

ORIGINAL ARTICLE

# Sentinel Node Biopsy as a Prognostic Factor in Cutaneous Melanoma

J.A. Avilés-Izquierdo and P. Lázaro-Ochaita

Servicio de Dermatología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

**Abstract** *Background:* The aim of sentinel node biopsy (SNB) is to identify subclinical lymph node metastases using a procedure with minimal morbidity, establish more accurate staging in patients with melanoma, determine prognosis, and choose the most suitable treatment in each patient.

*Objectives:* To analyze the outcomes of SNB in patients with cutaneous melanoma, and the impact of this procedure on survival.

*Material and methods.* Information was gathered retrospectively on all patients in whom this procedure was performed at Hospital General Universitario Gregorio Marañón, Madrid, Spain, over an 11-year period (1997-2007). Descriptive epidemiological analysis of the variables and survival analysis were performed.

*Results.* Sentinel node invasion by melanoma was present in 42 of 238 patients (17.6 %). Tumor thickness and nodular melanomas were associated with the presence of lymph node micrometastases. There were no differences in overall survival, but disease-free survival was significantly lower in patients with a positive SNB, who also had a higher melanoma-related mortality.

*Conclusions.* Detection of lymph node micrometastases by sentinel node biopsy is a marker of tumor aggressiveness and an important prognostic factor in melanoma patients. Information from SNB permits better staging and determines the diagnostic and therapeutic approach in these patients.

**Key words:** melanoma, sentinel node biopsy, epidemiology, survival.

## BIOPSIA DEL GANGLIO CENTINELA COMO FACTOR PRONÓSTICO EN EL MELANOMA CUTÁNEO

**Resumen.** *Introducción.* La biopsia del ganglio centinela (BGC) persigue la identificación de metástasis ganglionares subclínicas con una morbilidad mínima, una estadificación más precisa de los pacientes con melanoma, estimar el pronóstico de estos pacientes y adoptar el tratamiento más adecuado en cada caso.

*Objetivos.* Analizar los resultados obtenidos con esta técnica en pacientes con melanoma cutáneo y el impacto de la misma en su supervivencia.

*Material y métodos.* Se obtuvieron de forma retrospectiva los datos referentes a todos los pacientes a los que se les realizó esta técnica en el Hospital General Universitario Gregorio Marañón de Madrid durante 11 años (1997-2007). Se realizó un estudio epidemiológico descriptivo y un estudio analítico del impacto en la supervivencia.

*Resultados.* En 42 de 238 casos (17,6 %) se encontró afectación del ganglio centinela por melanoma. El espesor tumoral y el tipo histológico nodular se asociaron a la presencia de micrometástasis ganglionares. Aunque el resultado del ganglio centinela no se asoció con una mayor supervivencia global, el tiempo libre de enfermedad fue significativamente inferior en los pacientes con ganglio centinela positivo, que además presentaron una mayor tasa de mortalidad por melanoma.

*Conclusiones.* La detección de micrometástasis ganglionares gracias a la BGC supone un marcador de agresividad y un importante factor pronóstico en los pacientes con melanoma. La información que nos aporta esta técnica nos permite una mejor estadificación, determinando la actitud diagnóstica y terapéutica a seguir en estos pacientes.

ta esta técnica nos permite una mejor estadificación, determinando la actitud diagnóstica y terapéutica a seguir en estos pacientes.

