The use of sentinel node biopsy and selective lymphadenectomy in squamous cell carcinoma of the upper limb.

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Usefulness of sentinel node biopsy to avoid useless lymphadenectomies in high-risk upper limb SCC

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The use of sentinel node biopsy and selective lymphadenectomy in squamous cell carcinoma of the upper limb. Usefulness of sentinel node biopsy to avoid useless lymphadenectomies in high-risk upper limb SCC

BACKGROUND: *Squamous cell carcinoma (SCC) is the second most common skin cancer in humans.*
Because the incidence of metastasis from SCC of the skin is rare, regional lymphadenectomy is generally not recommended for the patients with clinically node-negative disease. However, in patients with an intermediate and high risk of metastasis, evaluation of the lymph nodes to detect the absence of metastatic nodal disease is a difficult task.
PATIENTS AND METHODS: *The authors reviewed the pertinent demographic and surgical data in a consecutive series of six patients with squamous cell carcinoma who underwent sentinel lymph node staging. The tumour size was greater than 2 cm (T2) and the patients had clinically non-palpable regional lymph nodes (N0). All nodes were examined using haematoxylin-eosin staining.*
Sentinel Lymph Node Biopsy (SLNB) and Selective Lymphadenectomy (SL) using preoperative lymphoscintigraphy and intraoperative radiolymphoscintigraphy and vital dye injections was used to identify the sentinel lymph node avoiding complete axillary node dissection.
RESULTS: *No false-negative results were observed. At a median follow-up of 10 months (mean 15 months), neither local or regional recurrences in sentinel node-negative basins have been noted.*
Conclusions: Sentinel node biopsy is a minimally invasive staging procedure useful in identifying occult regional lymph node disease in selected patients with squamous cutaneous malignancies of the arm. Furthermore sentinel lymph node histology is possibly the most important negative predictor of early recurrence and survival in patients with American Joint Committee on Cancer stage I and II squamous cell carcinoma. Although sentinel node-negative patients are a prognostically favourable group, this small series of patients demonstrates that further studies to verify these findings and develop formal guidelines are indicated.

KEY WORDS: SCC Sentinel Node Biopsy (Squamous cell carcinoma), Upper limb.

Introduction

Squamous cell carcinomas (SCC) are the most common malignancies of the arm [1] accounting for 75% to 90% of all upper limb malignancies and the most common malignancy of the nail bed [2].
A variety of inciting factors have been implicated in the histogenesis of these skin lesions, the foremost of which is sun exposure. Other risk factors include radiation, chronic ulcers, immunosuppression, xeroderma pigmentosum, epidermodyslpasia verruciformis and Bowen's disease. Patient on immunosuppressants have a fourfold increase in incidence of skin cancer that appears to be more invasive, has a greater recurrence and metastasis rate, and demonstrates a greater propensity for multiplicity [3].
The propensity of SCCs to metastasize is dependent on a number of factors and SCCs arising on sun-exposed areas of the body have a 0.1% to 3% incidence of metastasizing [4]. The 5-year survival for patients with metasta-

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tic SCC is reported to be only 20% to 40% [4-5-6]. Depending on the study and prognostic factors, rates of local recurrence and regional/systemic metastasis in high-risk SCCs have been reported to be between 10 and 47.2% and 11 to 47.3%, respectively [7-8].
Histologically a sign of lymphatic, hematogenous, and perineural spread are portals for metastasis. Epitrochlear and axillary nodes should be assessed for tumor as well as cold abscess formation. Metastasis in transit may be secondary to perineural invasion [1].
Once clinically detectable nodal metastasis has occurred, the prognosis is poor, with reported 5-year survival rates of approximately 26% [9].
The dilemma therefore lies in the management of high-risk cutaneous SCCs with no clinical or radiologic evidence of metastatic disease or a clinical N0 status.
Selective lymphadenectomy or sentinel lymph node (SLN) biopsy has been used in the staging and treatment of malignant melanoma, breast cancer, Merkel cell carcinoma, oral and genital SCC, and other solid tumors.
The concept of the sentinel node is based on the orderly progression of metastasis within the cutaneous lymphatics. The advantages of this procedure are the ability to identify the primary draining lymph nodes and nodal basins, accurately predict the histological status of the draining nodal basins, offer prognostic information, guide additional therapy, and avoid unnecessary morbidity. SLN biopsy in SCC has not yet been proven to influence survival [10].
The application of SLN biopsy in SCC has been mostly limited to oral, oropharyngeal, and genital SCCs. Its role in the management of these tumors is promising [11].
Although mucosal SCCs typically have a higher metastatic rate than cutaneous SCCs, SLN biopsy for cutaneous SCC has been shown to be feasible, even in conjunction with Mohs micrographic surgery. There are, however, few reported series examining the use of SLN biopsy in cutaneous SCC of the upper extremity [12]. We herein report our results, including short-term clinical follow-up.

