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Sentinel Node in Cutaneous Squamous Cell Carcinoma of the Trunk and Extremities: Experience in a Latin American Reference Center

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Abstract

This paper aims to assess the use of the sentinel node technique in squamous cell carcinoma (SCC) of the trunk and extremities in a Latin American oncology reference center. The descriptive retrospective cohort study included 60 patients diagnosed with SCC of the trunk and extremities, submitted to surgical treatment of the primary tumor and sentinel node biopsy at the breast and soft tissue tumor services of the National Institute of Cancerology (Bogotá, Colombia) over a period of 6 years. The sentinel node was identified in 96.6% (58/60) of the patients. The sentinel node pathology report was negative in 81.7% (49), positive in 15% (9). There were no complications due to the procedure in 85% of the patients. The mean recurrence-free survival time was 8.3 months (CI 95% 5.0 to 11.5 months) in patients with positive sentinel node and 58.6 months (CI 95% 47.8 to 69.3 months) in patients with negative results. Only 4 of 49 patients (8.1%) with negative sentinel node had regional relapse. The study evidenced that the sentinel node technique in patients with high-risk SCC of the trunk and extremities is an adequate staging tool for the lymph node chain, with a low rate of associated complications. This opens an interesting opportunity for prospective cohort studies that can demonstrate statistically significant differences.

Keywords

Skin Neoplasms, Squamous Cell Carcinoma, Sentinel Lymph Node Biopsy

1. Introduction

Squamous cell carcinoma (SCC) is the second most common cutaneous cancer in light skin people after basal cell carcinoma, accounting for 20% of non-melanoma skin cancers [1] [2]. Its incidence has increased in recent years, with 100,000 to 150,000 new cases diagnosed per year in the United States [1], where an estimate of 186,157 to 419,543 new cases of SCC were diagnosed in 2012, of which 5604 to 12,572 developed nodal involvement and 70% of them (nodes positive) died from SCC [3]. In the 2012 Statistical Yearbook of the Colombian National Institute of Cancerology, the SCC corresponded to 16.1% of skin cancer cases [4].

The majority of cases correspond to localized SCC [5] [6]. However, there is a subgroup of patients with high-risk SCC, which is characterized by a more aggressive biological behavior, a higher rate of regional and distant metastases and a greater locoregional recurrence. This group is characterized by tumors with a diameter greater than 2 cm, depth greater than 2 mm, a poor degree of histological differentiation, perineural invasion, and immunosuppression [5] [7] [8] [9]. In this group, metastasis rate reaches 4.5% for tumors with thickness between 2 and 6 mm, and up to 15% in tumors with thickness greater than 6 mm. The prognosis in cases of lymph node metastases is poor, with a 5-year survival in 26% to 34% of patients [10].

The therapeutic approach is determined by the characteristics of the patient and the tumor and by nodal involvement. In patients without adenopathy and with no risk factors, the initial treatment of Squamous cell carcinoma (SCC) includes wide local resection, Mohs surgery, radiation therapy, cryotherapy [11]. In cases of palpable adenopathy, its metastatic involvement must be studied by fine needle aspiration biopsy (FNAB) [12]. If the cytology report is positive, the patient will become a candidate for lymph node dissection. If the report is negative, it is necessary to make a differential diagnosis between a true negative (inflammatory/infectious adenopathy) and a false negative, for which a sentinel node study is recommended [13]. For the specific case of patients with squamous cell carcinoma of the trunk and extremities, unfortunate most of them have super infected and ulcerated tumoral lesions; thus, unlike in the case of melanoma or breast cancer, palpable adenopathies in the axillary and inguinal lymph node chains are very common, and it is very difficult to differentiate between tumoral and inflammatory nodes. For this reason, our clinical service has the following procedures: in the presence of a palpable lymph node, FNAB is always carried out; if the result is positive, the patient undergoes lymph node dissection. If the FNAB result is negative, the patient undergoes sentinel node procedure and the palpable node is always resected, if this is not the sentinel node.

