Incidence of axillary recurrence after a negative sentinel lymph node result in early stages of breast cancer: A 5-year follow-up

R. Ruano Pérez a,*, M. Ramos Boyero b, J.R. García-Talavera Fernández a, T. Ramos Grande b, J.M. González-Orúš b, F. Gómez-Camino López a, M.C. García Macià c, A. Martín de Arriba a

a Servicio de Medicina Nuclear, Hospital Universitario de Salamanca, Salamanca, Spain
b Servicio de Cirugía, Hospital Universitario de Salamanca, Salamanca, Spain
c Servicio de Anatomía Patológica, Hospital Universitario de Salamanca, Salamanca, Spain

ARTICLE INFO

Article history:
Received 7 October 2011
Accepted 11 November 2011

Keywords:
Breast cancer
Sentinel lymph node
Axillary recurrence
Prognosis
Survival

ABSTRACT

The sentinel lymph node (SLN) biopsy is currently the procedure of choice for axillary node staging in initial stages of breast cancer. The purpose of this study is to establish our false negative rate within a 5-year follow-up period in 258 patients with breast cancer staged with this procedure. Methods: A retrospective study on 258 consecutive T1–T2 < 3 cm pN0 staged breast carcinomas treated from January 1, 2001 to December 31, 2005 was performed. The combined technique of isotope plus blue dye was used for detection. The subjects underwent a minimum follow-up of 5 years, mean 81 months, with an end of follow-up at December 31, 2010. Evidence of axillary recurrence, tumor recurrence in the breast and signs of disease progression or death were the events collected and analyzed. Results: Of the 258 patients, 3 false negatives (1.1%) with axillary recurrence were detected at 10, 11 and 29 months of the surgery. This did not have a significant repercussion in the survival analysis on the contrary to the existence of breast recurrence or the appearance of distant metastasis in 4.7 and 6.2% patients, respectively. Global survival related with the cancer was 93.0 (240/258) and disease free survival was 89.1% (230/258). Conclusion: The risk of developing axillary recurrence after a negative SLN without axillary node dissection is low enough to consider the SLN procedure to be the best approach for axilla staging in early breast cancer. This staging technique also makes it possible to achieve local disease control without diminishing the survival of the patients.

© 2011 Elsevier España, S.L. and SEMNIM. All rights reserved.

Palabras clave:
Cáncer mama
Ganglio centinela
Recurrencia axilar
Prognóstico
Supervivencia

RESUMEN

La biopsia selectiva del ganglio centinela (GC) es en la actualidad el procedimiento de elección en la estadificación axilar en cánceres de mama en estadios iniciales. El objetivo de este estudio es establecer nuestra tasa de falsos negativos a lo largo de un periodo mínimo de 5 años de seguimiento de 258 pacientes con cáncer de mama estadificados mediante este procedimiento. Método: Estudio retrospectivo de 258 pacientes con cáncer de mama consecutivos T1–T2 < 3 cm estadificados como pN0 mediante GC entre enero-2001 y diciembre-2005. Se empleó la técnica combinada isotópica y colorante para la detección. Fueron sometidos a seguimiento con un período mínimo de 5 años, la media fue 81 meses, siendo el punto final del seguimiento el 31 de diciembre de 2010. La evidencia de recurrencia axilar, recidiva tumoral en la mama, presencia de enfermedad a distancia, y muerte fueron los eventos recogidos y analizados. Resultados: De las 258 pacientes, se detectaron 3 falsos negativos (1.1%), con recurrencia axilar a los 10, 11 y 29 meses de la cirugía. En el análisis de supervivencia este hecho no tuvo repercusión significativa, a diferencia de la existencia de recidiva mamaria o la aparición de metástasis a distancia que ocurrieron en un 4,7 y un 6,2% de las pacientes. La supervivencia global relacionada con el cáncer fue de un 93,0% (240/258) y la supervivencia libre de enfermedad del 89,1% (230/258).

