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ORIGINAL ARTICLE
Reconstructive

Prospective Randomized Study on the Use of Sentinel Node Biopsy for High-risk Cutaneous Squamous Cell Carcinomas of the Head and Neck

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Background: The use of sentinel lymph node biopsy (SLNB) for high-risk cutaneous squamous cell carcinoma (CSCC) is not yet clearly documented, especially for the head and neck area, due to its rich and cross-branching lymphatic system. We present the first prospective randomized study on the use of SLNB in high-risk CSCCs of the head and neck.

Methods: Seventy-six patients with high-risk CSCCs of the head and neck were randomly divided into two groups: A (n = 38) and B (n = 38). In group A, SLNB was performed additionally to the excision of squamous cell carcinoma, whereas in group B, only excision of the lesion was performed. The patients were followed up for 5 years postoperatively, and local recurrences, regional metastases (regional lymph nodes), and mortality were documented.

Results: One patient of group A, who never attended any follow-up, was excluded. Both groups had similar characteristics regarding Breslow thickness, perineurial invasion, peripheral limits, differentiation, size, previous incomplete excision, age, sex, education, sun exposure, Fitzpatrick score, previous incomplete excision, previous skin cancer, and smoking. Two patients had a positive sentinel lymph node and were submitted to regional lymphadenectomy. We documented deaths (three in group A and two in group B; $P = 0.674$), local recurrence (seven in group A and six in group B; $P = 0.768$), and regional metastasis (zero in group A and two in group B; $P = 0.159$).

Conclusion: There is no clear benefit on the use of SLNB in high-risk CSCCs of the head and neck regarding metastasis, mortality, or local recurrence control.
(Plast Reconstr Surg Glob Open 2024; 12:e6092; doi: 10.1097/GOX.0000000000006092; Published online 26 August 2024.)

INTRODUCTION

Cutaneous squamous cell carcinomas (CSCCs) are the second most common skin cancer.[1] They metastasize mostly via the lymphatic channels. There are several factors that characterize CSCCs as high risk and, hence, prone to local recurrence or distant metastases, the most important being tumor size more than 2 cm.[2] The American Joint Committee on Cancer mentioned that the presence of two or more of the following high-risk features increases the T stage independently of tumor size: poor differentiation of undifferentiated lesion, primary site on the ear or hair bearing lip, thickness of 2 mm or more, Clark level of at least IV, and perineural invasion.[3,4] Not all CSCCs spread first to a regional lymph node before metastasizing to a distant site. However, an estimated 80% spread first to a single regional lymph node, and consequently, they may spread to the lungs, liver, brain, skin, or bone.[5–7] Thus, the idea of sentinel lymph node biopsy (SLNB) in squamous cell carcinoma seems appealing. Malignant melanoma is also a tumor that may spread to distant sites without affecting regional lymph nodes. In their study, Dika et al[8] mentioned that 16 of 24 patients with negative SLNB had distant metastases in the follow-up. Despite the aforementioned

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Received for publication February 14, 2024; accepted June 26, 2024.

Presented at the ICOPLAST 2022 Congress in Lima, Peru.

All data are available to the journal editor.

DOI: 10.1097/GOX.0000000000006092

Disclosure statements are at the end of this article, following the correspondence information.

fact, SLNB is an established diagnostic tool in the staging of melanoma. However, this is not proven yet for CSCC. Although there are more and more studies examining if there is a place for SLNB in the prognosis and management of CSCC, according to our review of the literature, these are all retrospective. Especially in the head and neck area, there is greater variability and unpredictability of lymphatic drainage compared with other regions.[9,10] Also, the anatomical proximity of the tumor and sentinel lymph node at the head and neck area may pose difficulty in the detection of the sentinel node.[11] Finally, the lymphatic drainage may be altered by previous surgery with local flaps that are commonly used in the head and neck. Due to these extra hindrances, the use of SLNB in high-risk CSCCs of the head and neck needs thorough documentation. We present the first prospective randomized study on the use of SLNB in high-risk CSCCs of the head and neck.

Takeaways

Question: We present the first prospective randomized study to investigate the use of sentinel lymph node biopsy in high-risk cutaneous squamous cell carcinomas of the head and neck.

Findings: There was no statistically significant difference regarding mortality, local remission, or regional metastasis rate.

Meaning: The use of sentinel lymph node biopsy in high-risk cutaneous squamous cell carcinomas of the head and neck according to the results of this study does not provide a benefit to the patients regarding metastasis, mortality, or local recurrence control.