The clinical usefulness of sentinel node biopsy in breast cancer and melanoma has led to its application to other cutaneous malignancies [14]-[21]. Numerous studies have evaluated the usefulness of the sentinel node technique in squamous cell carcinoma of the head and neck and in the vulvar area, with results suggest-

ing that it may be useful in high-risk SCC in order to detect regional lymph node metastatic involvement in patients with non-palpable adenopathies and in those with palpable adenopathies but with negative cytology for malignancy [10] [22]-[27]. The percentage of false negatives by clinical palpation was between 15 and 30% for the detection of lymph node metastases [28].

Unlike patients with SCC of the head and neck and anogenital SCC, in patients with SCC of the trunk and extremities there is no solid scientific evidence available to establish the usefulness of the sentinel node biopsy. The evidence is limited to small case reports, which expose the use of this technique as an extrapolation of the procedure in SCC of the head and neck [29] [30] [31] [32].

Within the breast and soft tissue tumor services of the Colombian National Institute of Cancerology, it has been a practice for 10 years to perform the sentinel node procedure in patients with squamous cell carcinoma of the trunk and extremities with clinically negative lymph node chains and factors previously mentioned as high risk. The objective of this article is to describe the experience in the management of the sentinel node in cutaneous SCC of the trunk and extremities, as well as disease-free survival according to sentinel node positivity in a Latin American reference center.

2. Materials and Methods

A descriptive retrospective cohort study was performed. The cohort included patients with confirmed diagnosis of squamous cell carcinoma of the trunk and extremities, who underwent surgical treatment of the primary lesion and sentinel node biopsy at the breast and soft tissue tumor services of the National Institute of Cancerology (Bogotá, Colombia) during a period of 6 years (between January 1, 2007 and December 30, 2013). Patients with palpable lymph node and FNAB positive, patients with a diagnosis of anogenital squamous cell carcinoma and patients with head and neck SCC were excluded. The study was approved by the ethics committee of the National Institute of Cancerology (Proceedings 021 of 2014).

As a source of information for the selection of patients, the study used pathology and nuclear medicine reports as well as the surgery database of the breast and soft tissue tumor services of the institution. Data were extracted from the digital clinical history by two co-investigators with expertise in soft tissue surgery, and entered in the EpiDataEntryClient v2.0 software. The variables included in this study were age in years completed, sex, history of ulcers, chronic scars, chronic ultraviolet exposure, radiation, among others; tumor location and size, presence of palpable adenopathy, histopathological characteristics of the biopsy, type of surgical treatment performed, state of resection margins, location, number of resected nodes and technique used for the detection of the sentinel node. Postoperative complications 30 days after the initial surgery of the primary tumor and sentinel node biopsy were also described, as well as the histopathological characteristics of the resected specimen and sentinel lymph

nodes, characteristics of the complementary surgical treatment, management of positive margins, use of adjuvant radiotherapy, and location and treatment of recurrence.

A descriptive analysis of the variables was carried out using frequency measures for categorical variables and measures of central tendency according to the distribution of data for quantitative variables. The proportion of patients presenting with recurrence was calculated. The descriptive analysis of disease-free survival was performed according to sentinel node positivity using the Kaplan Meier test, reporting mean survival and confidence interval at 95%. No statistical comparisons were made between survival curves. The event was the diagnosis of recurrence reported in the clinical history. Time to the event was calculated as the difference between recurrence of the disease and surgical procedure of the sentinel node. Patients who did not present the event at the last follow-up recorded in the clinical history were censored. Median time in months and its inter quartile range (IQR) between the onset of the symptoms of the disease and surgery for the treatment of the primary tumor were calculated in patients with positive or negative sentinel nodes. Statistical analysis of the data was performed in the Stata Statistical Software: Release 11 (StataCorp. 2009 College Station, TX: StataCorp LP) licensed for the National Institute of Cancerology.

3. Results

3.1. Clinical Description

During the study period, 60 cases were found that met the eligibility criteria, of which 56% were men. The mean age at diagnosis was 70 years (SD 13.7 years). The median time between the onset of the symptoms of the disease and diagnosis was 15 months (IQR 16 months). Only 4 patients had a history of radiation or surgery in the lymphatic route.

As this was a retrospective study, in a significant number of cases no information was found on some relevant prognostic factors in the biopsy pathology and surgical specimen reports.