**Palabras clave:** melanoma, ganglio centinela, epidemiología, supervivencia.

Correspondence:  
José Antonio Avilés Izquierdo  
Servicio de Dermatología  
Hospital General Universitario Gregorio Marañón  
C/ Dr. Esquerdo, 46  
28007 Madrid, Spain  
dermaviles@yahoo.es

## Introduction

Sentinel node biopsy (SNB) procedures are performed in cases of cutaneous melanoma on the theory that this tumor spreads preferentially via the lymphatic system, making regional lymph nodes the most common initial site of metastasis. In most cases, metastasis is limited to the first node to receive lymphatic drainage from the tumor. This sentinel node, it is assumed, will be the place to look in order to detect early signs of lymphatic metastasis. Thus, the absence of metastasis in the sentinel node practically rules out involvement further along the lymphatic chain,<sup>1</sup> rendering lymphadenectomy unnecessary.<sup>2</sup>

Although ultrasound imaging is a highly sensitive noninvasive diagnostic technique for the early diagnosis of metastasis in melanoma, micrometastases cannot be detected by this method.<sup>3</sup> Positron emission tomography is similarly limited.

SNB is a technique with minimal morbidity that is performed in an attempt to identify subclinical metastasis, facilitating more accurate staging, appropriate treatment, and assessment of prognosis in melanoma.<sup>4</sup>

## Objectives

SNB has been part of the protocol implemented by the melanoma team of Hospital General Universitario Gregorio Marañón since 1997. Members of this multidisciplinary team come from the dermatology, pathology, general surgery, medical oncology, radiation oncology, anesthesiology, and nuclear medicine departments.

Our aim in this study was to present the results of 11 years' experience (1997-2007), compiling descriptive statistics and reflecting on the impact SNB has had on survival and its usefulness as a prognostic factor. We have also considered the influence of several variables on the results of SNB.

## Material and Methods

Data were collected on all patients with a diagnosis of cutaneous melanoma based on histopathologic findings and in whom SNB was performed during the study period between January 1, 1997 and December 31, 2007.

The criteria used to select patients for this procedure have been disputed.<sup>3</sup> Although the key indication for SNB is a tumor thickness of 1 mm or more, a considerable percentage (6%) of patients with tumors of less depth have been shown to have subclinical metastases when SNB has been performed.<sup>4</sup> Consequently, in addition to performing SNB in patients with melanomas that were

1 mm thick or more and with no signs of metastatic disease on physical examination, we also included patients with thinner tumors on an individual basis if there were histologic signs of ulceration or regression, or Clark level IV or V classification.

