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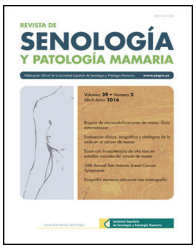

ORIGINAL ARTICLE

Is the result of breast Tc-99m mibi scintigraphy a prognostic factor for survival in invasive breast cancer?

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KEYWORDS
Breast cancer;
Tc-99m MIBI;
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Prognostic

Abstract
Background: Breast scintigraphy with Tc-99m MIBI showed utility in diagnosing and monitoring response to neoadjuvant treatment. This work studies if there are differences in long-term survival in breast carcinomas depending on the result of Tc-99 MIBI scintigraphy and to analyze their relationship with other variables of prognostic value.
Material and methods: A prospective observational study on a series of cases of breast cancer in which scintigraphy with Tc-99m MIBI was carried out prior to its treatment, and which had a minimum follow-up of ten years. Clinical–epidemiological, histopathological and immunohistochemical variables were recorded. Bivariate and multivariate analysis were performed studying the result of Tc99m-MIBI scintigraphy. Differences in OS and DFS were studied using Kaplan Meier curves with the log-rank test between factors.
Results: The significant relationship was found between Tc-99m-MIBI positive result and palpable tumors ($p = 0.0001$), poorly differentiated ($p = 0.003$), with lymph node involvement ($p = 0.038$) and high cell proliferation ($p = 0.007$), although only the palpability and tumor size are related after multivariate analysis.

Patients with Tc-99m MIBI positive tumors showed a worse OS ($p = 0.043$) and DFS ($p = 0.026$), independently of size and palpability of the lesión.
Conclusion: Tc-99m MIBI scintigraphy showed prognostic importance in invasive breast cancer, relating its positivity to reduced long-term survival.

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PALABRAS CLAVE
Cáncer de mama;
Tc-99m MIBI;
Sestamibi;
Gammagrafía;
Pronóstico

¿Es el resultado de la gammagrafía con Tc-99m MIBI un factor pronóstico para la supervivencia en el cáncer invasor de mama?

Resumen
Introducción: La gammagrafía mamaria con Tc-99m MIBI ha mostrado su utilidad en el diagnóstico y la monitorización de la respuesta al tratamiento neoadyuvante. Este trabajo estudia si hay diferencias en la supervivencia por cáncer de mama a largo plazo dependiendo del resultado de la gammagrafía con Tc-99m MIBI y analizar su relación con otras variables de valor pronóstico.
Material y métodos: Se realizó un estudio observacional prospectivo sobre una serie de pacientes con cáncer de mama en las que se realizó una gammagrafía con Tc-99m MIBI previa a su tratamiento, y con un seguimiento mínimo de 10 años. Se registraron variables clínico-epidemiológicas, histopatológicas e inmunohistoquímicas. Se realizaron análisis bivariante y multivariante para el resultado de la gammagrafía con Tc-99m MIBI. Se estudiaron la supervivencia glogal y libre de enfermedad mediante la curva de Kaplan-Meier y el test de *log-rank* entre factores.
Resultados: Se encontró una relación significativa entre la gammagrafía con Tc-99m MIBI positiva y las lesiones palpables (p = 0,0001), pobremente diferenciadas (p = 0,003), con afectación ganglionar (p = 0,038) y alta proliferación celular (p = 0,007), aunque solo la palpabilidad y el tamaño tumoral fueron significativos en el análisis multivariante. Las pacientes con gammagrafía positiva mostraron peor supervivencia global (p = 0,043) y libre de enfermedad (p = 0,026), independientemente del tamaño o la palpabilidad de la lesión.
Conclusión: La gammagrafía mamaria con Tc-99m MIBI presenta una relevancia pronóstica en cáncer invasor de mama, relacionando su positividad con menor supervivencia a largo plazo.

Introduction

Breast cancer can be considered the most frequent malignancy in women worldwide and, in the western world, it is estimated that it affects one in eight women throughout their lives. Its good prognosis depends on an early diagnosis and personalized management, considering both the staging and the biological characteristics of the tumor, adjusting the possible treatments in the most precise and specific way.

In the field of diagnosis imaging tests are fundamental, especially radiological, such as mammography, ultrasound and magnetic resonance imaging. In the last decades, imaging techniques based on molecular biology have constituted an important advance, since they allow to add a functional component to the morphological and get to obtain prognostic and predictive information, especially in the context of new therapeutic modalities, such as primary systemic therapies.

