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ORIGINAL ARTICLE

Scintimammography and single-photon emission computed tomography for postoperative image guidance for radiation treatment planning in breast cancer patients

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Summary

Purpose: *To evaluate post-surgical tumor-metabolic regions outside of the computed tomography (CT)-defined volume for radiation therapy (RT) planning using functional imaging of scintimammography (SMG) ± single photon emission computerized tomography (SPECT) in breast cancer (BC) patients.*

Methods: *62 operated high-risk BC females, mean age 50.45 years, underwent SMG±SPECT before RT planning. Twenty-one and twelve patients with stage I and IIa respectively had lumpectomy (LT) with axillary lymph node dissection (ALND), and modified radical mastectomy (Patay) + ALND was realized in 29 stage IIb-III patients. All SMG images, positive for viable tumor tissue (VTT) or metastatically involved lymph nodes (LNs) were verified cytologically/histologically. Three early planar and delayed images were acquired after i.v. administration of 550-740 MBq 99mTc-MIBI or 99mTc-TF. Uptake values (UV) > 1.65 revealed VTT.*

Results: *Data in 49 (79%) of 62 patients were characterized as true-negative (TN; UV<1.35). In 13 (21%) patients SMG visualized 22 true-positive (TP) malignant lesions: 2 residual VTT in scars, 1 newly defined BC in the contralateral breast and 18 regional LN metastases (6 axillary, 6 parasternal, 1 sub- and 5 supraclavicular). All 22 TP VTT lesions were imaged by scintigraphy using different tumor-seeking radiopharmaceuticals: 99mTc-MIBI - 17 (77%) and 99mTc-TF - 5 (23%) of the TP lesions.*

One false-positive (FP) (inflammation: UV>1.65) and one false-negative (FN) (UV<1.35) foci were found. Applying SMG±SPECT for BC restaging after surgery, the RT volume was changed in 13 of 62 (21%) patients.

Conclusion: *SMG is a reliable imaging method for evaluating residual VTT, LN metastases or altered biological activity in the scars after BC surgery and could modify the irradiated volume, optimizing the therapeutic effect and minimizing RT side effects.*

Key words: breast cancer, radiation therapy planning, scintimammography

Introduction

BC is the most common malignancy and the second leading cause of cancer deaths among women worldwide. Its incidence is steadily increasing [1-3]. At the same time the increasing number of organ-preserving operations of the breast has led both to the introduction of new lines of chemotherapeutic agents and to the need of an optimization of the RT volume since many trials have proven that locoregional RT after breast cancer surgery significantly reduces the risk of recurrences. The radiotherapy planning with CT has enabled the clinician to visualize the anatomy in 3 dimensions and to confirm the dose around the target viable tumor volume in order to irradiate the tumor to as high a dose as possible, whilst protecting the normal tissues [4].

The exact identification of treatment targets needs, however, not only advanced the anatomical but also the functional imaging modalities in order to achieve information about the biological features and changes that take place in the tumor tissue both before and after treatment. Such functional imaging modalities are in the form of SMG and SPECT and the more recently introduced positron emission tomography (PET). The

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general advantage of nuclear medicine imaging is that tumor-seeking radiopharmaceuticals are trapped in cancer lesions, which makes SMG and PET fundamentally different from the radiological techniques that image the tumor mainly on the basis of morphological alterations [5]. One of their main advantages is that they can visualize residual VTT after BC surgery, differentiating it from fibrosis, or detect engaged by metastases LNs or masses, and thus change the volume to be irradiated while CT anatomical imaging for RT planning has some limitations.

And while PET (PET/CT) is still costly and not widely available, SMG and SPECT together with CT could supply the clinician with the entire information about tumor anatomy and biological behavior.

The aim of this study was to evaluate post-surgical tumor metabolic regions outside the volume defined by CT for RT planning using functional imaging with SMG±SPECT in breast cancer patients.

Methods

Patient population

The study included 62 operated high-risk BC females with mean age 50.45 years (range 35-77). Breast-conserving surgery (lumpectomy +ALND) was done in 21 stage I and 12 stage IIa patients, and Patay modified mastectomy + ALND - in 29 stage IIb-III patients. The target volume to be irradiated was evaluated in different time intervals after the operation but not earlier than 1 month postoperatively.

