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Original

Positive sentinel node risk in relation to oestrogen receptors in breast cancer in premenopausal and postmenopausal women

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ABSTRACT

Objective: The influence of the relationship between pre- and post-menopausal stage of patients with breast cancer (BC) and the risk of sentinel lymph node (SLN) metastasis as well as the influence of oestrogen receptor (ER) status within each one of these groups were analyzed.
Method: A BC database with 1,388 patients was analysed. Three age groups were studied: A, elderly postmenopausal, 200 patients, ≥70 years old; B, younger postmenopausal, 89 patients, 55-69 years old; C, premenopausal, 85 patients, <55 years old. In each group 2 subgroups were analyzed: positive ER and negative ER tumours. Data analysed: SLN-positive patients, non-sentinel node (NSN)-positive patients, non-surgical detections (NSD) and non disease-free (NDF) patients after a follow-up of 52 months. Statistical analysis: chi-squared test, significance: P≤0.05.
Results: SLN metastasis was significantly (P<0.025) more common in premenopausal than in postmenopausal patients, and within those, mainly in negative ER tumours. Positive-NSN increases slightly in premenopausal patients (exclusively in negative ER tumours). NDF patients are similar in the 3 groups and in all of them it is much more frequent in negative ER tumours.
Conclusions: SLN metastasis varies significantly according to hormonal state and not according to age, being more frequent in premenopausal patients and mainly in ER negative tumours.

Relación entre el riesgo de metástasis en el ganglio centinela y los receptores estrogénicos en pacientes pre y posmenopáusicas con cáncer de mama

Palabras clave:
Ganglio centinela
Cáncer de mama
Receptores estrogénicos tumorales
Mujeres premenopáusicas y posmenopáusicas

RESUMEN

Objetivo: Investigar la relación entre el estado pre o posmenopáusico de la paciente con carcinoma de mama (CM) y el riesgo de metástasis en el ganglio centinela (GC) y dentro de cada uno de esos grupos el riesgo según el estado de los receptores de estrógeno (RE).
Método: Análisis de la base de datos de GC con 1.388 pacientes. Se estudiaron tres grupos de edad: A) posmenopáusicas ancianas, 200 pacientes, ≥70 años; B) posmenopáusicas más jóvenes, 89 pacientes, 55-69 años, y C) premenopáusicas, 85 pacientes, < 55 años. En cada grupo se analizaron 2 subgrupos: tumores con RE positivos o negativos. Factores estudiados en cada grupo y subgrupo: pacientes con GC positivo, pacientes con ganglios no centinela (GNC) positivos, número de no detecciones quirúrgicas (NDQ) y pacientes no libres de enfermedad (NLE) tras 52 meses de seguimiento. Análisis estadístico: test de chi-cuadrado; significancia p ≤ 0,05.
Resultados: En las premenopáusicas el número de GC positivos es significativamente (p < 0,025) mayor que en las posmenopáusicas y dentro de las premenopáusicas fundamentalmente en los tumores con RE negativos. El número de GNC positivos aumenta solo discretamente en las premenopáusicas y ocurre exclusivamente en tumores con RE negativos. El número de pacientes NLE es similar en los 3 grupos y en todos ellos es mucho más frecuente en pacientes con tumores con RE negativos.
Conclusiones: El número de pacientes con GC positivo varía significativamente con el estado hormonal y no con la edad de la paciente, siendo más frecuentes en las premenopáusicas y fundamentalmente en tumores con RE negativos.

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Introduction

The incidence of breast cancer increases with age, this being the most frequent cancer in women over 70 years of age.[1] Comorbidity also increases with age and may condition the duration and extension of the surgery. Therefore, if axillary surgery can be avoided without jeopardizing the control of the tumor, this would be a very important advantage in this group of patients. The need for lymph node staging in these patients is a controversial subject. The perception exists that regional staging in elderly patients has less influence in the subsequent treatment while there is a very extended belief that there is a lower risk of metastasis in regional lymph nodes in the older patients.[2]

There are various studies that confirm the clinical impression that the disease in elderly patients is more indolent and that they have a more favorable biological phenotype, as shown by the fact that there are lower rates of tumor cell proliferation, lower expression of human epidermal growth factor receptor 2 (HER 2), higher content of estrogen and/or progesterone receptors, lower rate of p53 accumulation and, what is more important, better evolution.[3-5]

It is well known that elderly patients have a greater likelihood of positive estrogen receptor tumors. Thus, hormone therapy in them plays a very important role, chemotherapy being relegated to a second place.[6]

It has already been demonstrated that the risk of metastasis in the sentinel node (SN) significantly decreases as age increases.[2] However, this risk has not been studied in relationship to the hormonal status of the patient (pre- and post-menopausal).

