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ORIGINAL RESEARCH ARTICLE

Correlation of ^{99m}Tc[Tc]-MIBI washout kinetics with breast cancer histologic grade and ki-67 index

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ABSTRACT

Introduction: ^{99m}Tc[Tc]-MIBI breast scintimammography offers a noninvasive method for assessing breast cancer biology. Studies suggest a potential prognostic value in washout analysis, as accelerated washout correlates with high histologic grade. The study examines whether the washout rate of ^{99m}Tc[Tc]-MIBI, a marker of mitochondrial dysfunction, correlates with the ki-67 index, a reliable predictive tool for breast cancer that estimates cellular proliferation.

Methods: In this study, 30 cases of breast cancer who were intact, without previous breast operation, prior chemotherapy, and previous radiotherapy, had prone scintimammagraphy. The diagnosis was approved by biopsy. The standard 20 mCi ^{99m}Tc[Tc]-MIBI was applied to all patients, and after 15 min and 60 min of injection, two imaging series were taken at each time. After different methods of calculation of washout, the washout percentage has been correlated with the Ki-67 index in the patients.

Results: All breast cancers showed significant tracer uptake at 15 minutes, mostly correlated with tumor angiogenesis. Imaging at 60 minutes revealed decreased activity, indicating a positive correlation between higher ^{99m}Tc[Tc]-MIBI washout and higher breast cancer grade as indicated by the Ki-67 index.

Conclusion: The significant association between increased ^{99m}Tc[Tc]-MIBI washout and increased cancer grade indicates that washout analysis may have potential prognostic utility before or during surgical treatment. Additionally, there is a suggestion of increased tumor grade correlating with increased mitochondrial dysfunction. While further prospective validation is necessary, this pilot study demonstrates that washout kinetics could serve as a noninvasive imaging biomarker for breast cancer grade to supplement clinical management algorithms.

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INTRODUCTION

Breast cancer is one of the most common cancers affecting women worldwide, with an estimated 2.3 million new cases diagnosed in 2020 [1]. Accurate histologic grading of breast cancer is essential for determining prognosis and selecting optimal treatment. The Nottingham histologic grade, based on the assessment of tubule formation, nuclear pleomorphism, and mitotic rate, is widely used for this purpose. Higher-grade tumors tend to be more poorly differentiated and aggressive in behavior [2]. Tumor grade is an important prognostic factor in breast cancer that provides information on the aggressiveness and differentiation of the disease. Higher grades correspond to poorer differentiation and a worse prognosis. Ki-67 is a proliferation marker that indicates the percentage of actively dividing cells. Several studies have demonstrated a strong correlation between increasing tumor grade and higher Ki-67 index levels. Grade I tumors typically have a Ki-67 index below 14%, grade II tumors range from 15-30%, and grade III or poorly differentiated cancers usually exceed 30%. As the tumor cells lose differentiation and the mitotic rate rises with elevated grade, this is reflected in a higher proportion of cells staining positive for Ki-67. Quantifying the Ki-67 index through immunohistochemistry has been shown to complement histologic grading in predicting patient outcomes. A high Ki-67 level in a high-grade tumor signifies particularly aggressive biology. Therefore, assessing grade and Ki-67 provides additional prognostic information beyond either factor alone in breast cancer. ^{99m}Tc[Tc]-MIBI is a radiopharmaceutical commonly used in breast cancer scintimammography (BSM) to detect breast lesions. One characteristic of ^{99m}Tc[Tc]-MIBI uptake in breast cancer is a washout, where the tumor's radiotracer activity decreases more rapidly over time than normal breast tissue [3]. Several studies have found that greater ^{99m}Tc[Tc]-MIBI washout correlates with higher breast cancer grade [4-6]. ^{99m}Tc[Tc]-MIBI is a radiotracer used in nuclear medicine imaging to evaluate heart and breast tissue. It is taken up by mitochondria in healthy, normally functioning cells. However, in cells with mitochondrial dysfunction, the tracer is not retained as well and tends to "wash out" more quickly over time. Studies have shown that increased washout of ^{99m}Tc[Tc]-MIBI from the myocardium, as seen on cardiac stress-rest imaging, correlates with impaired mitochondrial function in the heart muscle. Mitochondrial defects reduce the cell's ability to take up and hold on to the tracer, allowing it to diffuse back into circulation faster. Measuring the degree of ^{99m}Tc[Tc]-MIBI washout may provide insight into underlying mitochondrial energy production problems in tissues like the heart or breast that could impact cellular health and function. This article aims to comprehensively review the literature on the relationship between ^{99m}Tc[Tc]-MIBI washout kinetics and breast cancer histologic grade. The mechanisms underlying washout, methods for quantifying it, and potential clinical applications are discussed. Limitations and directions for future research are also explored.

