First Clinical Experience using Stereotactic Breast Biopsy Guided by ^{99m}Tc-Sestamibi

Abstract

Objective: To evaluate a new device using molecular breast imaging (MBI) for ^{99m}Tc-sestamibi-guided stereotactic lesion localization, as a complementary biopsy tool.

Materials and Methods: From December 2012 to May 2016, 38 consecutive women (mean age 59 years; range: 41-77 years) underwent ^{99m}Tc-sestamibi-guided biopsy using a new MBI-based device and were retrospectively reviewed. This biopsy modality utilizes 5 steps: *(1)* stereotactic localization of the ^{99m}Tc-sestamibi-avid lesion; *(2)* calculation of coordinates of the lesion location using dedicated software; *(3)* placement of the needle; *(4)* verification of the correct needle position and *(5)* tissue sampling with a vacuum-assistant device followed by placement of a radiological marker at the biopsy site and ex vivo measurement of the biopsy specimens.

Results: The procedure was technically successful in all 38 lesions. In all cases, biopsy samples were radioactive and adequate for histopathological analysis. A malignancy was found in 19 lesions (50%) and benign disease in the remaining lesions. The average procedure time was 71 minutes (range: 44-112 minutes). The radiological marker was successfully deployed in 37 lesions (97%). Two hematomas and three vasovagal reactions were observed.

Conclusion: ^{99m}Tc-sestamibi-guided biopsy using a dedicated MBI-based device is technically feasible and represents a valuable complementary biopsy tool in breast lesion diagnosis.

Introduction

Since 1994, technetium-99m (^{99m}Tc) sestamibi has been used as a tumor-seeking radiotracer to detect breast cancer (BC) [1, 2]. Uptake of ^{99m}Tc-sestamibi occurs within mitochondria of tumor cells and is related to regional blood flow, angiogenesis, mitochondrial density and activity [3-5]. Currently, ^{99m}Tc-sestamibi is the radiotracer of choice for molecular breast imaging (MBI). This modality, also called breast-specific gamma imaging (BSGI), consists of a single or dual-head small field-of view gamma camera, designed for breast imaging [6-10]. To date, magnetic resonance imaging (MRI) is the most commonly used imaging modality after mammography (MG) and ultrasound (US) in BC. However, due to limitations of MRI such as high costs, limited use in patients with claustrophobia, obesity and renal failure [11], and its association with high rate of unnecessary biopsies [12], MBI is evolving as a valuable complementary tool in the diagnostic workup of BC [12, 13]. MBI is recommended by the Society of Nuclear Medicine and Medical Imaging as an adjunct imaging tool to MG and US in patients: *(a)* with newly diagnosed BC to assess multifocal, multicentric or, contralateral disease; *(b)* at high risk for BC; *(c)* with indeterminate breast lesions and remaining diagnostic concerns and *(d)* with technically difficult breast imaging [14]. In patients with occult lesions on MG and US that are ^{99m}Tc-sestamibi-avid on MBI with BI-RADS (Breast Imaging Reporting and Data System) category 4 or 5 [14, 15], second-look US is mandatory. If a sonographic substrate is found on second-look US, US-guided biopsy is performed during the clinical work-up. However, in patients with suspicious MBI-detected lesions (BI-RADS 4 or 5) that remain occult after second-look US, or in patients with unclear lesions on MG and US in whom MG- or US-guided biopsy is considered technically impossible or has failed, other methods for accurate tissue sampling are necessary. Recently, a device for performing ^{99m}Tc-sestamibi-guided breast biopsy using dedicated MBI has been developed. This tool is based on stereotactic localization of ^{99m}Tc-sestamibi-avid lesions using a slant-hole collimator system and vacuum-assisted device (VAD) [16, 17]. The purpose of the present study is to evaluate the potential of this device as a complementary biopsy tool.