MATERIALS AND METHODS

The study protocol was approved by Papageorgiou General Hospital research committee (no 49/22-1-2013), and it was in accordance with the 1964 Declaration of Helsinki and its later amendments. The full protocol can be assessed in the database of the hospital. All patients were informed that they were going to participate in a study. Seventy-six patients with high-risk CSCCs of the head and neck were randomly divided into two groups: A (n = 38) and B (n = 38). To randomize the patients, we used block randomization.[12] The random allocation sequence and patient enrollment was performed by the principal investigator (G.-A.S.). In group A, SLNB was performed additionally to the excision of squamous cell carcinoma, whereas in group B, only excision of the lesion and reconstruction was performed.

The patients were recruited within 1 year (2013–2014); followed up for 5 years postoperatively (until 2019); and complications, regional metastases, and morbidity were documented. Inclusion criteria were as follows:

1. Tumor diameter greater than 2 cm;
2. Location in the ear or hair bearing lip;
3. Previous incomplete excision;
4. CSCC that appeared in irradiated area; and
5. Immunosuppression.

Exclusion criteria were as follows:

1. Age older than 85 years old;
2. Pregnancy;
3. Palpable nodal disease;
4. Metastatic disease; and
5. Other coexisting neoplastic disease (except basal cell carcinoma) or history of neoplastic disease the last 5 years.

Surgical Technique

Localization of the sentinel node was achieved by injection of radioactive technetium (Tc 99m) at the periphery of the lesion the morning of the procedure. All patients were operated on under general anesthesia. The lesion was excised with 1cm margin and fixed in formalin 10% neutral buffered, and the area was reconstructed. The defects were reconstructed with skin grafts or local flaps. The sentinel node was localized with the aid of a gamma probe (RMD Navigator GRP system with a 12-mm probe; Minogue Medical, Inc.), which was excised and again immersed in formalin 10%. The lesion and sentinel lymph node were sent for histology. The patients were followed up for 5 years postoperatively, and local recurrences, regional metastases (regional lymph nodes), and mortality were documented. Moreover, Breslow thickness, perineurial invasion, peripheral limits, differentiation, size, previous incomplete excision, age, sex, education, sun exposure, Fitzpatrick score, previous skin cancer, and smoking were recorded to document any differences between the two groups.

Lymphoscintigraphy

Lymphoscintigraphy was performed in a GE Healthcare Optima NM/CT 640 system by injecting 1 mCi of technetium Tc 99 m-labeled nanocolloidal human albumin (Lymphoscan, >95% of particles <80 nm in diameter) equally separated in four doses of 0.1 mL intradermally around the periphery of the primary lesion. Dynamic imaging was performed right after the injection (24 frames of 30 s in a 128 × 128 matrix, energy window 15% or 20% centered on the 140-keV photopeak) followed by static planar 5-minute images over the lymph node basin in which the sentinel lymph node is expected. Late 3- to 5-minute static images (1 h after tracer injection) were acquired to identify all relevant sentinel lymph nodes and to mark them on the skin surface. Moreover, single photon emission computed tomography/computed tomography was performed for better anatomic localization (360-degree orbit with 180-degree detector geometry, 128 × 128 matrix size, and 3-degree angle step with 20–25 seconds/frame with iterative reconstruction algorithms).

Pathology

All investigations were performed in the pathology department of Papageorgiou General Hospital. The specimen of the CSCC was fixated in formalin 10%. The size of the lesion was measured, and then it was dissected in parallel 2-mm slices and stained with hematoxylin–eosin stain. The sentinel lymph node was fixed in formalin. Then, it was processed into 2-mm-thick slices and fixated for 24 hours in

Table 1. Comparison of Demographic Variables between Groups

	Without SLNB (n = 38)	With SLNB (n = 37)	*P*
Age, y, mean ± SD*	73.97 ± 11.47	74.08 ± 10.75	0.967
Sex: male/female, n (%)	30 (78.9)/8 (21.1)	33 (89.2)/4 (10.8)	0.346
Education: primary/secondary/tertiary, n (%)	27 (71.1)/7 (18.4)/4 (10.5)	29 (78.4)/6 (16.2)/2 (5.4)	0.670
Sun exposure: low/high, n (%)	9 (23.7)/29 (76.3)	6 (16.2)/31 (83.8)	0.565
Fitzpatrick: I/II/III/IV, n (%)	2 (5.3)/14 (36.8)/18 (47.4)/4 (10.5)	2 (5.4)/13 (35.1)/19 (51.4)/3 (8.1)	0.979
Sun protection: low/medium/high, n (%)	28 (73.7)/9 (23.7)/1 (2.6)	29 (78.4)/7 (18.9)/1 (2.7)	0.881
Previous incomplete surgical excision: no/yes, n (%)	28 (73.7)/10 (26.3)	24 (64.9)/13 (35.3)	0.460
Smoking: no/yes, n (%)	20 (52.6)/18 (47.4)	22 (59.5)/15 (40.5)	0.644

There is not statistically significant difference of demographic variables between compared groups ($P > 0.05$).
*Independent samples *t* test.