Among these explorations are those related to Nuclear Medicine, with the use of tracers related to cell metabolism, which make detection, diagnosis, and even monitoring of the tumor response to treatments, more specific.

The scintigraphy with 99mTc-methoxy-isobutyl-isonitrile (Tc-99m MIBI) is a diagnostic exploration that has traditionally been used in the field of cardiology, to better understand myocardial perfusion and its impact on functionality[1] and, subsequently, in the detection of hyperfunctioning parathyroid glands[2,3] or, in the case of oncology, when the uptake of this isotopic tracer by tissue with a high metabolic rate was evidenced, as is the case of tumor tissue.

In this context, it has been proposed to be used in the management of breast tumors, to make the differential diagnosis between benign and malignant lesions[4,5] and even when evaluating the response to neoadjuvant chemotherapy.[6]

The aim of this study is to study if there are differences in long-term survival in breast carcinomas depending on whether or not they are positive for Tc-99 MIBI uptake, and to analyze their possible relationship with other variables of prognostic value.

Material and methods

This is a prospective observational study on a series of cases of breast cancer in which a scintigraphy with Tc-99m MIBI was carried out prior to its treatment, and which had a minimum follow-up of ten years.

Selection criteria included women with invasive breast carcinoma who underwent scintigraphy with Tc-99m MIBI during the diagnostic process, before starting any treatment. The scintigraphy was indicated in every suspicious lesion based on radiological criteria (BIRADS 4 or 5) and, in some cases, even BIRADS 3. The cases of male breast carcinoma, intraductal carcinoma and those who received neoadjuvant chemotherapy were excluded.

An analysis of the data included in a prospective database developed since 1999 was done. The data recording and processing was carried out following the current regulations regarding Data Protection and using the anonymization and complete disassociation of the data. The study was performed in accordance with the Declaration of Helsinki and it was approved by the corresponding IRB (NE-2018-6-2-HCUVA).

Clinical–epidemiological variables (menarche age, menopause and menopause age, palpability of the tumor),

and histopathological variables (histologic type, size – in mm – measured in the surgical piece, number of lesions, degree of differentiation using Scarr-Bloom-Richardson classification, percentage of intraductal carcinoma, presence of lymphovascular invasion, and lymph node involvement) were collected. Hormone receptors (estrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR)) states were assessed through immunohistochemistry (IHC) stain and defined as positive when >10% of tumor cells were stained. Her2neu overexpression was assessed using IHC as well, and it was defined positive if score was 3+. Fluorescent in situ hybridization was selective performed when IHC staining score was 2+, with the cutoff value being 2.2 times more signal than that of CEP17. Cell proliferation was measured through IHC with the expression of ki67 and considering a cut-off of 14%. Expression of p53 was studied through IHC and considered positive greater than 10%.

Tumoral staging was established using the TNM classification (8th version).

For the follow-up of patients, specific disease-free survival (DFS) was defined, that is, up to progression or event related to breast cancer, and overall specific survival (OS) or until death due to breast cancer-related cause, both measured in months.

Mammary scintigraphy was performed by intravenous injection of a dose between 740 and 925 MBq (20 and 25 mCi) of Tc-99m MIBI in the contralateral arm to the affected breast, then washing with 10 mL of saline. The scintigraphic images were obtained in prone position using a special stretcher, in order to obviate the physiological uptake of retromamary thoracic structures (fundamentally, liver and heart), and following the technique described by Khalkhali et al.[7,8] Planar images were acquired by an Elscint SP6 gammacamera equipped with a high resolution collimator at 5 min and one hour after the tracer injection. The time of acquisition of image × 256 matrix. The projections used were lateral in prone position and anterior in supine with the arms in abduction, behind the head. Positivity was considered for all focal uptake of Tc-99m MIBI superior to the background activity of the considered breast, later contrasting its location and coincidence with the findings of other complementary imaging tests (mammography and ultrasound). Diffuse breast aspirations were not considered suggestive of malignancy.