Imaging methodology

All 62 patients underwent a SMG/SPECT before RT planning. The studies were performed without previous special preparation of the patients on a Siemens-DIACAM gamma camera, with ICON commercial software. The radiopharmaceuticals used were the intracellular lipophilic cationic 99mTc-methoxyisobutyl-isonitrile (MIBI) and 99mTc-tetrofosmin (TF), injected i.v. in the contralateral to the tumor arm or in a vein of the foot in the case of confirmed or suspected bilateral breast tumor.

Three planar images were acquired 15 min after i.v. administration of 550-740 MBq 99mTc-MIBI or 99mTc-TF. Left and right lateral scans were obtained with the patient lying prone on a dedicated mattress with semicircular apertures for the breasts and anterior view in supine position including both breasts and regional axillae. Delayed planar or SPECT images were also obtained up to 2h. Semiquantitative analysis was carried out by drawing regions of interest over the pathological lesions with increased radiotracer uptake and background. Difference of UV was estimated by comparing the region of interest with increased uptake of the tracer with a symmetrical zone of interest, both having equal geometry and number of pixels. UV > 1.65 ($p<0.001$) was established to reveal VTT.

All SMG images, positive for VTT or metastatically involved LNs were correlated with the clinical status, CA 15-3 tumor marker levels, description of other imaging modalities (mammography, ultrasonography) and then verified cytologically or histologically.

Statistical analysis

The results were analyzed using SPSS/PC+v.10 for Windows with a level of 95% confidence interval (95% CI) and at least $p<0.05$ statistical significance. P-values were determined by Student's t-test. All reported lesions were classified as TP, TN, FP or FN. The sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were determined using appropriate formulas [6].

Results

After surgery and before RT planning, no evidence (UV<1.35) of 99mTc-MIBI/TF showing VTT or LN metastases was registered in 49 (79%) patients (Figure 1a). SMG was considered negative and surgical therapy successful. TN results were found in 30 99mTc-MIBI and 19 99mTc-TF scans ($p<0.05$).

In the remaining 13 (21%) patients, SMG was positive and visualized 22 TP malignant lesions (Table 1, Figure 1b): 2 residual VTT in scars, 1 newly defined breast cancer in the contralateral breast and 18 regional LN metastases: 6 axillary, 6 parasternal, 1 sub- and 5 supraclavicular.

Planar SMG gave not so convincing results (Figure 2a) for parasternal and supraclavicular LN metastases imaging, while they were better visualized at the coronal SPECT scan both with 99mTc-MIBI (Figure 2b) and 99mTc-TF (Figure 3a). The response to radiation therapy was evaluated by SPECT (Figure 3b).

All 22 TP VTT lesions were imaged by scintigraphy using different tumor-seeking radiopharmaceuticals: 99mTc-MIBI - 17 (77%), and 99mTc-TF - 5 (23%) of the TP lesions.

SMG established TP axillary LNs in one stage I, pT1N0M0 patient. Nine patients with VTT (R1) or metastatically involved LNs had stage Ia disease.

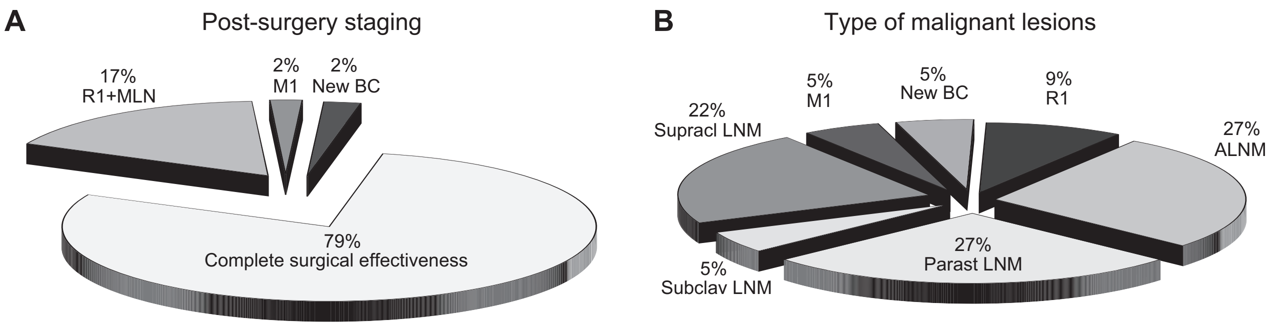

Figure 1. 99mTc-MIBI/99mTc-TF scintigraphic data for surgical effectiveness **(A)** and types of malignant lesions **(B)** before RT planning.