Conclusión: El riesgo de recurrencia axilar tras un ganglio centinela negativo sin vaciamiento linfático completo es lo suficientemente bajo como para considerar a este procedimiento como de elección en la estadificación axilar del cáncer de mama en estadios iniciales. Además, permite alcanzar un adecuado control local de la enfermedad sin disminuir la supervivencia de los pacientes.

© 2011 Elsevier España, S.L. y SEMNIM. Todos los derechos reservados.


* Corresponding author.
E-mail address: richardrua@hotmail.com (R. Ruano Pérez).
Introduction

Complete axillary lymph node dissection or axillary lymphadenectomy (AL) is considered the standard technique in the management of early stage breast cancer to obtain appropriate staging and design adjuvant systemic therapy. Selective sentinel lymph node (SLN) biopsy was developed with the aim of avoiding unnecessary AL in patients without lymph node involvement. Based on the histopathological results of the SLN, the status of the remaining lymph nodes may be predicted with a high sensitivity and diagnostic precision without extirpation. Different studies have demonstrated the safety of this technique, hence its recognition years ago by scientific consensus as the method of choice in early stage breast cancer with no clinical evidence of axillary involvement. One important aspect regarding SLN biopsy is the appearance of false negative results which carry early progression of malignant disease. The scientific data currently available on midterm and long-term follow-up are quite limited, although one randomized study with a 10-year follow-up reported promising results. In 2001 the Unit of Breast Disease of the Hospital Universitario de Salamanca began staging this type of cancer by biopsy of the SLN.

The aim of the present study was to determine our rate of false negatives based on axillary recurrences during a minimum follow-up period of 5 years in 258 consecutive patients with early stage breast cancer who underwent intervention from January 2001 to December 2005 and presented a negative SLN result and in whom AL was not performed.

Material and methods

Inclusion criteria

We included patients with clinically negative (cN0) T1–T2 breast cancer according to clinical examination and ultrasonography but who were classified as pN0 following SLN biopsy and in whom AL was not carried out. Cases with micrometastasis were ruled out in order to exclusively evaluate the pN0. All the patients provided signed informed consent for the SLN protocol approved by our hospital.

Sentinel lymph node biopsy procedure

To perform SLN biopsy the combined technique of radioisotopic with blue staining was used to identify and localize the SLN. Previous lymphoscintigraphy was carried out in all the cases (66% of the cases the same day, 34% the previous day). The injection was peritumoral in palpable lesions, periareolar in non-palpable lesions and on both sides of the surgical scar in cases with previous diagnostic biopsy or excision. The dose of the radiotracer was 74–111MBq of 99mTc-colloid rhodium sulfide (nanocis®). The images were obtained in anterior projection including the thora,

Introduction

Complete axillary lymph node dissection or axillary lymphadectomy (AL) is considered the standard technique in the management of early stage breast cancer to obtain appropriate staging and design adjuvant systemic therapy. Selective sentinel lymph node (SLN) biopsy was developed with the aim of avoiding unnecessary AL in patients without lymph node involvement. Based on the histopathological results of the SLN, the status of the remaining lymph nodes may be predicted with a high sensitivity and diagnostic precision without extirpation. Different studies have demonstrated the safety of this technique, hence its recognition years ago by scientific consensus as the method of choice in early stage breast cancer with no clinical evidence of axillary involvement. One important aspect regarding SLN biopsy is the appearance of false negative results which carry early progression of malignant disease. The scientific data currently available on midterm and long-term follow-up are quite limited, although one randomized study with a 10-year follow-up reported promising results. In 2001 the Unit of Breast Disease of the Hospital Universitario de Salamanca began staging this type of cancer by biopsy of the SLN.

The aim of the present study was to determine our rate of false negatives based on axillary recurrences during a minimum follow-up period of 5 years in 258 consecutive patients with early stage breast cancer who underwent intervention from January 2001 to December 2005 and presented a negative SLN result and in whom AL was not performed.