Statistical methodology: a descriptive study of the qualitative and quantitative variables and a bivariate analysis for the result of the scintigraphy with the rest of the variables was made by means of a comparison of means with the *t*-Student test for the quantitative ones and analysis by means of tables of contingency, with residue analysis and the chi-square test, for qualitative ones. In order to study the multivariate analysis, a binary logistic regression was performed with the significant variables or with theoretical relevance. The differences in OS and DFS were studied using Kaplan Meier curves with the log-rank test between factors. The software SPSS v.20.0 was used and a level of significance for $p < 0.05$.

Results

Two-hundred and five lesions from 204 women (one had bilateral cancer that were considered as independent samples), were operated on between 2003 and 2007, with a mean follow-up of 164.94 ± 19.05 months (range: 120–205).

Table 1 General characteristics of the series.

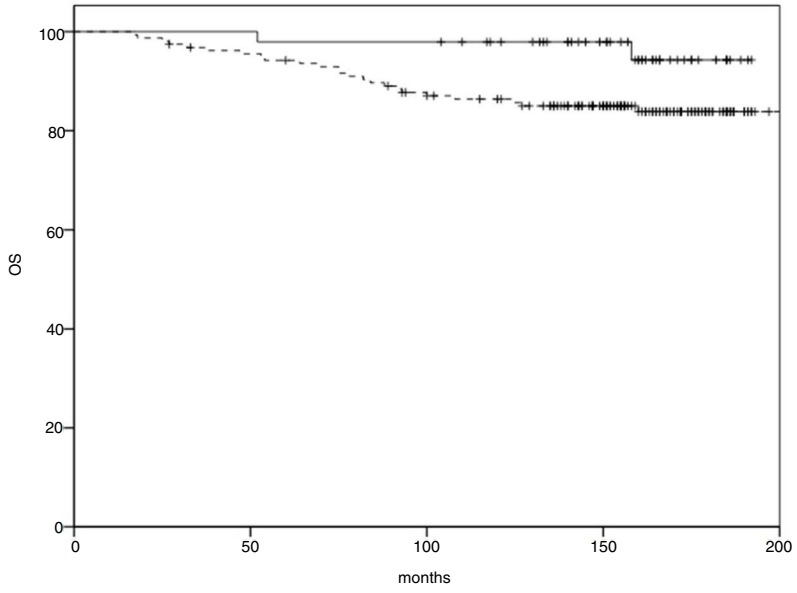
Variable	Value
Age (years) (n = 204)	57.51 ± 11.09
Age of menarche (years) (n = 171)	12.65 ± 1.62
Menopause (n = 198)	142 (71.7)
Age of menopause (years) (n = 123)	48.58 ± 5.51
Palpability (n = 203)	142 (70%)
Histologic type (n = 205)	
Ductal invasive – NOS	185 (90.2%)
Ductal invasive – specific type	11 (5.4%)
Lobular invasive	9 (4.4%)
Size (mm) (n = 204)	20.93 ± 12.55
Focality (n = 205)	
Unique tumor	181 (88.3)
Multiple tumor	24 (11.7)
Diferentiation (n = 192)	
Well (G I)	40 (20.8)
Moderate (G II)	101 (52.6)
Bad (G III)	51 (26.5)
Intraductal content (%) (n = 91)	18.48 ± 20.50
Lymphovascular invasion (n = 174)	32 (18.4)
Nodal involvement (n = 205)	68 (33.17)
ER expression (>10%) (n = 189)	153 (80.95)
PR expression (>10%) (n = 111)	69 (62.16)
AR expression (>10%) (n = 111)	49 (44.14)
Her2neu overexpression (n = 189)	24(12.7)
Ki67 > 14% (n = 116)	36 (31.03)
p53 expression (>10%) (n = 106)	22 (20.8)
TNM staging (n = 205)	
I	95 (46.3)
II	79 (38.5)
III	31 (15.1)

Values are expressed as mean ± standard deviation for quantitative variables and as absolute values and proportion for qualitative variables. ER: estrogen receptor; PR: progesterona receptor; AR: androgen receptor.

Table 1 shows the general characteristics of the series and Table 2 presents the results of the bivariate analysis of the Tc-99m MIBI result with the rest of the variables. Significant differences were found in favor of the positive result for scintigraphy with Tc99m-MIBI when patients had had palpable tumors ($p = 0.0001$), especially greater than 2 cm ($p = 0.0001$), poorly differentiated ($p = 0.003$), with lymph node involvement ($p = 0.038$) and high cell proliferation ($p = 0.007$). It is also significantly related to tumors in more advanced stages ($p = 0.010$).