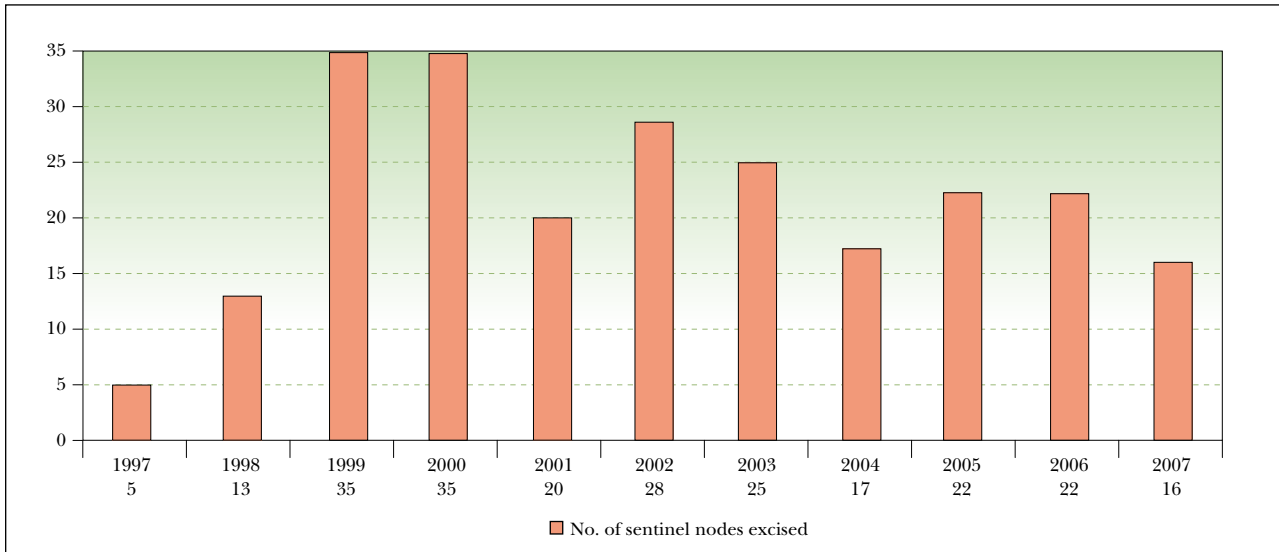
## SNB Technique

Patients admitted for interventions to increase surgical margins or fully excise the tumor also underwent SNB during the procedure. One day before surgery, lymphatic drainage was assessed by isotope lymphoscintigraphy (as an inpatient procedure). A variable dose (20-30 MBq) of technetium-99m nanocolloid was injected intradermally into the tumor or the skin around the excision biopsy scar. High resolution scintigraphy was performed between 1 and 2 hours after injection of the marker to record the distribution of the radioisotope. The sentinel node was considered to be located at the first point of persistent accumulation. Indelible ink was used to mark reference points on the skin on 2 planes. Depending on the number of lymphatic pathways draining the tumor, more than a single sentinel node might be identified.

During the first few years SNB was performed, a methylene blue solution was used to stain the sentinel node before the procedure. However, the development of radioactive nanocolloids introduced several technical advantages, such as identification of the sentinel node without the need to visualize the methylene blue stain and also the benefit of intraoperative guidance from data picked up by the gamma radiation probe (Navigator, Tyco Health Care RMD, Watertown, Massachusetts, USA). The probe also identifies a second or third sentinel node more readily than the methylene blue method does. An additional drawback to using the stain is the permanent tattooing left on the skin of patients after injection. Nonetheless, both methods were used for SNB in some patients in order to reduce the rate of false positives.

General or regional anesthesia was provided, after which the sentinel node was approached, using the gamma probe for guidance. Excised nodes with a radiation count 10-fold higher than that of the surgical field were considered sentinel nodes.

Sentinel nodes were fixed in 5% formaldehyde solution and then paraffin embedded for routine histologic examination with hematoxylin-eosin stain and immunohistochemical analysis using S-100, human melanoma antibody-45, and Melan-A. The previously excised nodes were sectioned along the long axis in at least 4 portions and fixed in paraffin, after which 5- $\mu$ m slices were prepared.



**Figure 1.** Number of sentinel node biopsies (bars) performed each year in Hospital General Universitario Gregorio Marañón.

### Statistical Analysis

Descriptive statistics for SNB variables were compiled and their associations with epidemiologic characteristics (age, sex, age at diagnosis), clinical and histologic characteristics (location, tumor thickness, ulceration, histologic type), and clinical course (vital status, survival, metastasis, etc) were studied. Values of *P* less than .05 were considered significant.

The Kaplan-Meier method was used to study the impact of SNB findings on survival. Univariate and multivariate analyses were also performed using the Cox proportional hazards model.

**Table 1.** Number of Sentinel Lymph Nodes Analyzed per Patient

No. of Sentinel Nodes	Frequency	Percentage
1	121	47.5
2	69	29.0
3	22	9.2
4	12	5.0
5	5	2.1
6	4	1.7
7	3	1.3
8	3	1.3
Not located	7	2.9
Total	238	100

The descriptive and analytical studies of the data were performed with SPSS software, version 12.0 (SPSS Inc, Chicago, Illinois, USA).

### Results

#### Descriptive Statistics

SNB was performed on 238 patients during the study period. Figure 1 shows the annual distribution.

The patients' mean age was 53.54 years, and the ratio of men to women was 1.07:1. The melanoma tumor was less than 1 mm thick in 32 cases (13.4%). In 60 (25.2%) the presence of ulceration was detected on histologic examination.