Materials and Methods

Patients

From December 2012 to May 2016, 38 consecutive patients (mean age, 59 years; range: 41-77 years) underwent ^{99m}Tc-sestamibi-guided biopsy using a dedicated MBI device. Prior to the procedure, two nuclear medicine physicians in consensus evaluated the MBI images and assessed the feasibility to perform MBI-guided biopsy. Clinical data were retrospectively reviewed. All patients gave written informed consent for retrospective analysis of the data and the study was approved by institutional review board. All biopsied lesions were ^{99m}Tc-sestamibi-avid on MBI (BI-RADS 4 or 5) and were occult after second-look US or unclear on MG and US without possibility for MG- and US-guided biopsy.

^{99m}Tc-sestamibi-guided biopsy procedure

All biopsies were performed using ^{99m}Tc-sestamibi as radioguidance. A dedicated MBI device equipped with a stereotactic localization system (GammaLōc®, Dilon Technologies, Newport News, VA), cleared by the Food and Drug Administration (FDA) in 2009, was used to localize the target lesion (Fig.1). The methodological aspects of this MBI-based biopsy device have been previously described [18]. All patients received analgesics for pain relief the day of the procedure. After fixation of the breast between the detector and compression paddle with the patient in seated position, a dose of 600 MBq ^{99m}Tc-sestamibi is intravenously administered. Subsequently, the biopsy procedure is performed in 5 steps. First, a scout image is acquired followed by left and right stereotactic images to determine lesion location (step 1). Second, the software (GammaLōc®, Dilon Technologies, US) calculates the X, Y, Z coordinates of the ^{99m}Tc-sestamibi-avid lesion location (step 2), which is followed by injection of local anesthetic, placement of the needle (step 3) and verification of the correct needle position **(step 4) using a ^{139}Ce source as previously described and illustrated in detail [18] [Rev. #2; Comment 1].** Subsequently, biopsy is performed using a VAD and as a rule six specimens are obtained. Immediately thereafter a radiological marker (clip) is placed at the biopsy site. After biopsy, the breast is removed from the detector and radioactivity of the tissue samples is

measured ex vivo using the MBI gamma camera to confirm the representativity of the biopsy specimens (step 5). The samples are subsequently sent for histopathological analysis. Finally, breast MG is performed immediately after the biopsy procedure in order to verify the correct position of the clip in all patients. In individual patients, further diagnostic steps are discussed during a multidisciplinary meeting, attended by a radiologist, a nuclear medicine physician, a breast surgeon and a pathologist. Subsequent decision-making depends on factors as histopathological diagnosis, pre-test likelihood for malignancy, activity of the acquired samples and visibility of the index lesion on radiological imaging. If the patient with a malignant lesion is scheduled for breast conserving surgery (BCS), the tumor is pre-operatively localized using a wire or Iodine-125 (^{125}I) seed, which is placed at the site of the clip using sonographic guidance. In patients with benign histopathology, the individual plan may vary from follow-up with MBI **or MRI [Rev. #2; Comment 1]** after 3-6 months, including re-sampling when indicated, follow-up with MG and US after 6-12 months or returning to the screening program (if applicable).

Data Collection and Analysis

Collected data were patient age, characteristics of the lesions based on ^{99m}Tc-sestamibi uptake according to the lexicon for MBI imaging [15], clip placement, complications, histopathology after vacuum-assisted biopsy and surgical excision. The procedure time was determined by calculating the interval between the start of the scout image and placement of the clip at the biopsy site. The histopathological results of biopsy and excision were classified as following: *(a)* malignant lesions (invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) and/or ductal carcinoma in situ (DCIS); *(b)* high-risk lesions such as atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS) [19] and *(c)* benign lesions. Data were entered into a computerized spreadsheet (Excel, Microsoft) for analysis. Categorical variables were summarized as counts and percentages in each class. Quantitative variables such as mean and standard deviation, median, minimum and maximum were calculated.