Since the utility of selective sentinel node biopsy in any population group depends on the pretest likelihood of detecting metastasis in the sentinel node, our study was conceived to investigate if the risk of metastasis in the sentinel node was related to, more than age, the pre- or post-menopausal status of the patient and to determine, within each one of these groups, what the risk would be according to whether the tumor has positive or negative estrogen receptors (ER).

Material and methods

Study design

This is a retrospective study of the prospective data base of sentinel nodes in breast cancer patients in the nuclear medicine department of the Hospital Universitario of Bellvitge. From June 2000 to December 2007, a total of 1388 patients suffering from breast cancer who had undergone a selective sentinel lymph node biopsy were included in the data base. Over the years, the cutoff age to consider a patient as elderly in the literature had been increasing, reaching up to 70 years, based on the prolongation that is being experienced in life expectancy.[7] For this reason, our study has considered those women 70 years or older as an elderly patient. We have considered 55 years of age as the age threshold that separates the premenopausal patient from the post-menopausal.

The number of positive lymphadenectomies, that is, the existence of other metastatic lymph nodes in the lymphadenectomy specimen, has also been studied, taking into account that lymphadenectomy had been done because metastasis in the SN had been detected.

Furthermore, the follow-up of the patents was recorded in order to calculate how many were disease-free at the time of the study in each group.

Each one of these factors studied was also analyzed within each age group according to whether the patients had positive or negative estrogen receptor (ER) tumors.

Study population

Of the 1388 patients, 374 patients with invasive breast cancer whose tumor size was $\leq$ 3 cm were included in the present study. These patients were followed-up at a mean of 52 months. Three groups were differentiated: group A, elderly post-menopausal, was made up of 200 patients, who were 70 years or older. They underwent a selective SN biopsy between June 2000 and December 2007 and were followed-up for a mean of 35 months. Group B is the group of the youngest post-menopausal subjects, made up of 89 patients, between 55 and 69 years, who underwent the SN technique between January 2001 and December 2004 and who were clinically followed-up for a mean of 66 months, and finally, group C, pre-menopausal, with 85 patients under 55 years of age, who were also operated on between January 2001 and December 2004 and had a mean follow-up of 54.5 months.

Pathological study

A SN was considered positive when metastasis was detected by hematoxylin and eosin stain or by immunohistochemistry. According to the TNM staging, if the size of the metastasis detected was >2 mm, it was considered a macrometastasis, if the size was between 0.2 and 2 mm, micrometastasis and if it was <0.2 mm, isolated tumor cells (ITC).

The lymph nodes of the lymphadenectomy specimen were only analyzed with hematoxylin and eosin stain.

Statistical analysis

Comparison between samples was made using the chi square test and the Yates correction was applied when the items calculated were between 3 and 5. Significance was determined with $p \leq 0.05$.

Results

The number of SN excised per patient was 1.46 in group A, 1.6 in group B and 1.7 in group C.

The number of patients in whom the SN was not detected surgically increased with age. In group A, elderly post-menopausal subjects, this occurred in 17 patients (17/200). In group B, the youngest post-menopausal, in 4 patients (4/89) and in group C, premenopausal, in one patient (1/85).

The number of patients with negative estrogen receptor tumors in group A was 18 (18/200), in group B, 14 patients (14/89) and in group C, 11 patients (11/85). No statistically significant differences were found between the different age groups.

Regarding patients with positive SN, this significantly increased ($p<0.025$) in the premenopausal patient group compared to the postmenopausal patients. In Group A, we found 37 patients (37/200), in B, 16 patients (16/89) and in C, 27 patients (27/85). However, the number of these patients in whom there were other metastatic lymph nodes in the lymphadenectomy specimen only slightly increased with age: 6 patients in Group A (6/200), 5 in group B (5/89) and 6 in Group C (6/85), no significant differences ($p>0.1$) being found between the different age groups.

The percentage of patients who were not disease-free at the time of the study was similar in the three age groups: 8 patients in the elderly patient group (8/200), 4 in the youngest postmenopausal group (4/89) and 5 in the premenopausal one (5/85) and no statistically significant differences ($p>0.05$) were found.