The distribution of cases according to the number of nodes analyzed is shown in Table 1. A single sentinel node was identified most often (in 47.5% of the cases). In 7 cases (2.9%), no sentinel node could be found. In 88.7%, sentinel nodes were located in only a single lymphatic chain. In 42 patients (17.6%) the presence of neoplastic cells was noted during conventional histologic examination or immunochemical analysis of the excised node or nodes. Table 2 shows the distribution of patients according to the number of sentinel nodes affected by melanoma tumor metastasis.

Regional lymphadenectomy was performed in 40 of the 42 patients with positive SNB findings. In only 11 cases (27.9%) were lymph nodes found to be colonized by melanoma cells.

Among the 189 patients with negative SNB findings, 13 (6.9%) later presented metastasis to local and regional lymph nodes.

### Predictors of SNB Findings

Tumor thickness according to T- stage was significantly associated with the presence of melanoma in the sentinel node ( $P=.02$ ) (Table 3).

Regarding the relevance of the histologic typing of the primary melanoma, we found that 19 of the 75 nodular type melanomas (25%) were associated with a positive SNB finding, whereas disease had spread to a sentinel node in only 15 of 113 (13.3%) patients with superficial melanomas ( $P=.04$ ).

No other epidemiologic, clinical, or histologic factors analyzed (age, sex, location, ulceration, etc) were associated with SNB findings.

### Survival Analysis

Survival at the end of the study differed considerably according to SNB result (Table 4). Ninety percent of patients with negative SNBs were alive at the end of the study period; only 9.5% of the patients had died due to the melanoma. In contrast, melanoma-related mortality among patients with positive SNBs was 26%. The difference, however, was not statistically significant ( $P=.07$ ).

The number of sentinel lymph nodes analyzed in a patient was not a significant predictor of overall survival, although a nonsignificant trend toward an association between that variable and shorter survival was observed.

Cox univariate regression analysis of risk in relation to overall survival showed that mortality was 4-fold higher among patients with positive SNB findings ( $P<.05$ ). However, SNB positivity did not emerge as an independent predictor in the multivariate analysis.

Kaplan-Meier survival analysis revealed no statistically significant differences according to SNB result. Figure 2 shows that overall survival was slightly lower among patients with positive sentinel nodes, especially in the first 5 years after diagnosis, but this difference disappeared

**Table 2.** Total Number of Positive Sentinel Nodes per Patient

No. of Positive Nodes	Frequency	Percentage
0	192	80.7
1	32	13.4
2	11	4.6
3	2	0.8
6	1	0.4
	238	100

after that point. Two aspects of the study must be borne in mind when interpreting the survival curves:

1. Patients with negative SNBs were fewer than those with positive findings, and this means that there was a deceptively lower proportion of patients with negative SNBs surviving at the end of the study period.
2. A portion of the patients with negative SNBs developed distant metastasis at a much later time, probably via the blood stream, and this will also have affected the long-term survival rate in this group.

The period of disease-free survival after treatment was, however, significantly longer for patients with negative SNBs, at a mean (SD) of 92 (2) months versus 58 (10) months for patients with positive SNBs ( $P<.001$ ) (Figure 3).

### Discussion

The spread of cutaneous melanoma to lymph nodes is one of the most important prognostic factors in patients

**Table 3.** Results of SNB, According to Thickness of the Melanoma in Millimeters<sup>a</sup>

SNB Result	T Stage				Total
	T1	T2	T3	T4	
Negative	32 (100 %)	75 (84.3 %)	60 (77 %)	22 (70 %)	189 (81.9 %)
Positive	0	14 (15.7 %)	18 (23 %)	10 (30 %)	42 (18.1 %)
Total	32 (13.8%)	89 (38.5%)	78 (33.7%)	32 (13.8%)	231 (100 %)

Abbreviation: SNB, sentinel node biopsy.

<sup>a</sup> Seven cases in which the sentinel node could not be identified were excluded from this table.