Results

Results are summarized in Table 1. MBI-based biopsy was technically successful in all 38 patients (38 lesions). In all patients, the sampling was radioactive and adequate for histopathological analysis. The procedure was well tolerated in all patients. The average procedure time was 71 minutes (range: 44-112 minutes). In 3 patients, the procedure time was longer than 89 minutes (mean+1standard deviation) due to low ^{99m}Tc-sestamibi-avidity (nº 10), patchy uptake pattern (nº 3) making localization more difficult and incorrect switching of the slant hole collimators (nº 8). The median size of the lesions was 14.5 mm (range: 5-60 mm). Among 38 lesions, 9 lesions (24%) were located in the posterior third of the breast, thus close to the chest wall. Nineteen lesions (50%) turned out to be malignant at histopathological analysis of the biopsy specimens, with IDC in 9, both IDC and DCIS in 2, ILC in 1, mucinous carcinoma in 1 and DCIS in 6 (Figs. 2-3). These 19 malignant lesions had a median size on MBI of 12 mm (range: 5-45 mm). Five patients underwent mastectomy. The other fourteen patients underwent BCS, using wire localization in 12 and ^{125}I seed localization in two. Of these 14 cases, the surgical margins were negative in 13 (93%) with a median margin of 4.5 mm (range: 2-12 mm). In one case (nº 15), the surgical margins were positive due to an extension of extra-lesional DCIS. In 18 of 19 malignant lesions, subsequent surgical excision confirmed diagnosis of cancer. In one patient (nº 11) in whom DCIS was diagnosed after vacuum-assisted biopsy, no in situ carcinoma or invasive carcinoma was found after surgical excision. Probably the small area of DCIS (11mm) had been completely excised during ^{99m}Tc-sestamibi-guided biopsy. No high-risk lesions were found at histopathological analysis of the biopsy specimens. Nineteen lesions (50%) were diagnosed benign: mastopathy in 11, adenosis in 4 and both mastopathy and adenosis in 4 (Fig. 4). The median size on MBI of these benign lesions was 15 mm (range: 7-60 mm). Placement of a localizing clip was successful in 37 of 38 lesions (97%). In one patient (nº 7), the marker-needle dragged out the clip from the biopsy site when it was removed from the breast. Post-biopsy MG showed correct position of the clip at the biopsy site in 33 of 37 patients (89%) and migration of the clip from the biopsy cavity in the remaining 4 patients. Complications were encountered in 5 patients (13%). Two patients developed a hematoma, which was resolved with compression. In another 3 patients, a vasovagal reaction occurred immediately after introduction of the trocar needle, but without the necessity to abort the procedure.

Discussion

In this first clinical experience, ^{99m}Tc-sestamibi-guided biopsy was successful in all 38 consecutively biopsied patients. On the basis of our results, this new biopsy tool appears to be technically feasible and may enable dedicated BC imaging specialists to obtain radioactive samples from ^{99m}Tc-sestamibi-avid lesions on MBI. Furthermore, our results show that this device allows to verify the success of the procedure by measuring ex vivo radioactivity in the biopsy specimens and to separate radioactive from inactive specimens in order to lead the pathologist to pay special attention towards the radioactive specimens (vital tissue), avoiding rebiopsy and delay in diagnosis. According to our results, this biopsy procedure permits to obtain adequate samples for histopathological analysis, due to the use of a VAD that acquires larger specimen volumes compared to automated core-needle biopsy [20, 21]. We have shown that ^{99m}Tc-sestamibi is useful to guide the localization and excision of ^{99m}Tc-sestamibi-avid breast lesions. Potentially, this may facilitate the selection of the most ^{99m}Tc-sestamibi-avid areas that reflect the part of tumor with high cellular proliferation [22], leading to a more accurate genomic profile analysis [23] and avoiding sampling of stroma, fatty and/or necrotic tissue especially in large heterogeneous lesions. In our series, this new device allows successful sampling of subcentimeter lesions as well as lesions located in the posterior third of the breast, thus close to the chest wall. However, some posterior lesions may not be captured within the biopsy grid if they are in close proximity to the pectoral muscle because they are not included in the field of view of the device [18]. Placement of a clip at the biopsy site, to facilitate subsequent excision if needed, was successful in 97%; this is in concordance with MRI-guided biopsies [24, 25]. In our series, the correct clip position was verified using MG, performed immediately after biopsy, revealing the successful rate of 89%, which is similar to data reported by Liberman et al. using MRI-guided biopsy [24]. Migration of the clip was encountered in 4 patients and is probably due to the well-known accordion effect [26]. The procedure time of this new biopsy appears to be comparable to MRI-guided biopsy [24, 27]. In our study, most of the time was principally spent on acquiring the initial images necessary to localize the target lesion. Encountered complications are comparable to those reported in MRI-vacuum-assisted biopsy [24, 25]. Hematoma can be controlled by post-procedural breast compression. Administration of anti-anxiolytic medication before the procedure could possibly reduce the amount

