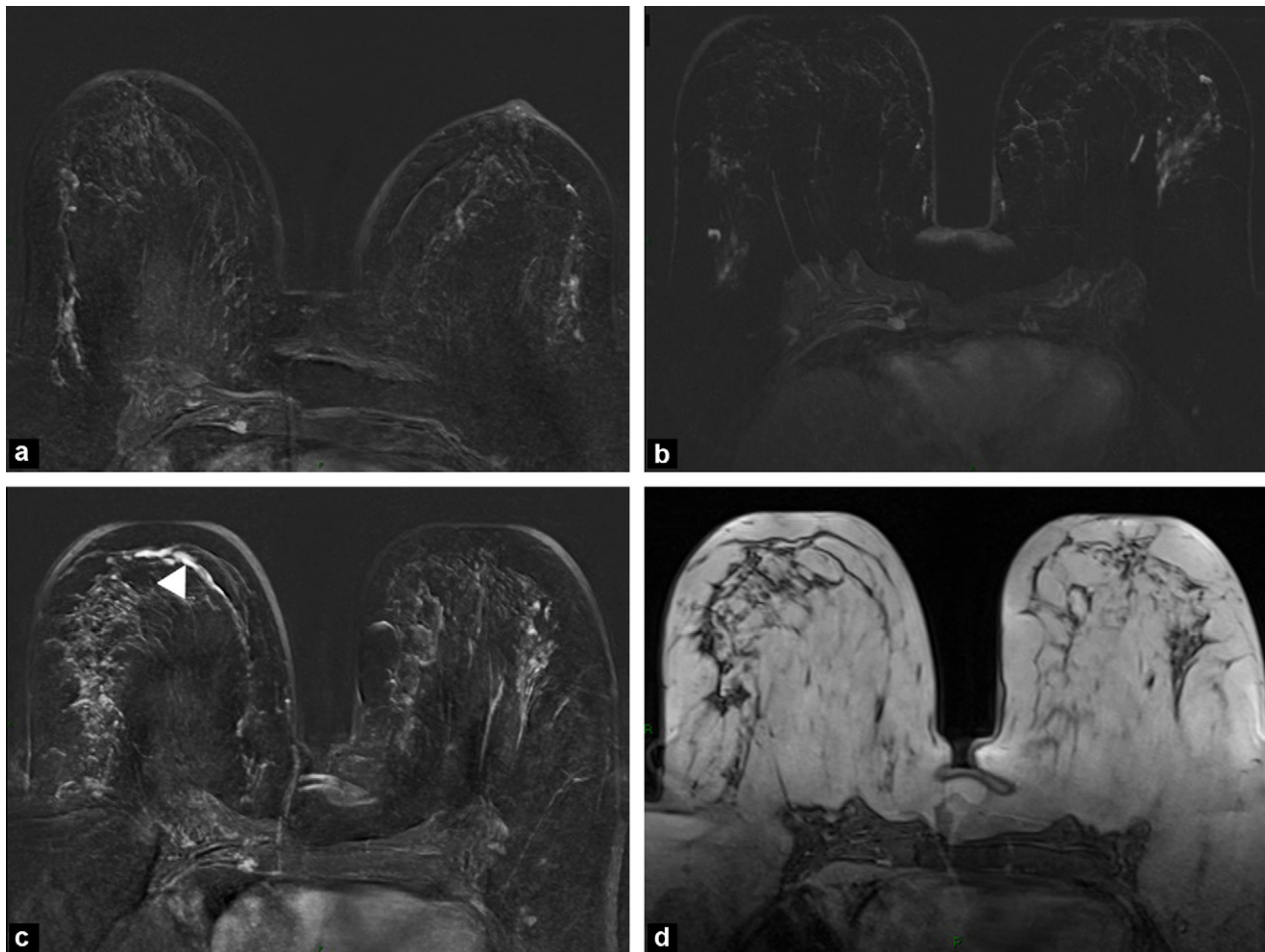


Figure 9. Breast MRI at 4 months, T1-weighted injected with subtraction (a) and breast MRI at 8 months, T1-weighted injected with subtraction (b). Initial breast MRI axial T1-weighted injected with subtraction (c), initial breast MRI T1-weighted (d).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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