Regarding the etiology of the disease, it was de novo in 30.0% of patients, 25.0% had association with ulcers or chronic scars, 21.7% were UV related, 5% had immunosuppression, 3.3% were recurrent, and 15% had no information in the clinical history.

The most frequent location of the tumor was on the hand (33.3%) with predominant right-side laterality (58.3%).

All patients included in the study presented with lesions greater than 2 cm. The median largest tumor diameter was 4 cm (IQR 5 cm).

The most frequent histological type was large cell keratinizing carcinoma (78.3%), followed by acantholytic (3.3%); 8.3% had other histological types; and there was no information in 10% of the cases.

Regarding the degree of differentiation, tumors were well differentiated in 58.3% of the patients and moderately differentiated in 38.3%. 23.3% of the pa-

tients had positive perineural invasion. There was no information on the presence of perineural invasion in 28.3% of the cases. Lymph vascular invasion was positive in 16.7% of the patients, negative in 42%, and data was not found in the remaining clinical records.

In the clinical examination report for admission to service, unilateral palpable adenopathies were reported in 20 patients (33%), all of whom had ulcerated tumors with sizes between 4 cm and 15 cm, and with fetid secretion. All patients were ordered FNAB, but it was performed only in 18 of them. In those 2 patients who did not have FNAB an ultrasonography-guided biopsy was ordered and the radiologist did not find adenopathies with suspicious radiological characteristics to be sent to biopsy (cortical thickening or loss of fatty hilum), thus all underwent sentinel node procedure based on the clinical opinion of the treating surgeon and in all of them the pathology report of the sentinel node was negative. Regarding the 18 patients who underwent FNAB, the result was negative for metastasis in 14 of them (in three of these patients the sentinel node biopsy resulted positive, meaning false negatives for FNAB). In the other 4 patients, FNAcytology results were not suitable for diagnosis; one of these patients had positive sentinel node result. That is, only in four of the 18 patients with palpable nodes who underwent FNAB the sentinel node was positive and in two of them the palpable node was the sentinel node.

Other clinical and histopathological characteristics of the patients included in the study are described in **Table 1**.

3.2. Surgical Treatment and Sentinel Node

The most frequent type of initial surgery was wide local resection (61.7%) followed by minor amputations (13.3%). Major amputations were distributed as follows: partial amputation hand or foot (3.3%), total amputation hand (1.7%), below-knee (10.0%), and above-knee amputation (10.0%).

The pathology report of the surgical specimen of the primary tumor showed that negative margins were obtained in most patients (91.7%). One positive margin was found in 6.7% of cases and two positive margins in 1.6%. Only one patient with positive margins under wentre-excision of margins. Five patients received radiotherapy on the tumor bed with a median radiation dose of 42.5 Gy (IQR 17.5 Gy).

For the identification of the sentinel node, radiocolloid technique was performed in 98% of the patients. In the remaining 2%, the dual technique (radiocolloid and methylene blue) was used. The sentinel node identification rate was 96.6% (58 patients).

One sentinel node was found in 4 patients (44.4%) and two nodes in 5 (55.6%). There were no complications related the sentinel node procedure in 85% (51) of the patients. Only seroma in 5 (8.3%) and superficial operative site infection in 4 (6.7%) patients. The sentinel node pathology report was negative in 81.7% of the patients (49), and positive in 15% [9]. The additional clinical characteristics of the sentinel nodes examined are presented in **Table 2**.

Table 1. Clinical and histopathological characteristics of patients with a diagnosis of cutaneous squamous cell carcinoma of the trunk and extremities who underwent sentinel node biopsy at the National Institute of Cancerology (n = 60).