All of these results are shown as percentages in table 1.

Table 2 shows the number of patients with positive SN and with other positive lymph nodes of the lymphadenectomy and the number of patients in which the SN was not detected surgically and the patients who were not disease-free at the time of the study in accordance with positive or negative ER of the tumors in each age group.

In the premenopausal group, 21 out of the 74 patients with positive ER had positive SN (28.4%) and 3 patients also had other positive lymph nodes of the lymphadenectomy (4%). Six of the 11 patients

Table 1
Results of the factors analyzed in the three age groups studied

	RE (–)	SN (+)	ALD (+)	NSD	NDF
Group A (≥70 y)	9% (18/200)	18.5% (37/200)	3% (6/200)	8.5% (17/200)	4% (8/200)
Group B (55-69 y)	15.7% (14/89)	18% (16/89)	5.6% (5/89)	4.5% (4/89)	4.5% (4/89)
Group C (<55 y)	12.9% (11/85)	31.8% (27/85)	7.1% (6/85)	1.2% (1/85)	5.9% (5/85)

y: years (age); SN: sentinel node; ALD: axillary lymphadenectomy; NSD: no surgical detection of the sentinel node; NDF: patients not disease free after follow-up; ER: estrogen receptor status.

Table 2
Results of the factors analyzed in the three age groups and in the two subgroups (positive and negative hormone receptors) studied

	SN(+)		ALD(+)		NSD		NDF	
	ER(–)	ER(+)	ER(–)	ER(+)	ER(–)	ER(+)	ER(–)	ER(+)
Group A (≥70 y)	22.2% (4/18)	18.1% (33/182)	0% (0/18)	3.3% (6/182)	5.5% (1/18)	8.8% (16/182)	16.6% (3/18)	2.7% (5/182)
Group B (55-69 y)	21.4% (3/14)	17.3% (13/75)	7.1% (1/14)	5.3% (4/75)	14.3% (2/14)	2.6% (2/75)	7.1% (1/14)	4% (3/75)
Group C (<55 y)	54.5% (6/11)	28.4% (21/74)	27.2% (3/11)	4% (3/74)	0% (0/11)	1.3% (1/74)	18.1% (2/11)	4% (3/74)

y: years (age); SN: sentinel node; ALD: axillary lymphadenectomy; NSD: no surgical detection of the sentinel node; NDF: patients not disease; free after follow-up; ER: estrogen receptor status.

Table 3
Size of the metastasis in the sentinel node in the three age groups and in the two subgroups (positive and negative hormone receptors) studied

	macroSN		microSN		TCI SN	
	ER (–)	ER (+)	ER (–)	ER (+)	ER (–)	ER (+)
Group A (≥70 y)	16.6% (3/18)	11% (20/182)	5.5% (1/18)	3.8% (7/182)	0%	3.3% (6/182)
Group B (55-69 y)	14.3% (2/14)	9.3% (7/75)	7.1% (1/14)	6.6% (5/75)	0%	1.3% (1/75)
Group C (<55 y)	45.4% (5/11)	13.5% (10/74)	9.1% (1/11)	5.4% (4/74)	0%	9.5% (7/74)

y: years (age); TCI: tumor cells isolated in sentinel node; macroSN: macrometastasis in sentinel node; microSN: micrometastasis in sentinel node; ER: estrogen receptor status.

with negative ER had positive SN (54.5%) and 3 others positive lymph nodes (27.2%). Even though the percentage of patients with positive SN in the patients with negative ER was almost twice that of those who had positive ER, this difference is not significant (p>0.1).

In the two postmenopausal groups, these differences were not as important between the patients with positive ER and those who were negative ER.

In the three age groups, the number of patients who were not disease-free increased notably in the subgroup of patients with negative ER tumors compared to the subgroup of patients with positive ER tumors.

Table 3 shows the patients with macrometastasis, micrometastasis or ITC in the SN in each subgroup of patients according to whether the tumors were positive or negative ER and for each age group.

In the premenopausal patient group, of the 74 patients with positive ER tumors, macrometastasis was found in 10 in the SN (13.5%) and of the 11 patients with negative ER, 5 had macrometastasis in the SN (45.4%). In the two other age groups, which included the elderly and youngest postmenopausal patients, such an important increase was not found in the patients with negative ER tumors versus those with positive ER tumors.