METHODS

The study involved 30 female patients diagnosed with intraductal carcinoma, aged between 27 and 67 years, with an average age of 37±10 years. Table 1 demonstrates the summary of patients' demographic data involved in the study. Table 2 summarizes the frequency of grading based on the Ki-67 index in all patients. Inclusion criteria encompassed patients with intraductal carcinoma and no history of breast surgery, chemotherapy, or radiotherapy. A standardized 20 mCi dose of ^{99m}Tc[Tc]-MIBI was administered intravenously to all 30 patients. This radiopharmaceutical, known for its application in breast cancer scintimammography, facilitates the detection of breast lesions. Scintimammography imaging was conducted at two distinct time points: 15 and 60 minutes post-^{99m}Tc[Tc]-MIBI injection with Siemens dual head SPECT/CT gamma camera (Symbia). The chosen time intervals align with established protocols for capturing radiotracer washout kinetics. To ensure the accuracy of the acquired imaging data, decay correction, and background activity subtraction procedures were implemented, accounting for the radioactive decay of the injected ^{99m}Tc[Tc]-MIBI over time and confounding background activity correction, respectively. A comparative analysis was performed on the two-image series obtained at 15- and 60-minutes post-injection. Washout rates were calculated by quantifying the difference between the initial tumor-to-background ratio (TBR) and the delayed TBR, expressed as a percentage. The formula employed for washout rate calculation is as follows:

Washout rate (%) = (Initial TBR – Delayed TBR) × 100 / Initial TBR

This method allowed for quantifying the radiotracer washout kinetics, providing valuable insights into the behavior of intraductal carcinoma. The obtained washout rates were then correlated with the Ki-67 index derived from the pathology reports of the respective patients. This correlation aimed to establish a link between ^{99m}Tc[Tc]-MIBI washout kinetics and the proliferative activity of the intraductal carcinoma as indicated by the Ki-67 index. Patients with a history of breast surgery, chemotherapy, or radiotherapy were excluded from the study to ensure a homogeneous cohort and eliminate potential confounding factors. Patients had only a core biopsy for tissue sampling.

Table 1. Demographic and clinical characteristics of patients

Patient number	Age (year)	^{99m}Tc[Tc]-MIBI washout (%)	Ki-67 (%)	ER	PR	HER2
1	40	7	10	+	+	-
2	38	10	13	+	+	-
3	42	11	15	+	+	-
4	67	12	17	+	+	+
5	55	15	19	+	+	-
6	27	16	21	+	-	-
7	43	18	22	+	+	+
8	32	19	23	+	-	-
9	34	20	23	-	-	-
10	34	6	5	+	+	-
11	36	21	22	+	-	+
12	53	22	23	-	+	+
13	28	23	23	+	+	+
14	30	23	24	-	-	-
15	27	24	25	+	-	-
16	40	23	22	+	+	+
17	28	27	25	+	+	-
18	49	20	23	+	+	+
19	27	26	25	+	+	-
20	49	25	26	+	-	+
21	37	24	23	+	+	-
22	46	25	27	-	-	-
23	27	26	28	-	-	+
24	27	27	28	-	+	+
25	31	26	29	-	-	-
26	23	25	23	+	+	+
27	28	26	30	+	-	+
28	29	30	34	-	-	+
29	48	25	26	+	+	+
30	37	30	34	-	-	+

ER: Estrogen receptor, PR: Progesterone receptor, HER2: human epidermal growth factor receptor 2

Table 2. Frequency of grading based on Ki-67 index in the patients

Number of patients	Grade	Ki-67
3	I	Ki-67 <14
26	II	14<Ki-67<30
1	III	Ki-67>30

Statistical analysis

The patients' age distribution and tumor characteristics were summarized using descriptive statistics. Categorical variables like tumor grade were presented as frequencies and percentages, and continuous variables like age were represented as means with standard deviations. The Shapiro-Wilk test was employed to evaluate if constant variables were normally distributed. Based on the distribution of the variables, the Pearson correlation coefficient or Spearman's rank correlation coefficient was computed to assess the relationship between ^{99m}Tc[Tc]-MIBI washout rates and the Ki-67 index. A statistically significant p-value was defined as one that was less than 0.05. To ensure robustness and reliability in assessing the study's results, SPSS version 27.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Ethical considerations

The study was conducted under the ethical guidelines by obtaining the required permissions from the research ethics board of Yazd University and obtaining written, informed consent from all participants (Ethical approval code: IR.YAZD.REC.1402.041).