of vasovagal responses. This new biopsy device appears to be well tolerated by patients, is easy to perform and may cause less discomfort in patients with claustrophobia. Additionally, it is not contraindicated in patients who are overweight or in patients with implanted devices or renal insufficiency. The relatively high percentage of malignancies found in our series emphasizes the value of this new biopsy tool for breast centers where MBI is implemented in the diagnostic pathway. Although half of the lesions biopsied due to MBI findings turned out to be benign, this percentage is lower than the false positive cases reported for MRI biopsy [24]. False positive MBI cases are due to uptake of ^{99m}Tc-sestamibi in benign conditions such as adenosis and mastopathy.

Our study has limitations. First, the study is retrospective. Second, the population is relatively small with a low enrollment rate; however, only patients with occult or unclear lesions excluding any possibility for MG- and US-guided biopsy were eligible. Third, possible limitations of this modality are related to difficult localization of the lesion due to low or patchy uptake of ^{99m}Tc-sestamibi or localization of the lesion in close proximity to the thoracic wall. **Furthermore, as in any other biopsy procedure, the possibility of sampling error should be considered in case of discordance between imaging features and histological results. In this regard, an advantage of MBI-based biopsy over MRI-guided biopsy is the possibility to verify ex vivo whether lesion sampling is successful by measuring the radioactivity in the samples. Further management in discordant cases will be accorded in the institutional multidisciplinary oncology committee and will depend on the initial level of suspicion on MBI imaging, the radioactivity of the obtained biopsy samples and the visibility/suspicion of the index lesion on MG and/or second-look US. If follow-up is requested, short-term (3 months) follow-up with MBI may be performed or follow-up with MRI after 6 months to avoid imaging of post-biopsy tissue changes [Rev. #2; Comment 1]. Another important aspect concerns the clip placed after biopsy. The fact that the clip is not visible on MBI images may theoretically hinder the verification of correct position of clip In our experience, the comparison of the cranio-caudal and latero-medial views of the MBI images with the corresponding views of the post-biopsy MG helps to solve this limitation, since clip position can be adequately judged visually. In the future, co-registration in the acquisition of**

MBI and MG followed by fusion of images might help to improve the procedure. Clip migration though may hamper preoperative lesion localization when the lesion turns out to be malignant and is radiological occult. Finally, [Rev. #2; Comment 2] this procedure involves intravenous injection of a radioactive tracer and thus the use of ionizing radiation. Although the mean glandular dose to the breast is lower with MBI compared with digital MG, the estimated whole body effective dose is 5 mSv with MBI (using 600 MBq ^{99m}Tc-sestamibi), compared to 0.5 mSv with digital MG and 1.2 mSv with MG combined with digital breast tomosynthesis [28]. A single MBI study with 740-1110 MBq ^{99m}Tc-sestamibi is associated with a lifetime attributable risk (LAR) of fatal cancer of 20-30 times that of digital MG in women aged 40 years [29]. One should notice that doses from both MG and MBI are way below the doses at which consideration of risks from radiation are warranted [30]. In addition, innovations in MBI technology allow a reduction of administered activity down to 150 MBq ^{99m}Tc-sestamibi, leading to a significant reduction of absorbed dose to the breast (0.25 mGy) and effective dose (1.1 mSv) [28]. **The fact remains though that in each individual patient one should strive to follow the As Low As Reasonably Achievable (ALARA) principle minimizing radiation exposure. In this context, the decision to currently perform MBI scans in the follow-up of patients with discordant pathology or miss-targeting during MBI guided biopsy needs to outweigh pros and cons based on patient characteristics, local options and expertise. The introduction of modern MBI devices, working with lower administered radioactivity and reduced effective whole body doses comparable with those delivered by digital MG, may help to solve this limitation in the future [Rev. #2; Comment 3].**