Discussion

Life expectancy has been increasing over time so that it is now beyond 80 years of age for Western women. Thus, it is necessary to take a defined position regarding the elderly patient with breast cancer in regards to the axillary approach. There is no consensus on this matter, as in others regarding the elderly patient, because a substantial number of elderly patients are not included in clinical trials. The influence of age in surgical detection of the sentinel node in patients suffering breast cancer is an already-studied factor. McMahon et al.[8] did not find any significant differences in the identification of SN among patients <70 years and those of ≥70 years. On the other hand, Sener described an increase in the likelihood ratio of 3.14 for failures in scintigraphic detection of the SN in patients over 70 years of age.[9] Our group published a study in 2005[10] in which the factors that could influence in the non-detection of SN in 703 patients with breast cancer were analyzed. After a multifactorial analysis, it was found that advanced age and non-scintigraphic detection independently showed a significant correlation with the non-surgical detection of SN. This statement has been made clear another time in the present work, the non-surgical detection of the SN increasing as age increases. In the premenopausal group of patients, non-detection is only 1.2%, this reaching 8.5% in the elderly post-menopausal patients.

There are also several works that have studied the factors influencing the existence of metastasis in the SN. Singh et al.[11] found among patients with breast cancer, those undergoing lymphadenectomy for staging, that it was less likely that patients over 70 years of age had metastasis in the lymph nodes than younger patients. Caywood et al.[2] demonstrated that the influence of age in the SN metastasis risk is independent of other risk factors and that the difference in the risk is more important in patients without lymph node invasion. Elderly age decreases independently the risk of metastasis in the SN.

In the present work, the number of positive SNs also significantly increased as age decreased, but did so in the premenopausal patients compared to the two groups of post-menopausal patients. It stands out that the incidence between the two groups of post-menopausal patients is similar. Thus, in our experience, more than age, what has a significant influence in the risk of finding metastasis in the SN is the hormonal status of the patients, according to whether the woman is pre- or postmenopausal.

However, this significant increase in the number of positive SNs in the premenopausal patients in regards to postmenopausal ones was not accompanied by a similar increase in the number of positive lymphadenectomies, that is, in the existence of other positive lymph

nodes in the lymphadenectomy specimen. The number of positive lymphadenectomies did increase in the different groups as age decreased, but slightly and non-significantly.

Regarding the hormone receptors, Aitken and Osman,[12] in an uni- and multivariant analysis, did not find a relationship between ER/PR (progesterone receptors) and lymph node positivity. In our case, if we analyze the results according to whether the patients had tumors with positive or negative hormone receptors, we can observe how premenopausal patients with positive ER had a positive SN had a positive SN 9-10% more frequently in regards to the post-menopausal patients with positive ER and that the likelihood of having a positive lymphadenectomy is similar in the three age groups. However, in premenopausal patients with negative ER, these proportions increase, the positive SNs being 33% more frequent in the premenopausal than in the post-menopausal subjects. It is also about 20% more frequent for the premenopausal subjects to have a positive lymphadenectomy compared to the younger postmenopausal subjects and 27% regarding elderly post-menopausal subjects.

In regards to the number of patients who are not disease free after a mean of 52 months of follow-up, it is very similar in the three age groups. Also found in common for the three age groups was the fact that the presence of adverse events related with breast cancer (patients not disease free) was much more frequent in the patients with tumors with negative ER versus those who had tumors with positive ER.

Conclusions

In the population studied, that is, patients with invasive breast cancer and a tumor size of $\leq$ 3 cm, the percentage of patients with positive SN significantly varies according to the hormonal status of the patient, and not according to age, it being more frequent in premenopausal patients. Furthermore, within the premenopausal patients, this increase fundamentally occurs in those who have tumors with negative ER and at the expense of a notable increase of the macrometastasis in the SN. The modest increase occurring in the number of positive lymphadenectomies in premenopausal patients versus postmenopausal ones only occurs in patients with negative ER.

In the postmenopausal patients, there are no important differences between patients with negative or positive ER tumors.

In regards to the number of patients who are disease-free after 52 months of follow-up, it is similar in the three age groups and, in the three groups, it is much more frequent in the patients with negative ER tumors.

Based on all these results, a question is posed: Can the selective SN biopsy be eliminated in patients after 70 years of age, with invasive tumors $\leq$ 3 cm and with positive estrogen receptors?

To finish up, it must be taken into account that the size of the subgroups of patients with negative ER in the present study is small and thus more studies would be necessary in order to have a sufficient number of patients to obtain more definitive conclusions.

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