Characteristic		N	%
Mean age at diagnosis	70 years (SD 13.7)	60	100%
Sex	Men	33	56%
	Woman	27	44%
Comorbidities	Arterial hypertension	25	69.4
	Viral immunodeficiencies	5	8.3
	Diabetes	4	6.7
	Hypothyroidism	4	6.7
	Cancer	3	5
	Burn	2	3.3
	Immunosuppression due to autoimmune disease	2	3.3
	Chronic ulcer	1	1.9
	Transplant-related immunosuppression	1	1.9
	Thrombosis	1	1.9
	None	17	28.3
Etiology	De novo	18	30
	Associated with chronic ulcer or scar	15	25
	Chronic exposure to UV rays	13	21.7
	Associated with immunosuppression	3	5
	Recurrent	2	3.3
	Not reported	9	15
Localization	Hand	20	33.3
	Leg	10	16.7
	Forearm	7	11.7
	Anterior thorax	7	11.7
	Foot	4	6.6
	Gluteus	3	5
	Knee	3	5
	Other	6	10
Breslow	<1 mm	0	0
	1 - 2 mm	2	3.3
	2 - 4 mm	4	6.6
	>4 mm	22	36.6
	Not reported	32	53
Clark	I	10	16.6

Continued

	II	1	1.6
	III	4	6.6
	IV	8	13.3
	V	25	41.6
	Not reported	12	20
Histological type	Large cell keratinizing	47	78.3
	Acantholytic	2	3.3
	Other histological types	5	8.3
	Not reported	6	10
Histological grade	Well differentiated	35	58.3
	Moderately differentiated	23	38.3
	Poorly differentiated	1	1.6
	Not reported	1	1.6
Lymphovascular invasion	Present (+)	10	16.7
	Absent (−)	25	42
	Not reported	25	41.3
Perineural invasion	Present (+)	14	23.3
	Absent (−)	29	48.3
	Not reported	17	28.3
Palpable adenopathy	No	40	66.6
	Yes	20	33.3
FNABPalpable adenopathy	No	2	10
	Yes	18	90
FNAB result (n = 18)	Negative	14	77.7
	Not suitable for diagnosis	4	22.3

All patients with positive sentinel node had tumors greater than 2 cm and a Breslow depth greater than 4 mm (n = 9). Clark's level IV or V was identified in 6 of the 9 patients, lymphovascular invasion in 7 patients, and perineural invasion in 5 of the 9 patients with positive sentinel node. Sentinel node positivity was associated with chronic ulcers and immunosuppression in only 2 patients.

Lymphadenectomy was performed in 5 of the 9 patients with positive sentinel node: axillary dissection in three patients; iliac and obturator dissection in one patient; and inguinal dissection in one patient. The median number of resected nodes during dissection was 21.5 (IQR 8 nodes) and the median number of involved nodes was 0.5 (IQR 4). Pernodal fat involvement was observed in only one patient. The morbidity of the dissection was present in two patients (one with lymphedema and the other with superficial operative site infection).

Adjuvant treatment of the lymph node chain with radiotherapy was performed

Table 2. Clinical characteristics of the sentinel node in patients with cutaneous squamous cell carcinoma of the trunk and extremities at the National Institute of Cancerology (n = 60).

	N	%
Type of surgical procedure for primary tumor		
Wide local resection	37	61.7
Minor amputation (fingers)	8	13.3
Below-knee amputation	6	10
Above-knee amputation	6	10
Partial amputation hand or foot	2	3.3
Total amputation hand	1	1.7
Sentinel node location		
Axilar	37	61.7
Inguinal	23	38.3
Complications		
None	51	85.0
Seroma	5	8.3
Superficial 0SI	4	6.7
Result		
Positive	9	15.0
Negative	49	81.7
No diagnosis	2	3.3
Involved lymph nodes (n = 9)		
One	4	44.4
Two	5	55.6
	Median	IQR
Resected lymph nodes in pathology	2	1
	0.5	4

in four of these patients (median radiation dose of 50 Gy, IQR 10 Gy). One of them was a patient who, despite having a positive sentinel node biopsy, did not accept axillary dissection. The other three patients had massive ganglionic involvement and perinodal fat extension.

3.3. Clinical Results

Mortality from the illness in the evaluated cases was 3% (n = 5), 75% (n = 45) of the patients were alive without disease and 22% (n = 10) were alive with disease.

3.4. Recurrence and Disease-Free Survival

Thirteen patients experienced a relapse of the disease, mostly regional recurrence (61.5%, n = 8), followed by systemic (22.1%, n = 3) and local recurrence (15.4%, n = 2) (Table 3).

Regarding the treatment of recurrences, four patients underwent wide local resection and two patients received radiotherapy to the epitrochlear and axillary lymph nodes; the other patients did not accept any further intervention. Six of the patients with regional recurrence had positive sentinel node.