Material and methods

Inclusion criteria

We included patients with clinically negative (cN0) T1–T2 breast cancer according to clinical examination and ultrasonography but who were classified as pN0 following SLN biopsy and in whom AL was not carried out. Cases with micrometastasis were ruled out in order to exclusively evaluate the pN0. All the patients provided signed informed consent for the SLN protocol approved by our hospital.

Sentinel lymph node biopsy procedure

To perform SLN biopsy the combined technique of radioisotopic with blue staining was used to identify and localize the SLN. Previous lymphoscintigraphy was carried out in all the cases (66% of the cases the same day, 34% the previous day). The injection was peritumoral in palpable lesions, periareolar in non-palpable lesions and on both sides of the surgical scar in cases with previous diagnostic biopsy or excision. The dose of the radiotracer was 74–111MBq of 99mTc-colloid rhodium sulfide (nanocis®). The images were obtained in anterior projection including the thorax, and lateral projection so that on visualization in the axilla, the internal mammary chain or both territories, the projection of the SLN was marked on the skin. After induction of anesthesia in the operating room, isosulfan blue (Lymphazurin®) was injected into the subareolar region approximately 20 min prior to the surgical incision. The most commonly used surgical approach was transversal incision of the axilla, although in the case of tumors located in the superoexternal quadrant of the breast or in cases with mastectomy without immediate reconstruction, the breast incision itself was used to carry out the excision of the SLN. The localization of the SLN was possible either by presenting significant radioactivity detected by the portable gamma probe and/or blue staining. In addition, a SLN was considered as any other suspicious lymph node after digital inspection of the axilla. In the case of multiple points of uptake in the lymphoscintigraphy, the use of blue staining was used as a reference, with extirpation of less than 3 SLN.

Histopathological analysis of the SLN was then performed after fixation in paraffin, sectioned and stained with hematoxylin and eosin and also by performing immunohistochemistry studies which were deferred in most of the cases. The SLN was classified as negative (those included in this study), isolated tumor cells (<0.2 mm), micrometastasis (>0.2 mm and <2 mm), and macrometastasis (>2 mm). At present, the analyses are performed with the OSNA amplification method which provides definitive intraoperative results.

Follow-up

The patients were followed at 15 days after surgery, every 3 months during the first 2 years, every 6 months in the 3 following years and annually after 5 years. Each consultation involved physical examination as well as the corresponding biochemical analysis with tumor markers and imaging techniques according to the follow-up protocol for breast cancer. False negative results of the technique were considered as those presenting axillary recurrence during the follow-up period until December 31, 2010. Likewise, local recurrence in the intervened breast was reported as was the presence of distant metastasis with the aim of evaluating the disease-free survival of the patients. The tumors were classified according to the TNM 2010 classification of the American Joint Committee on Cancer.

Statistical analysis was performed using the SPSS 15.0 program for Windows. A p value less than 0.05 was considered as significant. The analysis of survival was performed using Kaplan Meier curves and log rank results.

Results

The clinical and pathological characteristics of the 258 consecutive patients included and classified as pN0 are shown in Table 1. The most frequent histological type was infiltrating ductal carcinoma (80.6%), with multifocal tumors in 13 patients. The localization was in the superoexternal quadrant in 17.2%, being superointernal in 17.2%, inferointernal in 13.6%, inferoexternal in 13.2% and retroareolar in 8.4%. The lesions were palpable in 69.4%, with a mean final tumor diameter of 23.3 mm (range 0.5–30 mm). Eighty-five cases had undergone previous excision of the breast tumor. The surgical approach was conservative in 212 cases (82%) and immediate reconstruction of the breast was performed in 44% of those who underwent mastectomy. The mean in-hospital stay was 2.69 days.