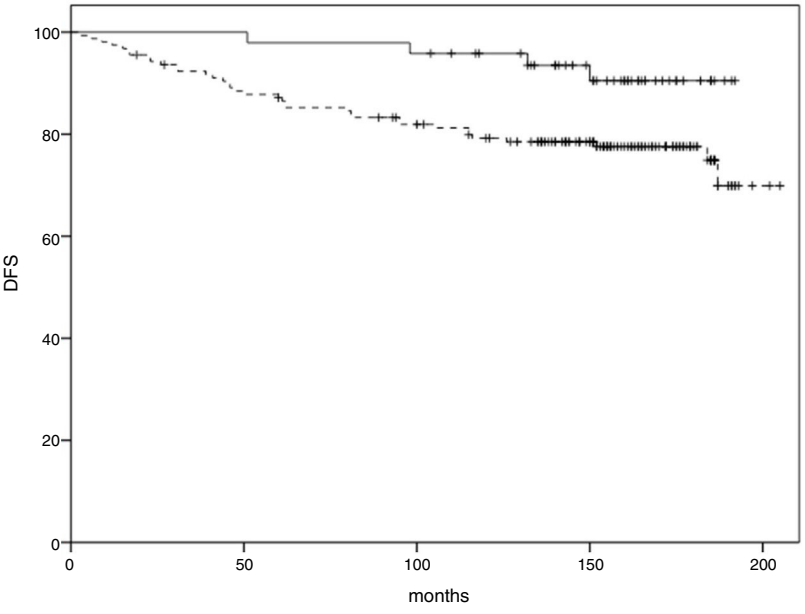
In the multivariate analysis, only two variables that are related to the positive Sestamibi result are significant: the palpability of the lesion ($p < 0.0001$, OR: 13.33, 95% CI: 3.11–43.45) and its size ($p = 0.039$; OR: 1.08; 95% CI: 1.00–1.17).

The mean DFS of the series was 176.62 ± 4.81 months (IC95%: 168.43–184.82) and the mean OS of 187.86 ± 3.24 months (IC95% 181.51–194.21). The OS of the cases with expression and without expression of Tc-99m MIBI in their



Patients at risk					
Negative MIBI	48	48	47	47	46
Positive MIBI	157	150	137	134	133

Figure 1 Kaplan–Meier curves for OS between Tc99m-MIBI positive lesions (dashed line) and Tc99m-MIBI negative lesions (continuous line); $p = 0.043$.



Patients at risk					
Negative MIBI	48	48	46	44	44
Positive MIBI	157	138	129	124	121

Figure 2 Kaplan–Meier curves for DFS between Tc99m-MIBI positive lesions (dashed line) and Tc99m-MIBI negative lesions (continuous line); $p = 0.026$.

Table 2 Bivariante analysis for Tc99m-MIBI result.