Of the four patients with positive sentinel node who did not undergo nodal dissection, one received radiotherapy to the lymph node chain, presenting with relapse eight months later. The other three patients did not accept any complementary treatment. Two of those patients who refused additional treatment had early recurrence to distant nodes; one of these patients died from the disease. The third patient was alive and with no evidence of the disease at the last control of the clinical history.

In the descriptive analysis, a median follow-up of 6.8 months was observed (IQR 17.2 months). Mean recurrence-free survival after surgical treatment was 50.4 months (CI 95% 39.5 to 61.4 months). In patients with positive sentinel node, mean recurrence-free survival after surgical treatment was 8.3 months (CI

Table 3. Type of tumor recurrence in patients with squamous cell carcinoma of the trunk and extremities who underwent sentinel node biopsy at the National Institute of Cancerology (n = 13).

	N	%
Local	2	15.4
Regional	8	61.5
Systemic	3	23.1
Lung	2	15.4
Soft tissues	1	7.7
Total	13	100%

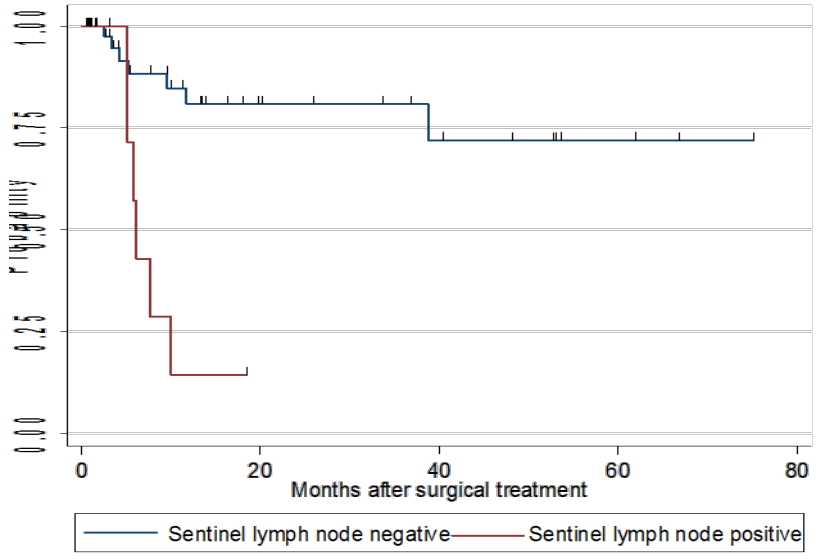

Figure 1. Recurrence-free survival after initial surgical treatment in patients with positive sentinel node (red line) and patients with negative sentinel node (blue line).

95% 5.0 to 11.5 months), and in patients with negative sentinel node it was 58.6 months (CI 95% 47.8 to 69.3 months) (**Figure 1**).

The cumulative probability of 1-year recurrence-free survival in patients with squamous cell carcinoma of the trunk and extremities with positive sentinel node after surgery was 14.3% (n = 8), and in patients with negative sentinel node after surgery it was 80.9% (n = 49).

3.5. Time Intervals and Sentinel Node

In patients with positive sentinel node, the median duration between symptom onset and surgical treatment was 95.5 months (IQR 60.5 months) and median duration between the date of complementary surgery and the diagnosis of recurrence of the disease was 6.5 months (IQR 11.8 months).

In patients with negative sentinel node, the median duration between symptom onset and surgical treatment was 110 months (IQR 76 months) and median duration between surgery and the diagnosis of recurrence was 9, 4 months (IQR 17.3 months).

4. Discussion

In the knowledge of the authors, after an exhaustive literature review, this is the series with the highest number of patients that uses sentinel node biopsy in SCC of the trunk and extremities.