Localization and sentinel lymph node results

At least one SLN was localized in the axilla of all the patients and thus, the best results related to detection were observed on combining the isotopic technique with blue staining, with improvement in the results if performed separately (isotopic 98.1%, blue staining 91.9%, p = 0.000). A mean number of 1.68 SLN were obtained per patient (range: 1–3) with no differences between the groups with or without previous surgery of the tumor (Kruskal–Wallis, p = 0.794). Internal mammary drainage was observed in 15.5% of the cases on lymphoscintigraphy. Taking the technical complexity of the surgical approach of these lymph nodes into account, in situ tumors and those in which the gamma probe detector was not able to specifically discriminate the intercostal space on the skin were excluded since hybrid SPECT-CT was not available at that time. In total SLN were extirpated in 10 patients, all with negative results for
Clinical and pathological characteristics of 258 patients pN0.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of breast cancer</td>
<td>45 (17.4%)</td>
<td>16 (6.2%)</td>
</tr>
<tr>
<td>Palpable lesion</td>
<td>179 (69.4%)</td>
<td>79 (30.6%)</td>
</tr>
<tr>
<td>Previous tumor surgery</td>
<td>85 (33.3%)</td>
<td></td>
</tr>
</tbody>
</table>

| Type of breast surgery | | |
|------------------------|-----------------|
| Tumorectomy            | 212 (82.1%)     |
| Mastectomy + reconstruction | 20 (7.8%) |
| Mastectomy             | 26 (10.1%)      |

<table>
<thead>
<tr>
<th>Isotope injection</th>
<th>Surgery day</th>
<th>Previous day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>169</td>
<td>89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Invasive ductal</th>
<th>In situ</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>211 (80.6%)</td>
<td>23 (8.9%)</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Receptors study</th>
<th>Estrogen+</th>
<th>Progestrone+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75.1%</td>
<td>72.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Tis</th>
<th>Ta</th>
<th>Tb</th>
<th>T1c</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>9</td>
<td>47</td>
<td>105</td>
<td>74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final stage</th>
<th>0</th>
<th>IA</th>
<th>IIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>161</td>
<td>74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events occurring during follow-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
</tr>
<tr>
<td>Breast cancer deaths</td>
</tr>
<tr>
<td>Ipsilateral recurrence of breast cancer</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
</tr>
<tr>
<td>Distant metastasis</td>
</tr>
<tr>
<td>Mammary recurrence</td>
</tr>
</tbody>
</table>

Events occurring during follow-up. Analysis of survival

At 5 years the global survival was 88.4% (228/258), with a cancer-related survival of 93% (240/258) and a disease-free survival of 89.1% (230/258). No differences were observed in survival between the presence of a false negative by axillary recurrence and the group without oncological events. The appearance of cancer in the contralateral breast had no effect on patient survival. However, the appearance of local breast recurrence or distant metastasis did imply a reduction in survival compared with the patients without events (Log rank, p = 0.000 Kaplan–Meier curves; Fig. 1).

Follow-up, events registered and analysis of survival

In this study the final point of follow-up was considered on December 31, 2010. Analysis of survival and events was achieved in all the 258 cases. The mean follow-up in the patients who did not die was 81 months, with a minimum time of 5 years (range: 60–119 months). The events registered were: 3 axillary recurrences representing 1.1% of the 258 cases with negative SLN, 12 local recurrences in the affected breast (4.7%), distant metastasis (bone, liver, brain, and lung) in 16 (6.2%), and cancer-related death in 16 (6.2%). Involvement of the contralateral breast was also reported in 6 cases (2.3%) (Table 2). The 3 axillary recurrences or false negative results detected were found in young women of 35, 37 and 42 years of age with removal of 3, 2, and 3 axillary SLN, respectively. All were detected with both the gamma probe and blue staining and histologically corresponded to infiltrating ductal carcinomas, two of which were multifocal and were treated with mastectomy followed by breast reconstruction. The time from surgery until recurrence was of 10, 11 and 29 months, respectively performing AL in all of the cases. The youngest patient with longer time-related axillary recurrence developed bone metastasis at 4 years after surgery, while the other two patients are in complete remission. Local breast recurrence was observed in 12 patients (2 in the mastectomy bed) who underwent adjuvant treatment with CT. The time from surgery until recurrence was a mean of 3.31 months (range: 9 months – 5.8 years). Of these patients, 6 died due to metastatic disease progression, and the others remain in complete remission. Distant metastasis developed in 16 cases (6.2%), most with bone involvement in the first case, followed by liver, lung and brain metastasis. The mean time after surgery was 2.45 years, with 12 having died at the end of the follow-up of this study.