RESULTS

The study enrolled 30 female patients diagnosed with intraductal carcinoma, aged 27 to 65 (mean age: 37). All participants met the inclusion criteria of having intraductal carcinoma without a history of breast surgery, chemotherapy, or radiotherapy. The primary breast tumors in all patients were sufficiently large and within the resolution of the gamma camera, ensuring that the partial volume effect was not a problem. This allowed for accurate imaging and assessment. All tumors exhibited significant radiotracer uptake on early 15-minute images, which correlated with tumor vascularity, suggesting an active blood supply to the tumors. Subsequent imaging at 60 minutes revealed a consistent decrease in activity across all tumors, indicating the washout phenomenon (Figure 1).

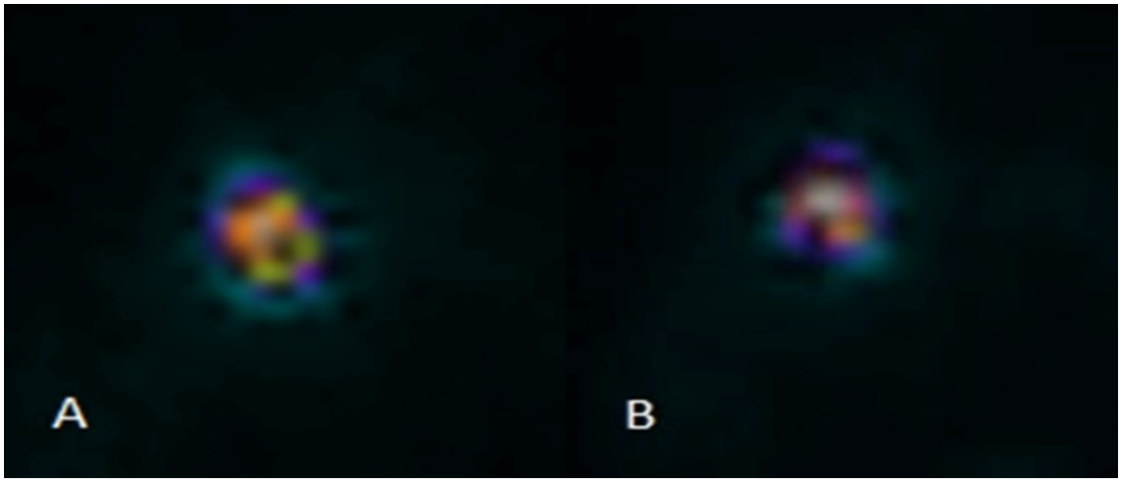

Figure 1. ^{99m}Tc[Tc]-MIBI SPECT images of the breast cancer lesion in a patient. (A) Fifteen minutes after radiopharmaceutical injection, (B) 60 minutes after radiopharmaceutical injection

^{99m}Tc[Tc]-MIBI washout rates varied among patients, highlighting tumor biology and behavior differences. Analysis of the washout rates demonstrated a positive correlation with breast cancer grade (Figure 2). Specifically, higher-grade tumors exhibited a more rapid washout of ^{99m}Tc[Tc]-MIBI, which is indicative of more aggressive tumor characteristics.

In addition to tumor grade, the study revealed a significant correlation between ^{99m}Tc[Tc]-MIBI washout rates and the Ki-67 index derived from patients' pathology reports. The Ki-67 index, a marker of cellular proliferation, was higher in tumors with faster ^{99m}Tc[Tc]-MIBI washout rates. This supports the idea that more rapidly proliferating tumors, typically more aggressive, have a quicker washout of the radiotracer. Furthermore, the study found that estrogen receptor (ER) and progesterone receptor (PR) expression in the breast cancers under study were associated with a lower Ki-67 index and lower-

grade tumors. This suggests that ER and PR-positive tumors tend to be less aggressive and have a slower rate of cellular proliferation. In contrast, HER2 (human epidermal growth factor receptor 2) expression was related to a higher Ki-67 index and higher-grade tumors, indicating that HER2-positive tumors are generally more aggressive and have a higher rate of cellular proliferation.