In conclusion, ^{99m}Tc-sestamibi-guided biopsy using a dedicated MBI device is technically feasible and seems to represent a reliable, complementary biopsy tool. Further studies with larger series of patients are needed to establish the definitive clinical relevance of this device.

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Table 1 Summary of results.

		Sestamibi characteristics								Histopathology	
Patient	**Age**	**Lesion size (mm)**	**Uptake pattern**	**Uptake score**	**Breast**	**Quadrant**	**Lesion depth**	**Clip failure**	**Complications**	**Biopsy**	**Excision**
1	52	12	F	3	L	UIQ	C	-	-	IDC + DCIS	IDC + DCIS
2	62	10	F	3	R	UIQ	P	-	hematoma	DCIS	DCIS
3	63	60	P	2	R	UOQ	C	migration	-	mastopathy	
4	68	40	F	3	R	UOQ	C	migration	-	DCIS	DCIS
5	56	7	F	2	L	LOQ	C	-	-	mastopathy	
6	77	5	F	3	R	UIQ	C	-	-	IDC	IDC + DCIS
7	69	15	F	3	R	LOQ	P	failed	-	mastopathy	
8	55	25	P	2	R	UOQ	C	-	-	mastopathy + adenosis	
9	57	20	F	2	R	LOQ	P	-	-	IDC	IDC
10	53	30	P	1	R	UOQ	C	-	-	mastopathy	
11	72	11	F	2	R	UIQ	C	-	-	DCIS	no malignant focus
12	56	11	F	1	L	UIQ	C	-	-	ILC	ILC
13	75	10	F	3	R	UOQ	C	-	-	DCIS	DCIS
14	75	11	F	3	L	UOQ	P	-	hematoma	IDC	IDC + DCIS
15	67	25	P	2	R	C	C	-	-	DCIS	IDC + DCIS
16	56	9	F	2	R	LIQ	C	-	-	mastopathy	
17	51	15	P	2	L	LIQ	P	-	-	DCIS	DCIS
18	69	30	F	3	L	UOQ	C	-	-	IDC	IDC
19	51	20	P	2	R	C	C	-	vasovagal	mastopathy	
20	41	20	P	2	R	UOQ	P	-	-	IDC	IDC
21	61	14	F	2	L	C	A	-	-	mastopathy	
22	50	20	F	2	R	UOQ	C	-	-	adenosis	
23	56	7	F	1	L	UOQ	C	-	-	mastopathy + adenosis	
24	67	45	F	3	R	UOQ	C	-	-	IDC + DCIS	IDC + DCIS
25	73	8	F	2	L	C	C	-	-	IDC	IDC + DCIS
26	57	20	F	2	L	C	C	migration	-	adenosis	
27	50	30	P	3	R	UOQ	P	-	vasovagal	mucinous carcinoma	mucinous carcinoma
28	66	11	F	3	R	LIQ	C	migration	-	IDC	IDC + DCIS
29	67	20	P	2	R	UOQ	A	-	-	mastopathy	
30	51	9	F	2	L	UOQ	C	-	vasovagal	mastopathy	
31	48	7	F	1	L	UOQ	C	-	-	adenosis	
32	50	15	F	3	L	UOQ	A	-	-	mastopathy	
33	71	11	F	1	R	UOQ	C	-	-	adenoma + mastopathy	
34	46	45	P	2	L	UOQ	C	-	-	adenosis	
35	51	12	F	1	L	UOQ	C	-	-	IDC	IDC + LCIS
36	48	11	F	2	L	LIQ	P	-	-	mastopathy	
37	47	11	F	3	L	UOQ	P	-	-	IDC	IDC
38	54	35	P	1	R	C	A	-	-	mastopathy + adenosis	