**Table 4.** Vital Status at the End of the Study, According to SNB Finding<sup>a</sup>

Vital Status	SNB-	SNB+	Total
Alive	171 (90.5 %)	31 (74 %)	189 (81.8 %)
Dead	18 (9.5 %)	11 (26 %)	42 (18.2 %)
Total	189	42	231

Abbreviation: SNB, sentinel node biopsy.

<sup>a</sup> Seven cases in which the sentinel node could not be identified were excluded from this table.

with this tumor. In fact, the 5-year survival rate has been reported to be 40% lower in patients with lymph node metastases.<sup>5</sup> The absence of tumor cells in the sentinel node rules out the presence of metastasis in other regional nodes, barring detection error.<sup>5-8</sup> The practice of performing SNB to stage tumors is being adopted more widely, not only in the context of other types of skin tumors but also in the staging of gynecologic, digestive, or lung tumors.<sup>9-14</sup>

At least 4 major reasons for performing SNB have been proposed, as follows:

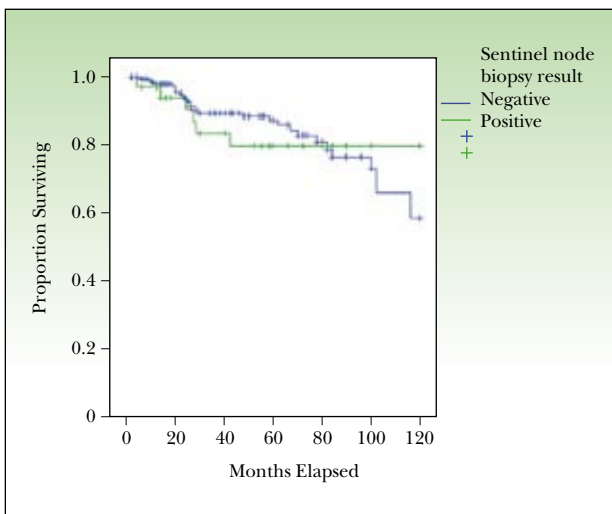
1. To identify subclinical lymph node involvement with minimal morbidity. The information SNB provides facilitates proper staging and helps the clinician decide on a diagnostic and therapeutic approach.
2. To identify patients who would benefit from therapeutic lymphadenectomy.
3. To identify candidates for concomitant treatment with interferon  $\alpha$ .

4. To classify patients in comparatively homogeneous subgroups for prognosis when performing clinical trials.

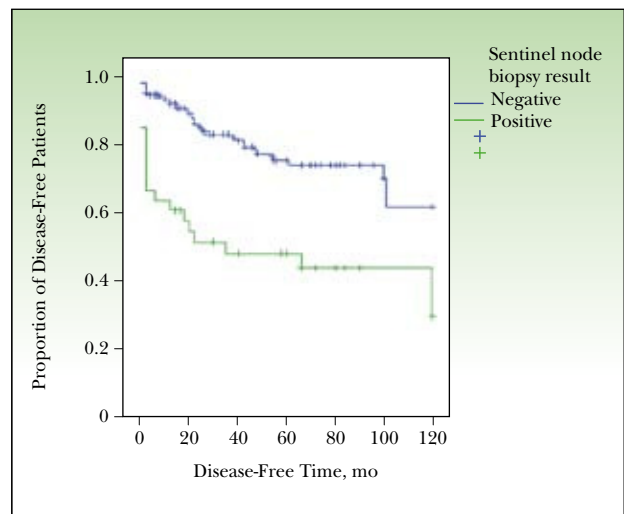
Nonetheless, several authors advise against performing SNB because of the unpredictability of metastasis in melanoma.<sup>15</sup> SNB can identify lymphatic metastasis early but not the behavior of cells transported through the blood stream, which would quickly bypass the lymphatic system and remain undetected by this procedure, meaning that a negative SNB does not imply the lack of distant metastasis.<sup>15,16</sup> The number of deaths due to distant metastasis would therefore be unaffected by performance of SNB. Authors who are critical of the practice of SNB point out that a positive finding would be a marker of tumor aggressiveness, not a reliable marker of disseminated disease.