Table 1. 99mTc-MIBI/TF imaging of malignant lesions before RT planning

Malignant lesions before RT planning	*MIBI n*	*TF n*	*MIBI+TF n (%)*
Residual tumor	2	0	2 (9)
Axillary MLN	6	0	6 (27)
Parasternal MLN	4	2	6 (27)
Subclavicular MLN	1	0	1 (5)
Supraclavicular MLN	3	2	5 (22)
Distant metastases	0	1	1 (5)
New breast cancer	0	1	1 (5)
Total number of malignant lesions	17	5	22

MLN: metastatic lymph nodes, MIBI: methoxyisobutylisonitrite, TF: tetrofosmin, RT: radiation therapy

In one of the patients a new breast carcinoma in the contralateral breast was recognized scintigraphically and histologically verified as pT1N0M0 (Table 1).

One FP (inflammation: UV>1.65 on the early SMG scan) and one FN (UV<1.35) scan were registered.

In 31 of the 49 (63%) patients the distribution of the tracer lacked foci of hyperfixation and no VTT or involved LNs were described (R0 and N0). In 16 (33%) patients the intensity of distribution of 99mTc-MIBI/TF was moderately elevated in the area of postoperative scars without separate foci of hyperfixation (UV=1.28±0.07 for 99mTc-MIBI and 1.23±0.02 for 99mTc-TF; $p<0.001$). Active postoperative fibrosis was described in these patients.

In 2 (4%) patients after mastectomy + ALND and slightly elevated CA15-3 (normal 38-45 U/ml) the early SMG image showed foci with UV of 1.54 and 1.41 respectively, in axillary LNs, which showed wash-out at the delayed images in the second hour post-injection (p.i.) This feature was not characteristic for malignant proliferation and SMG rejected the clinical suspicion of residual metastatic axillary LNs. Histologically his-

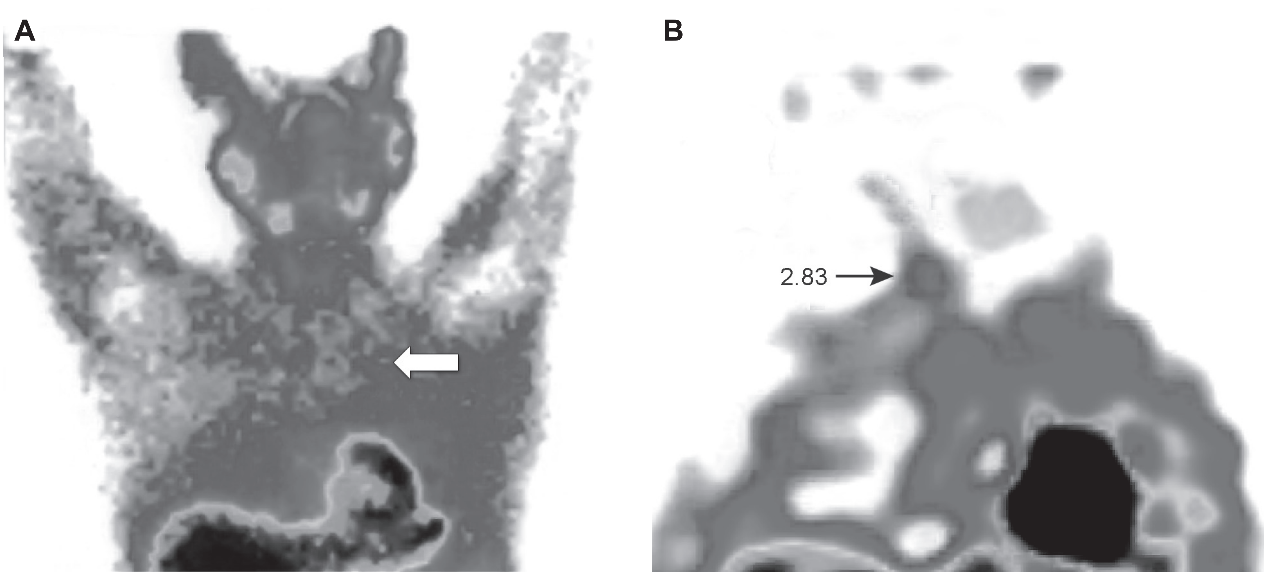

Figure 2. Left-sided breast cancer at the border of the upper two quadrants, pT1N1M0, ER+/PR–, invasive ductal carcinoma, CA15-3 tumor marker normal; before postoperative RT. **A:** Planar SMG after mastectomy+ALND visualized non-homogeneous hyperfixation of 99mTc-MIBI on the chest wall (arrow). **B:** Coronal SPECT showed a parasternal LN with UV=2.83 (arrow).