Additionally, we had 4 out of 30 cases that were triple-negative tumors, all of which showed a higher Ki-67 index compared to luminal-type breast cancers. These findings underscore the complex interplay between molecular receptor status, tumor grade, and proliferative activity in breast cancer. The results support the positive correlation between ^{99m}Tc[Tc]-MIBI washout kinetics, breast cancer grade, and the Ki-67 index. This correlation may provide valuable insights into the biological behavior of breast tumors and aid in the assessment of tumor aggressiveness and prognosis.

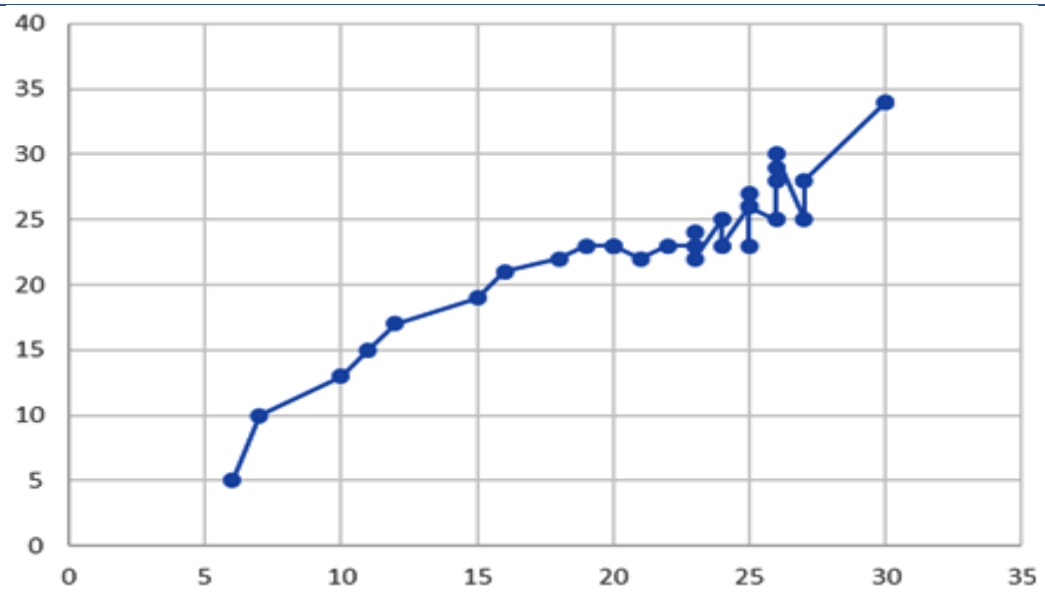

Figure 2. Correlation between ki-67 and ^{99m}Tc[Tc]-MIBI washout. The x-axis represents the ^{99m}Tc[Tc]-MIBI washout rate (%), and the y-axis shows the values related to the Ki-67 percentage

DISCUSSION

^{99m}Tc[Tc]-MIBI, known as methoxyisobutylisonitrile (MIBI), is a lipophilic cationic radiotracer that readily crosses cell membranes [7]. It is actively transported into mitochondria due to its high membrane potential and density in metabolically active cells [8]. ^{99m}Tc[Tc]-MIBI enters the mitochondria via transmembrane ion gradients in breast cancer cells and is sequestered within the mitochondrial matrix [9]. However, its uptake is not entirely specific to malignant cells, as some benign breast lesions can also demonstrate accumulation [10]. One characteristic feature of ^{99m}Tc[Tc]-MIBI kinetics in breast cancer is its washout or clearance over time. This occurs as the radiotracer leaks out of tumor cell mitochondria more rapidly than normal breast tissue [11]. The mechanism behind increased washout in higher-grade tumors is thought to involve disruption of mitochondrial membrane integrity and permeability [12, 13]. As the mitochondrial membrane becomes more permeable in aggressive cancers, ^{99m}Tc[Tc]-MIBI can diffuse out more quickly [14]. This washout phenomenon forms the basis for correlating radiotracer kinetics with tumor biology and behavior. ^{99m}Tc[Tc]-MIBI washout in breast cancer can be quantified using planar scintimammography. Imaging is typically performed immediately (early images) after intravenous injection of the radiotracer, and delayed images are acquired [15]. The semi-quantitative analysis calculates the tumor-to-background ratio (TBR) and washout rate [16]. The TBR is the ratio of average counts measured within a tumor region of interest (ROI) divided by counts in normal breast tissue [17]. A higher initial TBR indicates greater radiotracer accumulation. A greater percentage decrease in TBR from initial to delayed imaging reflects a more rapid washout