Still, information provided by SNB appears to be of unquestioned importance in weighing the likelihood of dissemination.<sup>16,17</sup> If the findings are positive, we can be certain the tumor has already spread through the lymphatic vessels and we can guess it has probably spread through the blood stream in some patients.

Furthermore, the rate of complications of this technique is practically nil, whereas selective lymphadenectomy-associated morbidity is high at up to 39%<sup>18</sup> and complications are often permanent, as in chronic lymphedema.<sup>19</sup> The greater precision of SNB in comparison with lymphadenectomy for locating the sentinel node in drainage pathways that might be anomalous or inconsistent, such as occurs when tumors are on the trunk, head or neck, also facilitates the early diagnosis of micrometastasis, with the added benefit



**Figure 2.** Overall survival according to sentinel node biopsy findings.



**Figure 3.** Disease-free survival according to sentinel node biopsy findings.

of low morbidity.<sup>20</sup> The routine use of this approach, however, and the indications for applying it, continue to be a subject of debate.<sup>21-24</sup>

The total percentage of patients with micrometastases to lymph nodes in our study was low (17.6%), similar to the rates reported by other authors.<sup>3,16,25</sup> None of the variables studied for possible correlation with the results of SNB, other than tumor thickness and histologic type, proved significantly related to a higher rate of micrometastasis.

Recent studies have reported inconsistent results when evaluating the role of SNB in predicting overall survival in melanoma. While some authors have observed higher survival rates in patients with negative SNB findings,<sup>3,25</sup> others have detected no significant differences.<sup>15,16</sup> All, however, agree on the importance of the presence of lymph node micrometastasis in pointing to a poor prognosis.

The results we report are consistent with both points of view on SNB. Mortality was initially significantly higher in our patients with positive sentinel nodes, but the analysis of overall long-term survival did not demonstrate a difference between the 2 groups. The period of disease-free survival, on the other hand, was significantly shorter in patients with positive sentinel nodes.

In conclusion, the detection of lymph node micrometastases by means of SNB is a sign of tumor aggressiveness and a prognostic marker in patients with melanoma. The information SNB provides can facilitate more accurate staging and provide guidance as to the diagnostic and therapeutic approach to take in the care of these patients.

#### Conflicts of Interest

The authors declare no conflicts of interest.