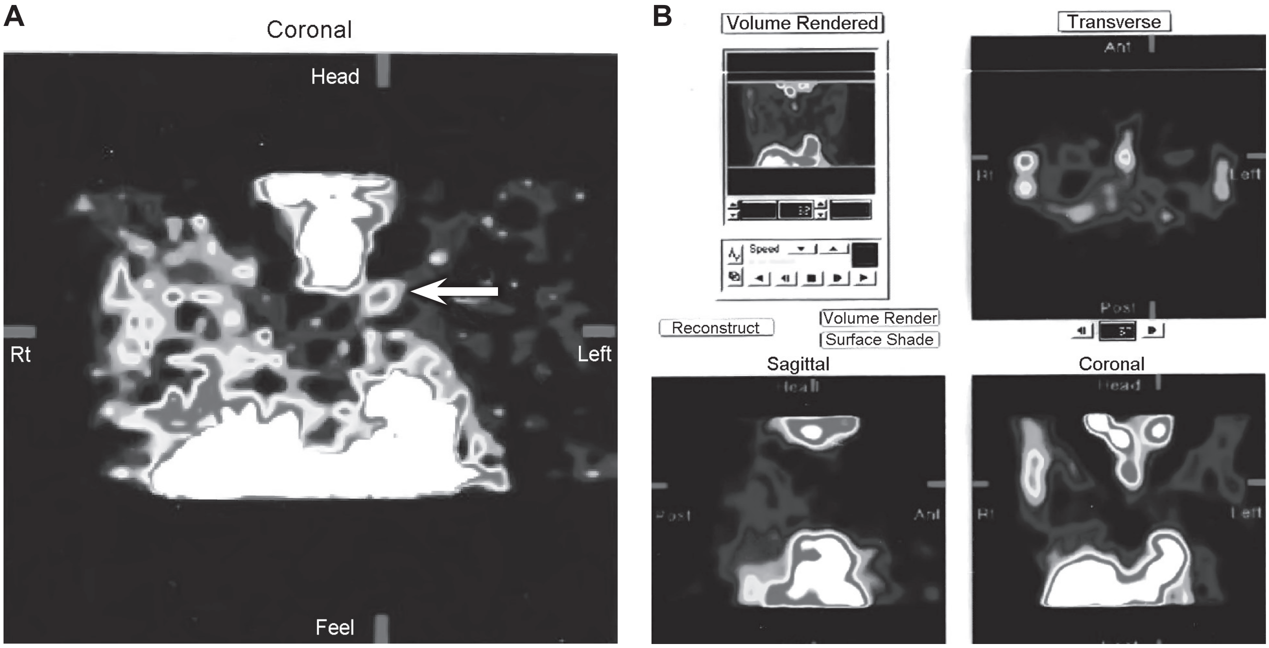

Figure 3. Left-sided breast cancer (upper medial quadrant) after breast-conserving surgery and ALND, pT1cN1dM0, G2, ER+/PR+. **A:** Before RT planning at coronal SPECT a hyperfixation in a supraclavicular LN is seen (arrow; UV=1.69). **B:** The "hot spot" is no longer visible after including the left supraclavicular zone in the RT volume (complete response to RT).

tiocytosis was verified. The serum level of CA15-3 was normalized in the 3rd month of follow-up. In these cases the scintigraphic result was indicative of inflammatory process with non-malignant adenopathy (Table 2; Figure 4a, b).