[18]. Computer-assisted quantitative analysis with dedicated breast imaging software can also objectively measure ^{99m}Tc[Tc]-MIBI kinetics over time [19]. Dynamic imaging protocols with multiple time-point acquisitions allow modeling tracer uptake and clearance kinetics [20]. Bombardieri et al. published one of the earliest studies correlating ^{99m}Tc[Tc]-MIBI washout with histologic grade in 95 breast cancer patients [21]. They found that the washout rate was significantly higher in grade III tumors compared to grades I and II. Blanks et al. also demonstrated a positive correlation between washout rate and grade, with sensitivity and specificity of 86.7% and 75%, respectively, for detecting grade III disease [22]. Larger retrospective series have validated these initial findings. Soliman et al. analyzed 406 breast cancers and reported a significantly greater washout rate in grade III tumors versus grades I/II [3]. Similarly, Hayashi et al. found that the washout rate independently predicted grade III status in multivariate analysis [5]. A meta-analysis by Moulika et al. pooled data from 11 studies, including 830 patients, reporting an area under the ROC curve of 0.81 for discriminating grade I/II from III based on washout rate [4]. More recently, quantitative kinetic modeling of ^{99m}Tc[Tc]-MIBI uptake and clearance has been applied in BSM. This involves fitting tumor time-activity curves to compartmental models to derive parameters such as influx (Ki) and efflux (k3) rate constants [23-25]. Several studies have found that k3 shows the strongest correlation with histologic grade compared to kinetic parameters like Ki. This supports the theory that increased mitochondrial membrane permeability underlies the association between greater washout and higher-grade disease [26-28]. If validated in prospective studies, the established correlation between more rapid ^{99m}Tc[Tc]-MIBI washout and higher breast cancer grade suggests potential clinical applications. Scintimammography washout analysis may provide prognostic information preoperatively, with higher washout tumors having a poorer prognosis requiring more aggressive adjuvant treatment [29]. It could help select breast cancers most likely to benefit from neoadjuvant chemotherapy before surgery, as grade III tumors with high washout may respond better [30]. Assessing washout may help identify mammographically and sonographically occult high-grade cancers requiring biopsy for accurate staging [31]. Kinetic modeling parameters derived from dynamic BSM like k3 show promise as non-invasive imaging biomarkers for breast cancer grading [32]. If validated, washout analysis could reduce unnecessary biopsies in some patients with benign-appearing low washout lesions on BSM [33]. Larger studies are still needed to fully evaluate if ^{99m}Tc[Tc]-MIBI washout correlates with other established prognostic factors in breast cancer. Higher-grade tumors tend to be larger [34]. One study found that the washout rate increased with tumor diameter [35]. However, others found no significant association [36]. Grade III cancers have a greater propensity for lymph node metastasis [37]. Preliminary evidence suggests washout may help predict nodal involvement [38]. Prospective data is required. ER+/PR+ tumors generally have a better prognosis than receptor-negative subtypes, which often correspond to a higher grade [39]. The correlation between washout and hormone status needs further exploration. HER2 overexpression is associated with poorer differentiation and increased grade [40]. One small study reported higher washout in HER2+ versus HER2- tumors, but larger cohorts are warranted [41]. The basal-like and HER2-enriched intrinsic subtypes tend to have a higher grade and worse prognosis [42]. Future work could assess if washout differs according to molecular classification. While the literature supports an association between greater ^{99m}Tc[Tc]-MIBI washout and higher breast cancer grade, some limitations remain that require addressing in future research. The retrospective design of prior studies introduces a potential for selection bias. Prospective multi-center trials are needed. Optimal time points for early and delayed imaging vary between studies. Standardization is required for the comparison of results. Semi-quantitative analysis of washout is observer-dependent. Fully automated quantitative methods may improve reproducibility. The correlation of washout with long-term patient outcomes like disease-free survival has not been well established. The ability of washout to predict response to specific neoadjuvant or adjuvant therapies requires dedicated investigation. Combining washout analysis with other functional imaging modalities like ^{18}FDG-PET may improve diagnostic accuracy over either technique alone. Larger cohorts are needed to fully validate if washout correlates with other prognostic factors beyond histologic grade. The impact of potential confounders like tumor size, breast density, and time between imaging acquisitions requires evaluation. Standardized imaging and analysis protocols between

institutions must be established to allow multicenter trials and data pooling. These considerations underscore the need for further research to refine and validate our findings, enhancing the robustness and applicability of ^{99m}Tc[Tc]-MIBI scintimammography as a non-invasive tool for assessing intraductal breast carcinoma.