Table 2. Comparison of Clinical Variables between Groups

	Without SLNB (n = 38)	With SLNB (n = 37)	*P*
Time to develop: <6/6–12/>12 mo, n (%)	1 (2.6)/17 (44.7)/20 (52.6)	2 (5.4)/15 (40.5)/20 (54.1)	0.800
Size: ≤2/2–5/≥5 cm, n (%)	22 (57.9)/13 (34.2)/3 (7.9)	13 (35.1)/17 (45.9)/7 (18.9)	0.109
Differentiation: poor/moderate-poor/moderate/well-moderate/well	2 (5.3)/3 (7.9)/18 (47.4)/5 (13.2)/10 (26.3)	3 (8.1)/7 (18.9)/16 (43.2)/4 (10.8)/7 (18.9)	0.637
Ki-67 index: median (IQR) [min–max]*	20.0 (32.0) [2.5–80]	30.0 (39.0) [5–90]	0.059
Breslow: ≤3.5/>3.5 mm, n (%)	10 (26.3)/28 (73.7)	5 (13.5)/32 (86.5)	0.249
Perineural invasion: no/yes, n (%)	33 (86.8)/5 (13.2)	31 (83.8)/6 (16.2)	0.754
Peripheral limits: ≤5/>5 cm, n (%)	24 (63.2)/14 (36.8)	11 (29.7)/26 (70.3)	0.626
Metastasis: no/yes, n (%)	36 (94.7)/2 (5.3)	37 (100.0)/0 (0.0)	0.159
Deaths: no/yes, n (%)	36 (94.7)/2 (5.3) One due to disease-specific causes	34 (91.9)/3 (8.1) Two due to disease-specific causes	0.674
Local remission: no/yes, n (%)	32 (84.2)/6 (15.8)	30 (81.1)/7 (19.9)	0.768

There is not statistically significant difference of clinical variables between compared groups ($P > 0.05$).
*Mann-Whitney test.
IQR, interquartile range.

formalin 10%. The slices were again stained with hematoxylin–eosin stain. To determine micrometastasis, immunohistochemical analysis (P-63, high molecular weight, and Ki-67 immunohistochemical stains) was performed.

Statistical Analysis

Data were expressed as mean ± SD or median (interquartile range) for quantitative variables and as frequencies and percentages for qualitative variables. The Shapiro-Wilk test was used for normality analysis of quantitative variables.

The comparison of quantitative and qualitative variables between groups was analyzed using the independent samples *t* test or Mann-Whitney test and Fisher exact test, respectively.

All tests are two-sided, statistical significance was set at a *P* value less than 0.05. All analyses were carried out using the statistical package SPSS vary 21.00 (IBM Corp., Somers, N.Y.).

RESULTS

One patient of group A, who never attended any follow-up, was excluded. Both groups had similar characteristics regarding demographic variables (Table 1): age, sex, education, sun exposure, Fitzpatrick stage, use of sun protection, previous incomplete surgical excision, previous skin cancer and smoking, and clinical variables (time to develop, size, differentiation, ki-67 index, Breslow thickness, perineurial invasion, and peripheral limits). In group A, two patients had a positive sentinel lymph node and were submitted to regional lymphadenectomy. In one patient, the initial lymph node was intraparotid; therefore, we performed superficial parotidectomy with excision of intraparotid lymph nodes, whereas in the other, the positive node was localized in the posterior triangle, and we performed selective node dissection. No extra positive nodes were found in either specimen. The precise anatomic locations of the lesions in the patients without SLNB (group B) were six nose, 11 scalp, 12 lower lip, three forehead, three external ear, and three cheek. For the patients with SLNB (group A), the locations were external ear, five; lower lip, 12; scalp, 11; cheek, six; nose, one; and forehead, two. One patient in group A developed seroma at the SLNB site that was treated with serial aspirations. There were no cases of lymphedema, infection, or nerve damage in group A. The primary outcome we identified was death, and secondary outcomes were local remission and regional metastases. Mortality rate was not statistically significantly different between two groups (Table 2): we documented three deaths in group A and two in group B ($P = 0.674$). Two deaths in group A and one in group B were disease-specific. There was no statistically significant difference in either local recurrence (seven in group A and six in group B; $P = 0.768$) or regional metastasis rate (zero in group A and two in group B; $P = 0.159$).