In postoperative SMG-SPECT with ^{99m}Tc-MIBI and ^{99m}Tc-TF the following results were observed: 96% (22/23) sensitivity, 98% (49/50) specificity, 97% (71/73) accuracy, 96% (22/23) PPV, 98% (49/50) NPV. The RT plan was changed in 17.7% of the patients and

Table 2. 99mTc-MIBI/TF imaging before RT planning and in the absence of VTT

Surgical effectiveness	*99mTc-MIBI+99mTc-TF n (%)*
Surgical effectiveness R0	31 (63)
Postoperative fibrosis R0	16 (33)
Inflammatory process	2 (4)
Total	49 (100)

R0: no residual cancer, VTT: viable tumor tissue. For other abbreviations see footnote of Table 1

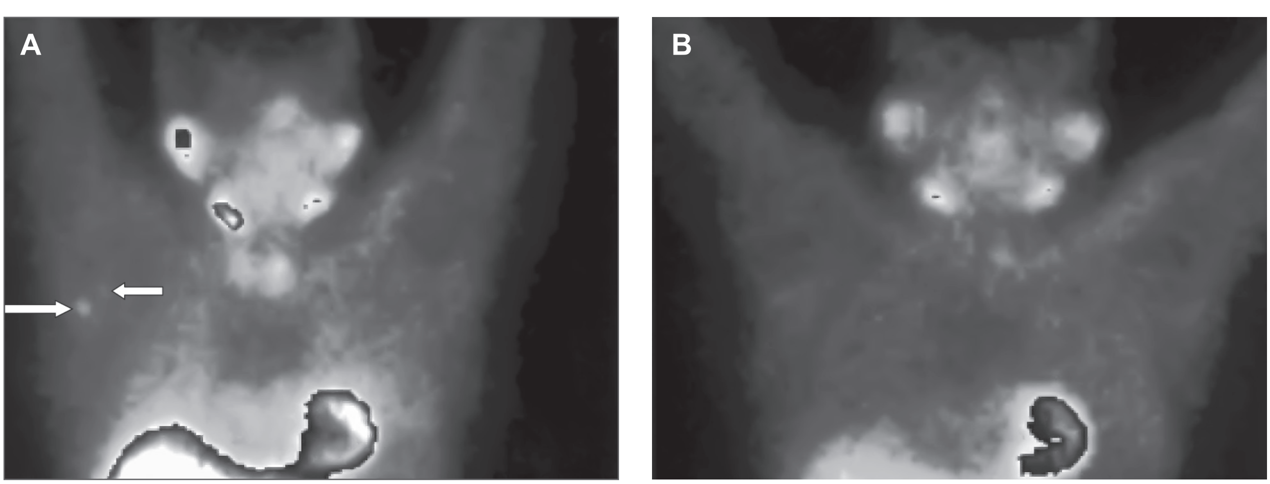

Figure 4. Left-sided breast cancer after mastectomy and ALND. **A:** Before RT planning SMG with 99mTc-MIBI discovered a focus of hyperfixation in the right axilla (UV=1.52) (arrow) and a second one with less intensity medially from the first (arrow). **B:** The delayed scan after 2 h was negative - inflammatory nonmalignant adenopathy.

the therapeutic plan - as a whole - in 3.2%, replacing RT with adjuvant chemotherapy.

Discussion

In 1992 Aktolun et al. reported for the first time the preoperative visualization of a BC with 99mTc-MIBI and the differentiation of a benign from a malignant process in a palpable formation in the breast [7]. While studying myocardial perfusion with 99mTc-MIBI Omar et al. established ectopic hyperfixation of the radiotracer in the left breast of a patient which proved to be BC [8]. This is how the tumor imaging with 99mTc-MIBI became part of many studies concerning BC. Clinical studies with 99mTc-TF are more limited than those with MIBI, but higher sensitivity in dense breasts has been reported with TF [9], and the radiopharmaceutical showed a good enough for tumor imaging tumor/background ratio [10].

SMG with the cationic lipophilic 99mTc-TF and 99mTc-MIBI is one of the most widely available functional non-invasive imaging methods employed both in pre- and postoperative evaluation of BC and LN status [11]. A lot of studies and metaanalyses were carried out and proved it as an effective tool for the evaluation of primary BC, recurrences and LN metastases [12,13]. Comparative studies have demonstrated that SPECT significantly improves the sensitivity and accuracy achieved with planar SMG, particularly when there are involved LNs which are nonpalpable, small in size and limited in number [14].