Analysis of survival

At 5 years the global survival was 88.4% (228/258), with a cancer-related survival of 93% (240/258) and a disease-free survival of 89.1% (230/258). No differences were observed in survival between the presence of a false negative by axillary recurrence and the group without oncological events. The appearance of cancer in the contralateral breast had no effect on patient survival. However, the appearance of local breast recurrence or distant metastasis did imply a reduction in survival compared with the patients without events (Log rank, p = 0.000 Kaplan–Meier curves; Fig. 1).

Fig. 1. Survival of the 258 patients pN0.
Discussion

There is currently great interest in the development of SLN biopsy as an alternative to axillary lymph node dissection. The high index of detection with the techniques available and the high percentage of concordance between the SLN and the non SLN both indicates that it is now feasible to replace AL in the surgical management of breast cancer, thereby avoiding the complications of the latter approach.6,7 The indications for SLN biopsy have extended from T1–T2 tumors <3 cm to larger tumors,8 tumors treated with previous CT9 or even patients who have undergone previous surgery for breast tumor.10

After more than 10 years of experience in the application of this technique in the Unit of Breast Disease of the Hospital Universitario de Salamanca in more than 1200 patients, we believed it was a good time to evaluate the rate of false negative results over a minimum follow-up of 5 years to analyze the safety and precision of this technique. Our group, similar to many others,11,12 prefers the combined radioisotopic technique with blue staining due to the improvement in the percentage of overall detection even, as reported previously, in patients who have undergone primary tumor resection.13 Our percentage of false negative results after a mean follow-up of 6.8 years was of 1.1%, being found in 3 out of the 258 patients classified as pN0 with a view to staging of the cancer. This percentage has fallen from the 3.2% obtained in the validation phase of the technique and is similar to what has been described by other groups with axillary recurrence ratios between 0 and 1.4%,14–18 with mean follow-up times between 3 and 5 years. Although this relationship may be raised, several authors have reported that more than 75% of the cases occur in the first 3 years after surgery.19 It is of note that the presence of axillary recurrence did not influence patient survival. The presence of local recurrence in the same breast was also evaluated and was found to take place in 4.7%, despite having received radiotherapy in 11 out of the 12 cases detected and in the contralateral breast (2.3%). These results are similar to those recently published by the group of Giuliano AE.20 Moreover, although recent publications21,22 have suggested that the tumor grade is the most important factor implicated in local recurrence, within the limitation of including only pN0 patients, we did not find a statistical relationship between the characteristics of the patient, tumor state (receptors, tumor grade, HER2 expression) or the adjuvant treatment received and this event. The appearance of local recurrence, which carries a high probability of distant dissemination, and the presence of distant metastasis led to a significant reduction in survival, despite the adjuvant therapies implemented (surgery and CT). Our data on overall oncologic survival of 93% and disease-free survival of 89.1% are similar to those recently published in the randomized phase 3 NSABP B–32 trial (91.8% and 82.4%, respectively).23

Conclusions

The risk of developing axillary recurrence after obtaining negative SLN without complete dissection of the axilla is sufficiently low to consider this procedure as the best in axillary staging in early stage breast cancer. This staging technique achieves adequate local disease control without diminishing patient survival and avoids the secondary effects derived from more invasive surgery.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We are very grateful to all the technical and nursing personnel of the Departments of Nuclear Medicine, General Surgery and Anatomy Pathology of the Hospital Universitario de Salamanca.

References