Limitations

Acknowledging several limitations that may influence generalizability is critical, although the study adopted a prospective design. The current study cohort includes only 30 patients diagnosed with intraductal carcinoma and describes the kinetic behavior of ^{99m}Tc[Tc]-MIBI washout. Although this small sample size provides valuable data points, it potentially limits the extrapolation of such outcomes to a larger at-risk population. A more diverse patient population in future investigations will strengthen the robustness and generalizability of the current study. However, despite such limitations, the present study has paved the way for further research on ^{99m}Tc[Tc]-MIBI washout kinetics in intraductal carcinoma. Resolving these limitations in the future can contribute to developing noninvasive imaging biomarkers for breast cancer grading and prognosis.

CONCLUSION

Our study shows that analyzing tumor radiotracer washout kinetics can help differentiate between high- and low-grade breast cancers. If validated in prospective studies, this technique could improve patient management by serving as a non-invasive imaging biomarker for breast cancer grading. The correlation between ^{99m}Tc[Tc]-MIBI washout kinetics and mitochondrial dysfunction in higher-grade tumors suggests potential for innovative therapeutic strategies. We can enhance treatment efficacy and minimize adverse effects by tailoring treatment based on individual mitochondrial profiles. Further research is needed to understand and fully utilize this relationship for therapeutic purposes.

REFERENCES

1. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, Vignat J, Gralow JR, Cardoso F, Siesling S, Soerjomataram I. Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast. 2022 Dec;66:15-23.
2. Ginter PS, Idress R, D'Alfonso TM, Fineberg S, Jaffer S, Sattar AK, Chagpar A, Wilson P, Harigopal M. Histologic grading of breast carcinoma: a multi-institution study of interobserver variation using virtual microscopy. Mod Pathol. 2021 Apr;34(4):701-9.
3. Soliman NA, Yussif SM. Ki-67 as a prognostic marker according to breast cancer molecular subtype. Cancer Biol Med. 2016 Dec;13(4):496-504.
4. Moulika JS, Kalawat T, Manthri RG, Hulikal N, Kadiyala S, Bhargavi D, Prayaga AK. Role of 99mTc-sestamibi scintimammography in predicting response to neoadjuvant chemotherapy in locally advanced breast cancer: a prospective study. Indian J Nucl Med. 2023 Oct-Dec;38(4):354-361.
5. Hayashi D, Ohshima S, Isobe S, Cheng XW, Unno K, Funahashi H, Shinoda N, Okumura T, Hirashiki A, Kato K, Murohara T. Increased (99m)Tc-sestamibi washout reflects impaired myocardial contractile and relaxation reserve during dobutamine stress due to mitochondrial dysfunction in dilated cardiomyopathy patients. J Am Coll Cardiol. 2013 May 14;61(19):2007-17.
6. Petranović Ovčariček P, Giovanella L, Carrió Gasset I, Hindié E, Huellner MW, Luster M, Piccardo A, Weber T, Talbot JN, Verburg FA. The EANM practice guidelines for parathyroid imaging. Eur J Nucl Med Mol Imaging. 2021 Aug;48(9):2801-2822.
7. Rizk TH, Nagalli S. Technetium 99m Sestamibi. 2023 Jul 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–.
8. Park JW, Hong SP, Lee JH, Moon SH, Cho YS, Jung KH, Lee J, Lee KH. 99mTc-MIBI uptake as a marker of mitochondrial membrane potential in cancer cells and effects of MDR1 and verapamil. PLoS One. 2020 Feb 12;15(2):e0228848.
9. Moriguchi SM, DE Luca LA, Griva BL, Koga KH, DA Silva ET, DE Luca Vespoli H, Uemura G. Accuracy of (99m)Tc-sestamibi scintimammography for breast cancer diagnosis. Exp Ther Med. 2010 Jan;1(1):205-9.
10. Rahman WT, Neal CH, Nees AV, Brown RKJ. Management of incidental breast lesions detected at nuclear medicine examinations. Radiol Imaging Cancer. 2020 Mar 20;2(2):e190037.
11. Mankoff DA, Dunnwald LK, Gralow JR, Ellis GK, Schubert EK, Tewson TJ, Lawton TJ, Petra PH, Livingston RB. [Tc-99m]-sestamibi uptake and washout in locally advanced breast cancer are correlated with tumor blood flow. Nucl Med Biol. 2002 Oct;29(7):719-27.
12. Matsuo S, Nakajima K, Kinuya S. Evaluation of cardiac mitochondrial function by a nuclear imaging technique using Technetium-99m-MIBI uptake kinetics. Asia Ocean J Nucl Med Biol. 2013 Spring;1(1):39-43.
13. Bonora M, Pinton P. The mitochondrial permeability transition pore and cancer: molecular mechanisms involved in cell death. Front Oncol. 2014 Nov 17;4:302.
14. Maffioli L, Steens J, Pauwels E, Bombardieri E. Applications of 99mTc-sestamibi in oncology. Tumori. 1996 Jan-Feb;82(1):12-21.
15. O'Connor MK, Morrow MMB, Hunt KN, Boughey JC, Wahner-Roedler DL, Conners AL, Rhodes DJ, Hruska CB. Comparison of Tc-99m maraciclatide and Tc-99m sestamibi molecular breast imaging in patients with suspected breast cancer. EJNMMI Res. 2017 Dec;7(1):5.
16. Wang Y, Liu Y, Li N, Xu K, Zhang W. Quantitative application of dual-phase 99mTc-sestamibi SPECT/CT imaging of parathyroid lesions: identification of optimal timing in secondary hyperparathyroidism. EJNMMI Phys. 2023 Apr 20;10(1):29.
17. Lee SJ, Choi YY, Kim C, Chung MS. Correlations between tumor to background ratio on breast-specific gamma imaging and prognostic factors in breast cancer. J Korean Med Sci. 2017 Jun;32(6):1031-7.