Note— F =focal; P = patchy; score 1 = mild uptake; score 2 = moderate uptake; score 3 = marked uptake [12]; L= left; R = right; UOQ = upper outer quadrant; LOQ = lower outer quadrant; UIQ = upper inner quadrant; LIQ = lower inner quadrant; C = central; P = posterior; A = anterior; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

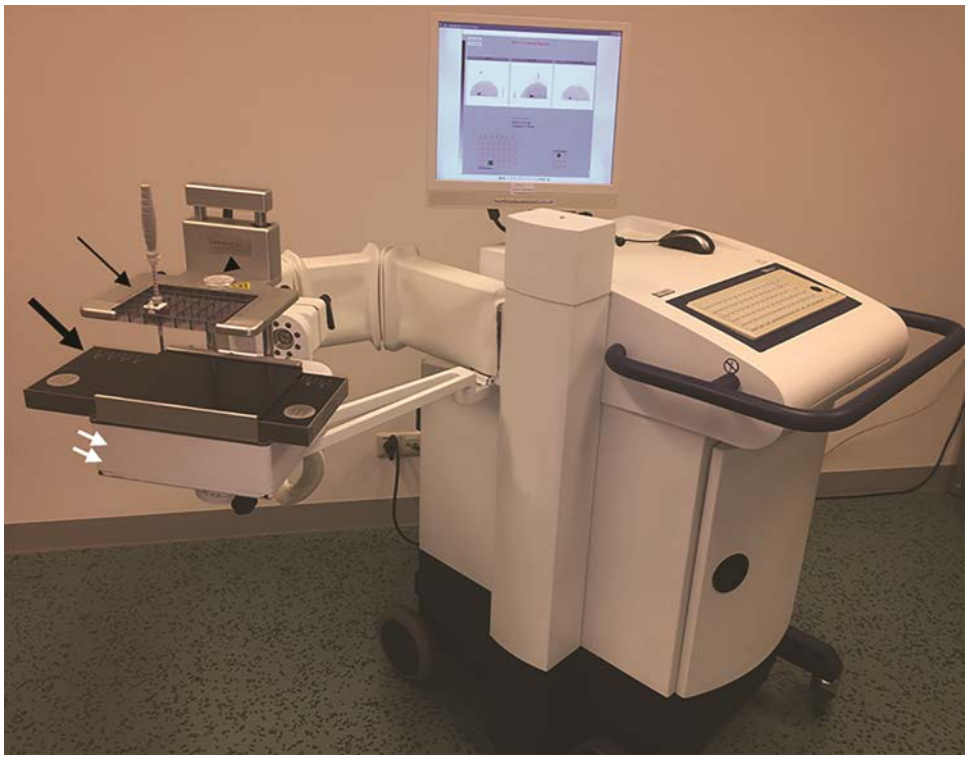
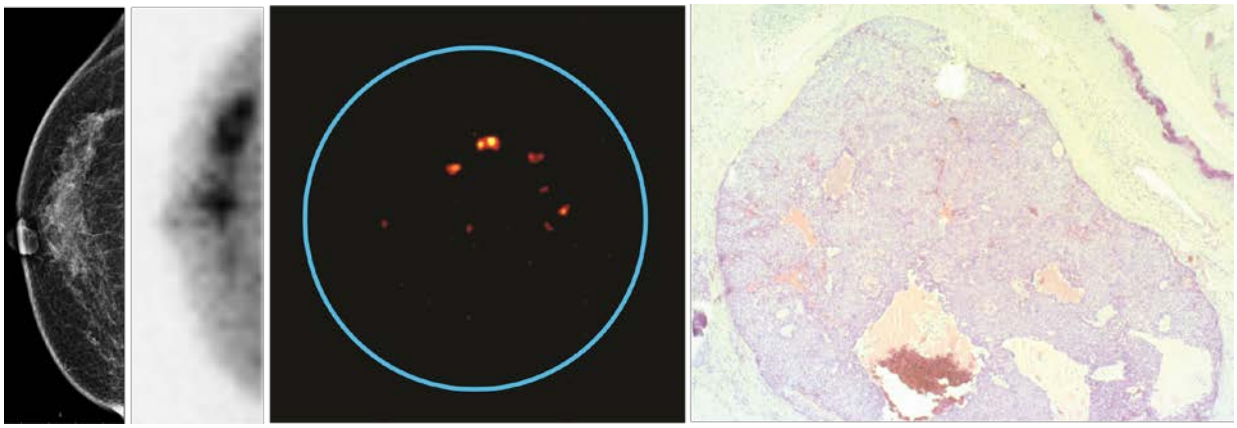