## References

- Gershenwald JE, Thompson W, Mansfield PF, Lee JE, Colome MI, Tseng CH, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol.* 1999;17:976-83.
- Jansen L, Nieweg OE, Kapteijn AE, Valdés Olmos RA, Muller SH, Hoefnagel CA, et al. Reliability of lymphoscintigraphy in indicating the number of sentinel nodes in melanoma patients. *Ann Surg Oncol.* 2000;7:624-30.
- Cuéllar FA, Vilalta A, Rull R, Vidal-Sicart S, Palou J, Ventura PJ, et al. Small cell melanoma and ulceration as predictors of positive sentinel lymph node in malignant melanoma patients. *Melanoma Res.* 2004;14:277-82.
- Bedrosian I, Faries MB, Guerry D 4th, Elenitsas R, Schuchter L, Mick R, et al. Incidence of sentinel node metastasis in patients with thin primary melanoma (< or = 1 mm) with vertical growth phase. *Ann Surg Oncol.* 2000;7:262-7.
- Morton DL, Davtyan DG, Wanek LA, Foshag LJ, Cochran AJ. Multivariate analysis of the relationship between survival and the microstage of primary melanoma by Clark level and Breslow thickness. *Cancer.* 1993;71:3737-43.
- Essner R, Cochran AJ. Sentinel node biopsy: not only a staging tool? *Recent Results Cancer Res.* 2002;160:133-48.
- Belli F, Lenisa L, Clemente C, Tragni G, Mascheroni L, Gallino G, et al. Sentinel node biopsy and selective dissection for melanoma nodal metastases. *Tumori.* 1998;84:24-8.
- Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. *WHO Melanoma Programme. Lancet.* 1998;351:793-6.
- Kelley MC, Hansen N, McMasters KM. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Am J Surg.* 2004;188:49-61.
- Werner JA, Dünne AA, Folz BJ, Moll R, Behr T. Value of sentinel lymphadenectomy in head and neck cancer. *Ann Surg Oncol.* 2004;11(3 Suppl):267S-70S.
- Micali G, Nasca MR, Innocenzi D, Schwartz RA. Invasive penile carcinoma: a review. *Dermatol Surg.* 2004;30:311-20.
- Carlini M, Carboni F, Petric M, Santoro R, Guadagni F, Marandino F, et al. Sentinel node in gastric cancer surgery. *J Exp Clin Cancer Res.* 2002;21:469-73.
- Blumberg D, Ramanathan RK. Treatment of colon and rectal cancer. *J Clin Gastroenterol.* 2002;34:15-26.
- Liptay MJ. Sentinel node mapping in lung cancer. *Ann Surg Oncol.* 2004;11(3 Suppl):271S-4S.
- Perrott RE, Glass LF, Reintgen DS, Fenske NA. Reassessing the role of lymphatic mapping and sentinel lymphadenectomy in the management of cutaneous malignant melanoma. *J Am Acad Dermatol.* 2003;49:567-88; quiz 589-92.
- McMasters KM, Reintgen DS, Ross MI, Wong SL, Gershenwald JE, Krag DN, et al. Sentinel lymph node biopsy for melanoma: how many radioactive nodes should be removed? *Ann Surg Oncol.* 2001;8:192-7.
- Lázaro Ochaita P, Bittini Copano Á, Bueno Marco C, Escat Cortés JL, Lecona Echevarría M, Pérez Santos S. Mapeo linfático y biopsia del ganglio centinela en el melanoma cutáneo. *Actas Dermosifiliogr.* 2001;92:319-33.
- Sim FH, Taylor WF, Pritchard DJ, Soule EH. Lymphadenectomy in the management of stage I malignant melanoma: a prospective randomized study. *Mayo Clin Proc.* 1986;61:697-705.
- Ingvar C, Erichsen C, Jonsson PE. Morbidity following prophylactic and therapeutic lymph node dissection for melanoma—a comparison. *Tumori.* 1984;70:529-33.
- De Wilt JH, Thompson JF, Uren RF, Ka VS, Scolyer RA, McCarthy WH, et al. Correlation between preoperative lympho scintigraphy and metastatic nodal disease sites in 362 patients with cutaneous melanomas of the head and neck. *Ann Surg.* 2004;239:544-52.
- Mangas C, Paradelo C, Rex J, Ferrándiz C. La biopsia del ganglio centinela: su papel diagnóstico y pronóstico en el melanoma maligno. *Actas Derm-Sif.* 2008;99:331-48.
- Bleicher RJ, Essner R, Foshag LJ, Wanek LA, Morton DL. Role of sentinel lymphadenectomy in thin invasive cutaneous melanomas. *J Clin Oncol.* 2003;21:1326-31.
- Medalie NS, Ackerman AB. Sentinel lymph node biopsy has no benefit for patients with primary cutaneous melanoma metastatic to a lymph node: an assertion based on

- comprehensive, critical analysis: part I. *Am J Dermatopathol.* 2003;25:399-417.
24. Pizarro A. ¿Por qué la biopsia del ganglio centinela no aumenta la supervivencia en pacientes con melanoma? *Actas Derm-Sif.* 2008;99:323-30.
25. Nowecki ZI, Rutkowski P, Nasierowska-Guttmejer A, Ruka W. Sentinel lymph node biopsy in melanoma patients with clinically negative regional lymph nodes—one institution's experience. *Melanoma Res.* 2003;13:35-43.