Radionuclide imaging for breast cancer diagnosis and management: Is technetium-99m tetrofosmin uptake related to the grade of malignancy?

Güler Silov[1] MD, Arzu Taşdemir[2] MD, Ayşegül Özdal[1] MD, Zeynep Erdoğan[1] MD, Esma Mehtap Başbuğ[1] MD, Ayşe Esra Arslan[1] MD, Özgül Turhal[1] MD

1. Department of Nuclear Medicine, and
2. Department of Pathology, Kayseri Training and Research Hospital Department of Nuclear Medicine, 38010 Kayseri, Turkey
E-mail: gulersilov@yahoo.com, Tel: +905446146154, Fax: +903523207313

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Breast cancer is characterized by clinical, histopathological factors, TNM staging, oestrogen and progesterone receptors (ER and PR), angiogenesis, S-phase fraction, p53 cell fraction, oncogene expression and other factors [1]. The histological malignancy grade and the number of involved lymph nodes are considered the most important predictive factors for breast cancer survival. Malignancy grade significantly affects the 5 and 10 years relapse-free and the total survival rates [2].

There are different scoring systems available for determining the grade of breast cancer malignancy. Breast cancer tumors have been described for grades 1-3 using the modified Nottingham-Bloom-Richardson grading system comprising of the Architectural grade, the Nuclear grade, and the Mitotic grade. In this system, 3 elements are assessed: tubules formation, nuclear size and pleomorphism and mitotic counts (Table 1).

In the Architectural grade: score 1 is characterized by more than 75% of tumor area forming glandular/tubular structures. Score 2 by 10% to 75% of tumor area forming glandular/tubular structures and score 3 by less than 10% of tumor area forming glandular/tubular structures.

In the Nuclear grade: pleomorphism score 1 is characterized by small nuclei with little increase in size in comparison with normal breast epithelial cells having regular outlines, uniform nuclear chromatin and little variation in size. Score 2 by cells larger than normal with open vesicular nuclei, visible nucleoli with moderate variability and shape in both size and score 3 by vesicular nuclei, often with prominent nucleoli, exhibiting marked variation in size and shape, which are occasionally found in very large and bizarre forms.

The Mitotic grade is characterized by the mitotic counts score, which depends on the field diameter of the microscope used by the pathologist. The pathologist is supposed to report the mitotic figures seen in 10 high power fields. Using a high power field of 0.50mm diameter, these criteria are as follows: Score 1: less than or equal to 7 mitoses per 10 high power fields. Score 2: 8-14 mitoses per 10 high power fields and score 3: equal to or greater than 15 mitoses per 10 high power fields [3].

The grade of breast cancer tumors is determined as shown in Table 1.

***Table 1**. Modified Nottingham-Bloom-Richardson grading system*

Microscopic grade	Tubular formation	Nuclear pleomorphism	Mitotic count/10HPF
Grade I	>75%	Uniform nuclear chromatin, little variation in size	≤7
Grade II	10%-75%	Vesicular nuclei, visible nucleoli, moderate size	8-14
Grade III	<10%	Vesicular nuclei, prominent nucleoli, exhibiting marked in size and shape	≥15

The grade of a breast cancer malignancy indicates the aggressive potential of the tumor. Determining the grade is very important for the clinicians to choose the best treatment options [3]. Nevertheless, some researchers have stated that high-grade tumors show lower ER and PR expression, overexpression of HER2 and p53, high Ki67 and DNA aneuploidy [4].

During the past decade, and particularly since the widespread application of adjuvant treatment for primary breast cancer, research for new prognostic factors has been more systematic. These modalities such as technetium-99m methoxy isobutyl isonitrile (^{99m}Tc-MIBI) and pentavalent ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc(V)-DMSA) scintigraphy have been used and are under evaluation for being prognostic factors for breast carcinoma [5-7].

Technetium-99m-tetrofosmin (^{99m}Tc-TF) is a lipophilic cationic diphosphine with remarkable tumor imaging properties. Its uptake mechanism bears similarities to that of ^{99m}Tc-MIBI, depending on regional blood flow and cell membrane integrity, entering cells mainly via passive transport driven by negative potential of the intact cell membrane, and mostly localizing within cytosol, with only a fraction passing into mitocondria [8]. In a study by Kım I.J. et al (2008), the double phase scintimammography (SMM) performed at early (10min) and delayed (1h) phases after the intravenous injection of the radiotracers ^{99m}Tc-MIBI and ^{99m}Tc-TF showed favorable diagnostic accuracy in differentiating benign from malignant breast lesions, visually and semi-quantitatively. For semi-quantitative analysis, regions of interest were drawn around the tumor and over the normal breast tissue in the same breast. Early and delayed lesion to non-lesion ratios (L/N) were also determined. The optimal semi-quantitative indices of ^{99m}Tc-MIBI-SMM for the detection of breast cancer were 2.06 for early L/N and 1.72 for delayed L/N. The same indices for ^{99m}Tc-TF-SMM were 3.13 for the early, and 2.56 for the delayed images [9].