Fig. 1— Molecular breast imaging-guided biopsy device equipped with a compact stereotactic localization system containing a fiducial source (arrowhead), grid paddle (thin arrow), slant-hole collimators (thick arrow) and detector (double white arrows). Monitor displays breast images from two angles for calculation of the X-Y-Z coordinates of the lesion and for determination of the corresponding grid hole to insert the needle.



A **B** **C** **D**

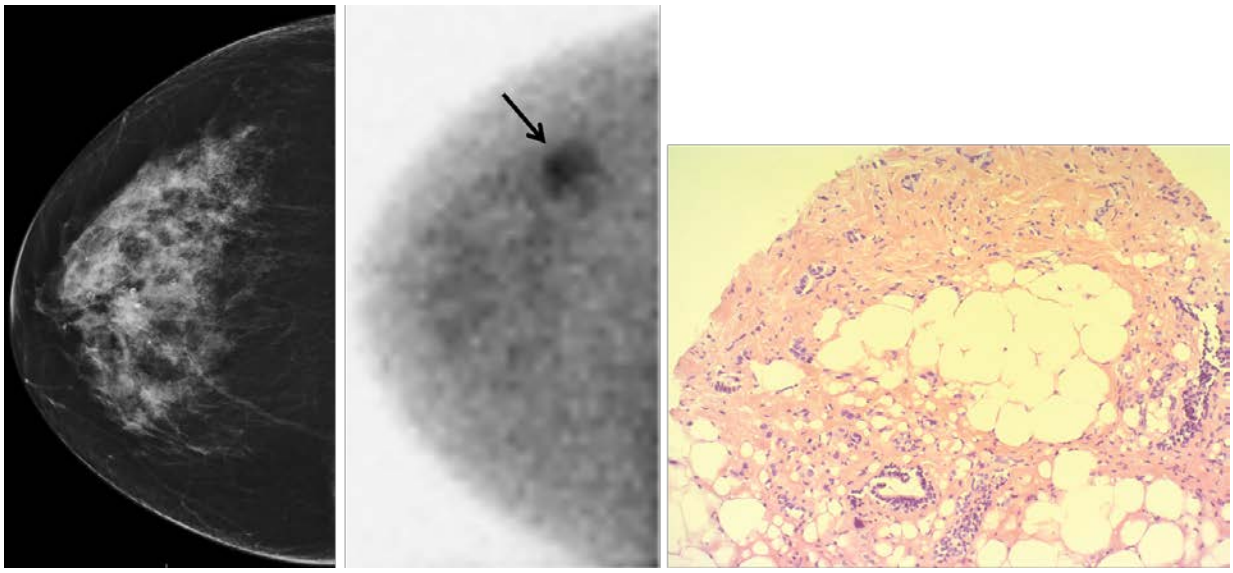
Fig. 2— 68-year-old woman (patient n° 4) with ductal carcinoma in situ.

A, Right craniocaudal mammographic view showing no suspicious breast mass.