SMG has established its place in supplying additional information in nonconclusive mammograms, in women with dense breasts, implants or in patients with locally advanced breast cancer for predicting and monitoring the response to chemotherapy. SMG-SPECT have some limitations which mainly consist of complicated anatomical localization of the hypermetabolic lesions, more difficult visualization of lesions under the diaphragm, and lower resolution of SPECT-scanners. The latter limitation - high sensitivity mainly for tumor lesions >1 cm – has recently been at least partly overcome by the use of high-resolution cameras dedicated for breast imaging. These also allow the detector to be placed in direct contact with the breast thus increasing the sensitivity. Higher sensitivity in the detection of axillary LN metastases has also been established in SMG with specially equipped with a pinhole collimator SPECT-camera [15]. These new devices have the potential of increasing the total number of breast scintigraphies performed, thereby enhancing the role of nuclear medicine in BC imaging [16].

At the same time, the recent trends in BC management are directed towards breast-conserving surgery whenever this is allowed by the clinical status and stage [17,18]. Breast-conserving surgery followed by RT to the whole breast has been clearly demonstrated in randomized trials to provide local control and survival comparable to Patay mastectomy [19]. Combined data from 78 randomized clinical trials show that RT after either breast-conserving surgery or Patay mastectomy in women with early BC significantly reduces both 5-year recurrence and 15-year mortality rates, thus helping this group of patients to live longer in addition to lowering their risk of local recurrence [20].

The locoregional control achieved with RT after BC surgery depends strongly on the volume to be irradiated, especially in the presence of positive LNs which wouldn't always be traditionally involved in the target volume, e.g. parasternal lymphatic chains. That's why RT planning with its essential acquisition of information about the patient's anatomy is one of the main cornerstones in BC patients' management. The individualization of RT target volume is a prerequisite for more accurate targeting, lower cumulative dose, less side effects, better quality of life for the patients and better overall survival. CT is the method most widely used for 3D imaging, owing to its acceptable cost, wide availability and ability to provide tissue density information needed for dose calculation [21]. One of the main disadvantages of CT is the suboptimal soft tissue imaging and lack of functional and biological information. Preparing BC patients for postoperative RT based only on the anatomical criteria of CT carries the risk of missing VTT, non-differentiated from the postoperative fibrosis and to increase of recurrences and worsening in survival rates. The correct RT process though requires the use of imaging to provide both anatomical and functional information which could modify the borders of the target volume to be irradiated. That's why in the last years CT is more often used along with other modern imaging modalities, such as magnetic resonance imaging (MRI) and PET. Efforts have even been made to estimate the real size of BC by fusion of MRI and SMG [22].

There is still not enough data about the place of PET/CT in the postoperative RT planning in BC, but an increasing number of studies explores its role in target definition and RT planning and its application in the treatment of this oncological entity [23]. The 2nd edition of Frog Manual for Clinical Use confirms that treatment planning with PET/CT scans will diminish the rate of marginal misses in the treatment of the breast, chest wall, and/or surrounding nodal regions.

However, despite all its advantages, PET/CT is still an expensive and not widely available imaging tool.

The use of SMG and SPECT has revealed the role of nuclear medicine imaging in restaging BC patients who have already undergone breast surgery and wait for the most appropriate adjuvant treatment [24]. Finding VTT or metastatic LNs the therapeutic plan is immediately changed.

Using SMG-SPECT with 99mTc-MIBI/TF 17% (11/62) of our patients were diagnosed with residual VTT and metastatically involved LNs after surgery, which led to optimization of the radiotherapeutic plan with surdosage and enlargement of the target volume. Following SMG with tumor-seeking lipophilic radiopharmaceuticals the therapeutic plan as a whole was changed in 3.2% (2/62) of the patients submitted to this nuclear medicine study. In the patient with the newly discovered with 99mTc-TF BC a totally different therapy followed. In another patient where 99mTc-MIBI discovered distant metastases RT was substituted by chemotherapy. Our results have shown that in patients staged I-IIa with high risk or after breast-conserving surgery, as well as in those with BC localized in the medial quadrants, it is advisable to perform SMG with ^{99m}Tc-MIBI and ^{99m}Tc-TF.

Realizing the needs for high-precision RT and the development of competing modern imaging techniques like CT, MRI, metabolism-MR spectroscopy [19], and PET/CT, our results have shown that SMG and SPECT still have the potential to help determine the target volume to be irradiated and haven't lost their role in the correct therapeutic decision-making for BC patients. This fact holds promise that in the era of modern SPECT combined with CT in a multimodal SPECT/CT scanner, clinicians will be sufficiently supplied both with the desired exact anatomical targeting and biological information of metabolically active VTT.

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