18. Sogbein OO, Pelletier-Galarneau M, Schindler TH, Wei L, Wells RG, Ruddy TD. New SPECT and PET radiopharmaceuticals for imaging cardiovascular disease. Biomed Res Int. 2014;2014:942960.
19. O'Connor MK. Molecular breast imaging: an emerging modality for breast cancer screening. Breast Cancer Manag. 2015 Jan 1;4(1):33-40.
20. Dorbala S, Ananthasubramaniam K, Armstrong IS, Chareonthaitawee P, DePuey EG, Einstein AJ, Gropler RJ, Holly TA, Mahmarian JJ, Park MA, Polk DM, Russell R 3rd, Slomka PJ, Thompson RC, Wells RG. Single Photon Emission Computed Tomography (SPECT) myocardial perfusion imaging guidelines: instrumentation, acquisition, processing, and interpretation. J Nucl Cardiol. 2018 Oct;25(5):1784-846.
21. Bombardieri E, Aktolun C, Baum RP, Bishof-Delaloye A, Buscombe J, Chatal JF, Maffioli L, Moncayo R, Mortelmans L, Reske SN. Breast scintigraphy: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging. 2003 Dec;30(12):BP107-14.
22. Blanks RG, Wallis MG, Alison RJ, Given-Wilson RM. An analysis of screen-detected invasive cancers by grade in the English breast cancer screening programme: are we failing to detect sufficient small grade 3 cancers? Eur Radiol. 2021 Apr;31(4):2548-58.
23. Goldfarb JW, Zhao W, Patel D. Three-compartment (3C) pharmacokinetic modeling is more accurate than two-compartment (2C) modeling of myocardial fibrosis gadolinium kinetics. J Cardiovasc Magn Reson. 2012 Feb 1;14(Suppl 1):P248.
24. Chung E, Russo DP, Ciallella HL, Wang YT, Wu M, Aleksunes LM, Zhu H. Data-driven quantitative structure-activity relationship modeling for human carcinogenicity by chronic oral exposure. Environ Sci Technol. 2023 Apr 25;57(16):6573-88.
25. Okada RD, Glover DK, Nguyen KN, Johnson G 3rd. Technetium-99m sestamibi kinetics in reperfused canine myocardium. Eur J Nucl Med. 1995 Jul;22(7):600-7.
26. Lebok P, Schütt K, Kluth M, Witzel I, Wölber L, Paluchowski P, Terracciano L, Wilke C, Heilenkötter U, Müller V, Schmalfeldt B, Simon R, Sauter G, Von Leffern I, Krech T, Krech RH, Jacobsen F, Burandt E. High mitochondrial content is associated with breast cancer aggressiveness. Mol Clin Oncol. 2021 Oct;15(4):203.
27. Koit A, Shevchuk I, Ounpuu L, Klepinin A, Chekulayev V, Timohhina N, Tepp K, Puurand M, Truu L, Heck K, Valvere V, Guzun R, Kaambre T. Mitochondrial respiration in human colorectal and breast cancer clinical material is regulated differently. Oxid Med Cell Longev. 2017;2017:1372640.
28. Clemente-Suárez VJ, Martín-Rodríguez A, Redondo-Flórez L, Ruisoto P, Navarro-Jiménez E, Ramos-Campo DJ, Tornero-Aguilera JF. Metabolic health, mitochondrial fitness, physical activity, and cancer. Cancers (Basel). 2023 Jan 28;15(3):814.
29. Trehan R, Seam RK, Gupta MK, Sood A, Dimri K, Mahajan R. Role of scintimammography in assessing the response of neoadjuvant chemotherapy in locally advanced breast cancer. World J Nucl Med. 2014 Sep;13(3):163-9.