	Tc99m-MIBI+ $n = 157$	Tc99m-MIBI− $n = 48$	p
Age (years) (n = 204)	57.34 ± 11.76	58.06 ± 8.63	0.694
Age of menarche (years) (n = 171)	12.56 ± 1.51	12.68 ± 1.66	0.673
Menopause (n = 142)	104 (26.8%)	38 (73.2%)	0.111
Age of menopause (years) (n = 123)	49.12 ± 5.51	48.37 ± 5.53	0.504
Palpability (n = 142)	126 (88.7%)	16 (11.3%)	0.0001
Histologic type			
Ductal invasive – NOS (*n* = 185)	143 (77.3%)	42 (22.7%)	0.727
Ductal invasive – specific type (*n* = 11)	8 (72.7%)	3 (27.3%)	
Lobular invasive (*n* = 9)	6 (66.7%)	3 (33.3%)	
Size (mm) (n = 204)	23.08 ± 13.09	13.74 ± 6.77	0.0001
T category (TNM)			
T1 (<2 cm) (*n* = 130)	89 (68.5%)	41 (31.5%)[a]	0.001
T2 (2–5 cm) (*n* = 67)	61 (91%)[a]	6 (9%)	
T3 (>5 cm) (*n* = 7)	7 (100%)	0 (0%)	
Focality			
Unique tumor (*n* = 181)	139 (76.8%)	42 (23.2%)	0.845
Multiple tumor (*n* = 24)	18 (75%)	6 (25%)	
Diferentiation			
Well (G I) (*n* = 40)	26 (65%)	14 (35%)[a]	0.003
Moderate (G II) (*n* = 101)	75 (74.3%)	26 (25.7%)	
Bad (G III) (*n* = 51)	48 (94.1%)[a]	3 (5.9%)	
Intraductal content (%) (n = 91)	15.38 ± 16.78	19.43 ± 21.51	0.431
Lymphovascular invasion (n = 32)	29 (90.6%)	3 (9.4%)	0.069
Nodal involvement (n = 68)	58 (85.3%)	10 (14.7%)	0.038
ER expression (>10%) (n = 153)	117 (76.5%)	36 (23.5%)	0.064
PR expression (>10%) (n = 69)	47 (68.1%)	22 (31.9%)	0.113
AR expression (>10%) (n = 49)	32 (65.3%)	17 (34.7%)	0.068
Her2neu overexpression (n = 24)	20 (83.3%)	4(16.7%)	0.523
Ki67>14% (n = 36)	33 (91.7%)	3 (8.3%)	0.007
p53 expression (n = 22)	19 (86.4%)	3 (13.6%)	0.182
TNM staging			
I (*n* = 95)	64 (67.4%)	31 (32.6%)	0.010
II (*n* = 79)	65 (82.3%)	14 (17.7%)	
III (31)	28 (90.3%)[a]	3 (9.7%)	

Values are expressed as mean ± standard deviation for quantitative variables and as absolute values and proportion for qualitative variables. ER: estrogen receptor; PR: progesterona receptor; AR: androgen receptor.
[a] Sense of statistical relationship.

tumors was significantly different in favor of the second ones (positive Tc99m-MIBI: 184.07 ± 5.05 months (95% CI: 176.13–192.01) vs negative Tc-99m MIBI: 187.85 ± 3.10 (95% CI: 181.76–193-93) $p = 0.043$) (Fig. 1). Regarding DFS (Fig. 2), significant differences were also found between the group with positive Tc-99m MIBI (170.73 ± 5.18 months (95% CI: 160.57–180.90)) and the group with negative Tc-99m MIBI (184.43 ± 3.84 months (95% CI: 176.89–191.97) ($p = 0.026$).

It was not possible to stratify the survival curves according to the TNM stages, since in none of the cases classified in stages II and III were Tc-99m MIBI negative tumors.

When OS and DFS of the cases with palpable lesions were analyzed according to the result of the Tc-99m MIBI scintigraphy, no significant differences were obtained ($p = 0.437$). Neither significant differences were found in OS or DFS between positive and negative Tc-99m MIBI lesions in non-palpable cases ($p = 0.758$).

Discussion

In the case of breast cancer, scintigraphy with Tc-99m MIBI presents adequate sensitivity and a high negative predictive value[9–11] both for the diagnosis of the tumor and for the existence of axillary metastases.[12] It has also been shown to be a good predictor of increased risk in benign lesions.[4,13] In spite of this, from a point of view of the diagnostic precision and, above all, of its efficiency, no use has been observed in routine clinical practice as a diagnostic test.

Other relevant aspects, in addition to the strictly diagnostic, would be the potential prognostic and predictive

values of this exploration, and that could be related to the mechanisms of uptake and accumulation of the tracer by the tumor cells, mechanisms that, on the other hand, are not completely defined. As will be seen below, it has been associated with an increase in tumor vascularization, an increase in cellular metabolism, and especially mitochondrial activity, and differences in the expression of certain glycoproteins of the cell membrane, such as P-glycoprotein, the multidrug-resistance associated protein (MDRP1), or located in the outer mitochondrial membrane, such as Bcl-2.