Since the publication of the first report on the use of sentinel lymph node biopsy as a method to evaluate the lymphatic anatomy of the penis and its usefulness as a marker of lymph node metastases [14], this technique has been extrapolated to other types of cancer such as melanoma and breast cancer. In these tumor types, there are important clinical trials such as the NSABP32, ACOZOG Z0011 and ALMANAC studies in breast cancer [33] [34] [35] and MSLT 1 and 2 in melanoma [36], which seek to establish indications, surgical characteristics and the impact of the sentinel node in terms of disease-free survival and overall survival. In contrast, the studies published to date on the sentinel node in squamous cell carcinoma of the trunk and extremities are small series of cases, which are limited to the establishment of scientific guidelines for the use of this technique [30] [31] [32]. The Italian study by Cuccia *et al.* presents the results of a series of 6 patients with a diagnosis of SCC of the trunk and extremities, with tumors greater than 2 cm and non-palpable lymph nodes, who underwent sentinel node biopsy with dual technique, reporting that none of the patients presented with locoregional relapse in a follow-up period of 10 months. The study reported no false-negative results with this technique [31]. Another study with similar design features was carried out by Liu *et al.* It presented the results of a series of 32 patients with sentinel node positivity in 28.1% and low false-positive and false negative rates. They reported no complications associated with the procedure [32]. The Japanese study by Hatta *et al.* reported 14 patients who underwent sentinel node biopsy in the popliteal fossa, with ambiguous findings,

since the pathologies included had very different biological characteristics [30].

Sentinel node biopsy is currently performed in all patients with squamous cell carcinoma of the trunk and extremities with non-palpable lymph nodes or palpable but with negative results in fine needle cytology and with poor prognostic factors such as: size greater than 2 cm, perineural or lymph vascular invasion, Breslow depth greater than 4 mm, Clark's level greater than IV, and association with chronic ulcers or scars. Sentinel node biopsy in cases of squamous cell carcinoma *in situ* is not performed.

As a general rule, the use of the sentinel node technique in pathologies such as melanoma or breast cancer is conditioned by a clinically negative lymph node chain. However, we included in our study 20 patients with palpable adenopathies, equivalent to 33% of the study population, most of them with a negative FNAB report and no association with increased risk for positive sentinel node, which was found in only 3 patients with a negative FNAB report, which could be considered as false-negative results for this intervention. On the other hand, in the rest of the patients with clinically positive lymph node chain, pathology reports compatible with inflammatory nodes were found, which accounts for possible tumor infection. Due to this, we consider that nodal dissection should not be performed in patients with ipsilateral palpable adenopathy without previous cytological study of the same or the sentinel node.

Most of the patients underwent wide local resection with margins of 2 cm; in 98% of them, the sentinel node technique with radiocolloid was used, with a detection rate of 96.6%, which is similar to that reported in the literature. This technique has been used worldwide in melanoma for more than 10 years, with high success rates of localization, and has displaced the use of methylene blue marking alone. The gold standard is the combination of both techniques (radiocolloid and methylene blue) [37] [38].

The probability of sentinel node positivity has been related to the presence of adverse prognostic factors of squamous cell carcinoma, such as tumor size greater than 2 cm, perineural invasion, Breslow index, and Clark level.

The recognized advantages of the sentinel node biopsy include reduction in morbidity resulting from elective lymph node dissection (81%), in the costs of these procedures and in their subsequent complications. Although the surgical mortality of nodal dissections is very low, wound complication rates reported in the literature are close to 40% [38], a percentage similar to that reported in this series.

Regional recurrence after negative sentinel node biopsy is an important indicator of false-negative results. A systematic review published by Ross and Schmults in 2006 report a false-negative rate of 5% [39]. In the present study, we found that 4 of 49 patients (8.1%) with negative sentinel node presented regional recurrence, which is close to that reported in the literature.

5. Conclusions

The demographic data of the study are similar to those already reported in the

literature, in SCC of other locations; the importance of this study, however, lies in the number of patients, since after a broad literature review it is evidenced that our series is the largest worldwide, with regard to sentinel node biopsy in SCC of the trunk and extremities.

The sentinel node technique in patients with high-risk SCC of the trunk and extremities is an adequate staging tool for the lymph node chain, with a low rate of associated complications.

In this cohort, patients with positive sentinel node had a high percentage of regional recurrence and lower 1-year recurrence-free survival rate.

The present work opens an interesting opportunity to carry out prospective cohort studies that can demonstrate statistically significant differences.

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Conflicts and Editorial Independence

The authors of this research state that they have no conflict of interest regarding the purpose of this study.

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