DISCUSSION

Squamous cell carcinoma accounts for 20% of nonmelanoma skin cancers.[13,14] Although potentially lethal, it is often curable when detected at an early stage.[15] According to the seventh edition (that was up to date when the study started)

of the *AJCC Cancer Staging Manual*, high-risk factors are the 2-cm cutoff diameter that continues to differentiate T1 from T2 lesions, and also, the presence of two or more of the following high-risk features that increase the T stage independently of tumor size: differentiation (poorly differentiated or undifferentiated), primary anatomical site on the ear or the hair bearing lip, thickness of greater than 2 mm, Clark level of at least IV, and perineural invasion.[5] Other high-risk criteria are prior radiation therapy, immunosuppression, and previous incomplete excision.[16,17] We included the following criteria in our study: tumor size greater than 2 cm, primary anatomic site on the ear or hair bearing lip, prior radiation, previous incomplete excision, and immunosuppression. We did not include a punch biopsy in the methodology to document perineurial invasion, differentiation, or lymphovascular invasion because this would probably cause the patients difficulty to comply. In our groups, we did not manage to recruit any immunocompromised patients. Although the term high risk is relatively ambiguous, this cohort of patients seems to fit that label when published metastatic rates of 4%–5% for all patients with CSCCs are considered.[18–20] In our study, two of 37 SLNBs were positive in group A. This is a percentage of 5.4%. Our percentage is similar to other studies but different than the results in the article by Janković et al,[24] in which they documented a positive SLNB rate of 21.9%.[21–23] However, this was a retrospective study and was designed to map the lymphatic drainage in the head and neck with the help of SLNB. Regional metastasis (regional lymph nodes) rate was similar in the group with SLNB (zero metastasis: 0.0%) and in the group without SLNB (two metastasis: 5.3%, $P = 0.159$). This is similar to the results of Kofler et al,[21] in which they mentioned similar rates of lymph node metastasis in SLNB group patients (11.9%) and observation group patients (11.4%). On the contrary, they documented more frequent local recurrence in the SLNB group (19.84%) compared with the observation group (10.35%; $P = 0.003$). This is different than our results, where we found similar rates for local recurrence in the SLNB group (seven cases) and observation group (six cases, $P = 0.768$). This again was a retrospective study, and they used tumor thickness more than 5 mm as criteria. The authors were not limited to the head and neck area only but included CSCCs in all parts of the body. The patients chose the method of the treatment, so it was not a blind study either. Also, the SLNB group showed a higher average tumor thickness ($P = 0.001$) and higher proportions of male patients ($P < 0.001$) and immunosuppressed patients ($P < 0.001$). In contrast, a higher mean patient age was found in the observation group ($P < 0.001$). In our article, we had homogenous samples that presented similar demographic and clinical variables. Mortality had no statistically significant difference between our two groups: we documented three deaths in group A and two in group B ($P = 0.674$). However, only two deaths in group A and one in group B were disease-specific. In the systematic review by Ross and Schmults,[25] they showed that SLNB is a possible option for diagnosing lymph node metastases of CSCCs. However, the results were based mainly on case series, and the cases were not entirely CSCCs, as a high proportion of anogenital squamous cell carcinomas were included. Navarrete-Dechent et al[26] and Allen and Stolle[27] could not define a subgroup of patients who would benefit from SLNB. In our study of head and neck patients also, we did not find that patients would clearly benefit from SLNB because there was no statistically significant difference between two groups regarding metastasis, mortality, and local recurrence. A limitation of this study is the lack of inclusion of all high-risk features such as Clark level IV, lymphovascular invasion, differentiation, or perineural invasion because we did not submit the patients to a punch biopsy before the definite treatment. Possibly, adopting a two-stage procedure akin to the approach for melanoma, with an initial excision of the CSCC followed by wide excision and SLNB, could address this concern. A future study with inclusion of punch biopsy in the study design to document more high-risk features would provide more information. Also, at the time of study, *AJCC Cancer Staging Manual* version 7 was used, as it was a prospective study with long-term follow-up. The patients were recruited within 1 year (2013–2014); therefore, the criteria were outdated when the new version of AJCC was implemented in January 2018.[28] An updated study according to the updated *AJCC Cancer Staging Manual* would be necessary in the future, especially since we used only AJCC 7 as part of the selection process for identifying high-risk features. Moreover, prospective studies for the use of SLNB in CSCCs in other parts of the body with more predictable lymphatic drainage patterns, for example, hand and foot, would be necessary to document the use of SLNB in high-risk CSCCs in general.

CONCLUSION

The use of SLNB in high-risk CSCCs of the head and neck, according to the results of the present study, does not provide a benefit to patients regarding metastasis, mortality, or local recurrence control.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

ETHICAL APPROVAL

All procedures performed in the study were in accordance with the ethical standards of Papageorgiou General Hospital research committee and with the 1964 Declaration of Helsinki and its later amendments.

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