B, Right craniocaudal molecular breast imaging view shows two suspicious areas with focal ^{99m}Tc-sestamibi uptake in the upper outer quadrant of a small breast.

C, Image of biopsy samples measured ex vivo shows radioactive specimens.

D, Composite photomicrograph showing cancerization of a lobule by an intraluminal proliferation of atypical epithelial cells (ductal carcinoma in situ; hematoxylin/eosin staining).



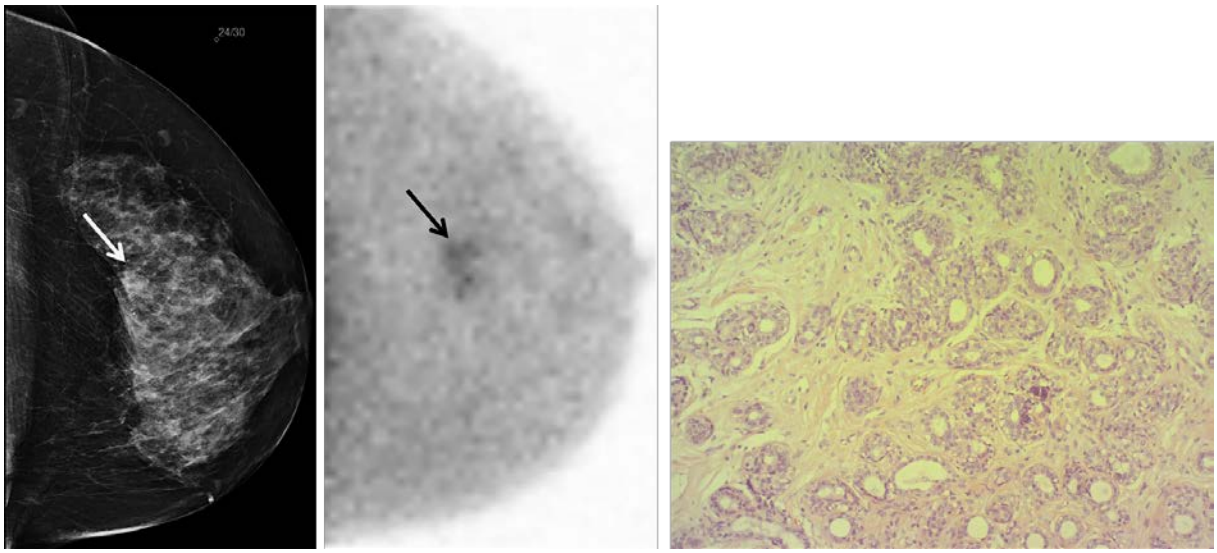
A **B** **C**

Fig. 3— 57 year-old women (patient n° 9) with invasive ductal carcinoma.

A, Right craniocaudal mammographic view, showing no suspicious breast mass.

B, Right craniocaudal molecular breast imaging view shows one suspicious area with focal ^{99m}Tc-sestamibi uptake in the lower outer quadrant of breast (arrow).

C, Composite photomicrograph showing normal ductolobular units, surrounded by irregular invasive glands and strands of atypical epithelial cells in stroma with desmoplastic changes and microcalcifications (invasive ductal carcinoma of no special type; hematoxylin/eosin staining).



A **B** **C**

Fig. 4— 57 year-old women (patient n° 26) with adenosis.

A, Left craniocaudal mammographic view, showing focally dense tissue (*arrow*) at the central dorsal site of the breast, considered being overprojection of normal fibroglandular tissue (probably benign, BI-RADS category 3).

B, Left craniocaudal molecular breast imaging view shows suspicious focal uptake of ^{99m}Tc-sestamibi in the center of the breast, the same area as the BI-RADS 3 lesion on mammography (arrow).

C, Composite photomicrograph showing a lobulocentric proliferation of mammary glands, lined with two epithelial layers with glandular compression, distortion due to stromal proliferation and micro-calcifications in lumina (adenosis; hematoxylin/eosin staining).