The authors of this paper have studied whether there was a correlation between ^{99m}Tc-TF uptake and malignancy grade in breast carcinoma. Such a correlation could identify patients prior or after surgery, who need adjuvant treatment.

A total of 27 patients with positive mammography, clinical and histology findings of invasive ductal carcinoma showed increased ^{99m}Tc-TF, uptake related to the higher grade of malignancy ($P<0.05$) (Table 2). Although the number of patients studied was small, results indicated that ^{99m}Tc-TF uptake may early provide useful information for therapeutic planning of ductal cell breast carcinoma.

Scintimammography is a quite useful and low cost diagnostic technique for breast lesions. Other researchers [10] showed that fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and breast SMM with ^{99m}Tc-MIBI are equivalent in monitoring tumor response to neoadjuvant chemotherapy. The prediction of therapeutic effectiveness using ^{18}F-FDG PET/CT parameters could help to individualize treatment and to minimize ineffective treatments and their attendant toxicities. In the scope of targeted therapies ^{18}F-FDG PET/CT has limited diagnostic value [11]. Novel radiotracers for specific imaging of hormone receptor expression, such as (16-α-[^{18}F] fluoro-17-β-estradiol -[FES]), HER2 and proliferation rate (3'-deoxy-3'-^{18}F-fluorothymidine -[FLT]) may provide valuable clinical information as compared to the information provided by ^{18}F-FDG PET/CT [12].

***Table 2**. Comparison between Microscopic grade and TF L/N ratios*

Microscopic grade	N	Early TF L/N	Late TF L/N
Grade I	10	2.12±0.60	1.88±0.54*
Grade II	11	2.78±0.96	2.37±0.70
Grade III	6	3.03±0.79	2.67±0.46*

*(P>0.05) *(P<0.05). L/N: Lesion/Non-lesion*

Mechanisms of accumulation and efflux of ^{99m}Tc-MIBI in breast carcinoma involve cellular processes that are important in tumor response to treatment [13]. Early and increased concentration of ^{99m}Tc-MIBI in breast carcinoma is associated with high proliferation rate, indicating more aggressive tumor behavior, and better tumor response to treatment [14]. In a small number of breast cancer patients ^{99m}Tc-MIBI SMM was a better diagnostic modality than ultrasonography, X-rays mammography and MRI [15]. Dedicated systems with improved spatial resolution have thus allowed for a better breast cancer diagnosis and response to treatment [16]. Other researchers, in a small series of patients showed that a dedicated for molecular breast imaging γ-camera using ^{99m}Tc-TF after neoadjuvant treatment visualized multifocal, sub-cm residual cancers [17].

It has been reported that SMM with a novel radiotracer ^{99m}Tc-3PRGD2 can diagnose breast cancer with an overall 83% sensitivity and 73% specificity in palpable and non palpable breast lesions and thus avoid biopsy. At the same time, ^{99m}Tc-3PRGD2 SMM can provide good image quality of avβ3 expression in breast cancer. This technique may also allow response monitoring to breast cancer treatment through longitudinal imaging [18].

It is noteworthy, that from a SMM the breast absorbs only half the radiation dose of an X-rays mammogram [19].

Breast is highly radiation sensitive, and the risk for radiation-induced cancers from imaging studies such as mammography should be considered. Efforts to bring the effective dose administered by other modalities down to at least the level of a mammography are desirable. Based on the International Commission on Radiological Protection, the weighting effective dose for injecting 74MBq, 148MBq, 296MBq or 592MBq of ^{99m}Tc-MIBI for SMM are, 0.67mSv, 1.33mSv, 2.66mSv and 8.3mSv, respectivelly. Furthermore, for injecting 370MBq of ^{18}F-FDG for SMM the effective dose is 7.03mSv. However, in some high risk patients, such as patients with dense breasts, the risk-to-benefit ratios suggest that even a higher dose of an administered radiopharmaceutical may be acceptable in case of imaging studies that are unique in identifying breast cancers [20].

Radionuclide breast imaging not only visualizes the lesion site but also reflects specific biological and functional lesion features, including perfusion, proliferative potential, metabolic activity and receptor status. Thus, radionuclide breast imaging represents not only a complementary method, but also a study of choice by applying the proper radioligand in the corresponding clinical background [11, 21].

The authors declare that they have no conflicts of interest.

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