30. Masood S. Neoadjuvant chemotherapy in breast cancers. Womens Health (Lond). 2016 Sep;12(5):480-91.
31. Planche K, Vinnicombe S. Breast imaging in the new era. Cancer Imaging. 2004 Jan 12;4(2):39-50.
32. Nam SY, Ko ES, Lim Y, Han BK, Ko EY, Choi JS, Lee JE. Preoperative dynamic breast magnetic resonance imaging kinetic features using computer-aided diagnosis: association with survival outcome and tumor aggressiveness in patients with invasive breast cancer. PLoS One. 2018 Apr 12;13(4):e0195756.
33. Huang J, Schafer SM, Aben GR, Hoisington LA. Using lesion washout volume fraction as a biomarker to improve suspicious breast lesion characterization. J Appl Clin Med Phys. 2015 Sep;16(5):389-95.
34. Cwikla JB, Buscombe JR, Kolasinska AD, Parbhoo SP, Thakrar DS, Hilson AJ. Correlation between uptake of Tc-99m sestaMIBI and prognostic factors of breast cancer. Anticancer Res. 1999 May-Jun;19(3B):2299-304.
35. Liu Z, Stevenson GD, Barrett HH, Kastis GA, Bettan M, Furenlid LR, Wilson DW, Woolfenden JM. Imaging recognition of multidrug resistance in human breast tumors using 99mTc-labeled monocationic agents and a high-resolution stationary SPECT system. Nucl Med Biol. 2004 Jan;31(1):53-65.
36. Campennì A, Siracusa M, Ruggeri RM, Laudicella R, Pignata SA, Baldari S, Giovanella L. Differentiating malignant from benign thyroid nodules with indeterminate cytology by 99mTc-MIBI scan: a new quantitative method for improving diagnostic accuracy. Sci Rep. 2017 Jul 21;7(1):6147.
37. Luo M, Lin X, Hao D, Shen KW, Wu W, Wang L, Ruan S, Zhou J. Incidence and risk factors of lymph node metastasis in breast cancer patients without preoperative chemoradiotherapy and neoadjuvant therapy: analysis of SEER data. Gland Surg. 2023 Nov 24;12(11):1508-24.
38. Caudle AS, Kuerer HM, Le-Petross HT, Yang W, Yi M, Bedrosian I, Krishnamurthy S, Fornage BD, Hunt KK, Mittendorf EA. Predicting the extent of nodal disease in early-stage breast cancer. Ann Surg Oncol. 2014 Oct;21(11):3440-7.
39. Bae SY, Kim S, Lee JH, Lee HC, Lee SK, Kil WH, Kim SW, Lee JE, Nam SJ. Poor prognosis of single hormone receptor-positive breast cancer: similar outcome as triple-negative breast cancer. BMC Cancer. 2015 Mar 18;15:138.
40. Nassar A, Khoor A, Radhakrishnan R, Radhakrishnan A, Cohen C. Correlation of HER2 overexpression with gene amplification and its relation to chromosome 17 aneuploidy: a 5-year experience with invasive ductal and lobular carcinomas. Int J Clin Exp Pathol. 2014 Aug 15;7(9):6254-61.
41. Gajria D, Chandarlapaty S. HER2-amplified breast cancer: mechanisms of trastuzumab resistance and novel targeted therapies. Expert Rev Anticancer Ther. 2011 Feb;11(2):263-75.
42. Orrantia-Borunda E, Anchondo-Nuñez P, Acuña-Aguilar LE, Orozco-Morales M, Villarreal-Garza C. Subtypes of breast cancer. In: Mayrovitz HN, editor. Breast Cancer [Internet]. Brisbane (AU): Exon Publications; 2022 Aug 6. Chapter 3. Available from: https://www.ncbi.nlm.nih.gov/books/NBK583808/