The first requirement for tumor tracer uptake is that it reaches the tumor cells. In this sense, and although the blood supply to the tumor is an important factor, there are studies in which no differences have been found in the vascular density of tumor uptake and non-uptake for Tc-99m MIBI[14] nor, specifically, in cancer of breast.[15,16]

Among the mechanisms that explain the greater retention of the tracer in the lesion than in the rest of the breast parenchyma, an increase in metabolic requirements has been proposed, due to the content of mitochondria or a deficit in their functionality.[17–19]

Finally, the uptake or not of the tracer is intimately related to the overexpression of multidrug resistance-associated plasma membrane proteins such as P-glycoprotein and the antiapoptotic Bcl-2 protein on the outer mitochondrial membrane,[20] so that it has been postulated as a possible indicator of chemoresistance, identifying cases that could present low responses to neoadjuvant chemotherapy.[6,21,22] Trock et al., in a meta-analysis of breast cancer trials, found a reduction of up to three times in the chemotherapy response of tumors that showed p-glycoprotein expression after treatment.[23] In fact, in the meta-analysis of Collarino A et al. over 14 studies, a low sensitivity and high specificity was reported to predict the pathological response to neoadjuvant treatment in breast cancer with the use of conventional planar scintigraphy with Tc-99 MIBI and, although the experience is limited, they found greater utility in its use as a monitoring of the clinical response during neoadjuvancy.[24] In this sense, there are also experiences with other neoplasms, such as lung cancer[25] or in lymphomas.[26]

Overexpression of Bcl-2 has been related to a relative resistance to chemotherapy and radiotherapy due to the defects in the associated apoptotic cell program.[27] Although the mechanism by which overexpression of Bcl-2 prevents the uptake of Tc-99m MIBI in breast cancer is not fully known at present, it seems to have to do with the difficulties involved in permeabilization of the mitochondrial membrane to this agent.[28]

Another aspect also related to the pathophysiology of tracer uptake and retention on Tc-99m MIBI scintigraphy is the higher rate of cell proliferation in positive lesions. This specific data is endorsed by the results of the present work, insofar as there is a relationship between a positive Tc99m-MIBI scintigraphy and an immunohistochemical expression of ki67 greater than 14%. Anyway, and although it is accepted that an early and increased concentration of Tc-99m MIBI in breast carcinoma is associated with higher proliferation rate and more aggressive tumor behavior,[29] the reported results are still controversial, and so on, while Cutrone et al.,[14] found a significant relationship between the degree of tracer uptake and cell proliferation, other studies[30] only found it in small diameter lesions (smaller than 1.5 cm) and, even in other series,[28] no differences were found between Tc-99m MIBI uptake and mitotic index, although the mitotic index was much lower in negative lesions.

This may be relevant, since, although instinctively the proliferation rate and the rate of apoptosis may seem complementary and antagonistic, the fact that both pathways overlap and dock in human malignant tumors is increasingly evident,[31] coinciding both functions in the expression of certain oncogenes,[32,33] so it is not surprising that both have been related in the literature to the result of the capture of Tc-99m MIBI by breast cancers.[34,35]

On the other hand, the findings of the present study also related in a significant way a positive result of the Tc-99m MIBI scintigraphy with other variables, likewise, of poor prognosis: tumors of greater size and worse differentiated that present lymph node involvement, and therefore with advanced clinical–pathological stages, which coincides with what was also reported by other author.[36]

However, and from a direct prognostic point of view, the functional nature of this test raises its usefulness when it comes to differentiating cases with better or worse long-term survival, although in the authors' knowledge, this is the first work that addresses it directly. The study found that those cases with invasive breast tumors that had a positive Tc-99m MIBI scintigraphy showed a lower DFS and a lower OS after more than 10 years of follow-up. Despite being related to the size of the lesion and, especially with its palpability, it was found that there were no differences in OS nor DFS when the cases of positive and negative Tc-99m MIBI were subdivided depending on whether they were or not palpable. This infers greater independent prognostic importance to the fact that the lesions are positive with Tc-99m MIBI.

The above, considered together with the fact that in the most advanced stages (TNM II and III) no lesion with negative Tc-99m MIBI was found, has an impact on the greater biological aggressiveness of the tumors that are positive with this technique and, therefore, in the potential consideration of the same before scenarios of lesions with uncertain prognosis or subjected to primary therapies prior to locoregional treatments in order to optimize them.

Conclusion

Tc-99m MIBI scintigraphy is an exploration with prognostic importance in invasive breast cancer, relating its positivity to reduced long-term survival.

Confidentiality of data

The authors declare that they have followed the protocols of their Center on the publication of patient data and the corresponding consents have been obtained.

Conflict of interest

APM is a member of the Editorial Committee of the journal. The rest of the authors do not have any conflict of interest.

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