Patients and Methods

From 2002 to 2005, six patients with high-risk cutaneous SCCs of the arm and clinically negative regional nodes consented to undergo preoperative lymphoscintigraphy and sentinel lymphadenectomy at the time of tumor excision (Table I).
Each of these cases was identified as high risk for metastasis by meeting at least one of nine criteria reported by Rowe applied to a single anatomic site (Table II) [13]. All patients had no clinical evidence of nodal metastases or a N0 status. The diagnosis of SCC was confirmed on histological examination.
The appropriate treatment for SCC of the arm is local excision. The lesion is excised with 1 cm of margin and including areas of contiguous induration. All margins demonstrating induration should be removed. The tumor should be excised to a depth of tissue below the tumor. SCC of the finger often requires amputation due to the early involvement of bone. We recommend amputation at the distal interphalangeal joint for tumors arising at the perionychium site. SCCs of the hand in fact have been observed to be more aggressive locally and have a higher rate of regional metastasis.
All patients underwent preoperative lymphoscintigraphy to identify the approximate number and location of SLNs. Filtered (0.2-micron filter) technetium-labeled sulfur colloid was injected intradermally in a four-quadrant pattern around the primary tumor. Dynamic and delayed images were obtained to show the lymphatic drainage pattern of the primary tumor, as well as the anatomic relationships of potential SLNs. An intradermal tattoo was used to mark the location of potential SLNs.
Vital blue dye Patent blue® (Blue Patentè, Labatoire Guerbet, Aulnay-sous-Bois, France) was injected around the primary tumor or previous biopsy site at the beginning of the surgical procedure. Ten minutes after the injection, a small incision was made at the site of the intradermal tattoo. Lymph nodes with a blue-stained afferent lymphatic or tinged a blue colour were excised and submitted as SLNs. Using a hand-held gamma probe, "hot" lymph nodes with sufficient ratios of radioactivity versus background (more than 3:1 in vivo) or versus a neighbouring non-SLN (more than 10:1 ex vivo) were also harvested as SLNs [14] (Figs.1-2).

Results

Conventional histological examination of primary tumor wide local excisions confirmed complete excision in all cases. The mean tumor diameter was 3.45 cm (range 2.25-4.6 cm) (Fig.3).
SLNs were identified and excised in all patients. No nodal metastases were identified with hematoxylin and eosin staining in all three cases.
Although immunostaining of SLN for detection of micrometastatic disease is considered by many to be the "standard of care" in melanoma and breast carcinoma, it is not performed on a routine basis for the detection of micrometastatic SCC. This is because the tumor cells are characteristically quite large and/or present in large clusters. In our small series, in one case in which cytokeratin immunostaining was used, no additional metastases were noted.
All patients with negative SLNs are alive and without disease at a median follow-up of 10 months (mean of 15 months). Preoperative lymphoscintigraphy and SLN biopsy were well tolerated by all patients.

TABLE I

Name	Sex	Age	SNB	TH	NH
CM	M	68	yes	lozange Size 1.2x0.6 cm; on the top a brownish lesion 1.4 cm; moderately differentiated dermal SCC with intratumoral phlogistic reaction. Perilesional skin 3rd stage sun keratosis	Negative for metastases
CG	F	73	yes	lozange Size 2x1.5 cm. Ulcerated lesion sizing cm 1.5x1; ulcerated moderately differentiated G3 SCC; the whole dermis involved, with perineural infiltration	Negative for metastases
PS	M	84	yes	lozange sizing 4.5x5 cm. Esophytic lesion 6x5x2.5 cm. Well-differentiated polipoid SCC infiltrating the whole dermis, close to ectasic vessels; acantolysis on the surface	Negative for metastases
MC	F	84	yes	lozange sizing 2x1,5 cm. Sebaceous-lke ulcerated SCC with a cornu cutaneum on its top sizing 1,5 cm infiltrating the whole dermis; an important peritumoral phlogistic reaction is detectable	Negative for metastases
BS	M	71	yes	1st op: lozange 6x5 cm: esophytic, ulcerated, moderately differentiated SCC sizing 5x4 cm, infiltrating the whole dermis; samples from the wound bed are neoplastic; 2nd op: a) ulcerated lozange 4.5x5 cm: moderately differentiated SCC infiltrating the soft tissues up to the periosteum (safe) b) lozange 2x1 cm with esophytic lesions: hypertrophic keratosis 3rd stage with some areas in progression. In the meantime sentinel node biopsy. 3rd op (radicalization) (22-03-05): a) lozange 2x1 cm: moderately differentiated ulcerated SCC infilltrating the deep dermis and neural structures; b) lozange 1.4x0.3 cm with the same histologic features of the sample a) involving a half, the other half does not present neoplastic features	Negative for metastases
GA	F	67	yes	lozange Size 1.5x 2.8 cm; undifferentiated dermal esophytic SCC (0.7x 1.5 cm) with intratumoral phlogistic reaction.	Negative for metastases

SNB=Sentinel Node Biopsy; TH= Tumour Histology; NH= Node Histology.

TABLE II - *Rowe's Criteria of very high risk cutaneous SCC for metastasis (1992).*

Age
Diameter of Lesion
Anatomic Location
Recurrent SCC
Tumor Depth- Clark's Level
Tumor Depth- Breslow Thickness
Histologic Differentiation
Stromal Desmoplasia
Perineural or Lymphatic Invasion

Discussion

Selective lymphadenectomy has the potential to play an important role in the management of high-risk cutaneous SCCs in patients with clinical N0 status. Although this case series is small and with limited follow-up, the data illustrate several important points regarding the possibility of enhanced management of this malignancy.

Similar to its use in melanoma and breast cancer, SLN biopsy may contribute to the staging of high-risk cutaneous SCCs [8-15].

Detection of regional nodal spread, which accounts for 85% of metastases, depends on either clinical detection of lymphadenopathy or radiological studies. Detecting distant metastases is based on a thorough history and physical as well as appropriate radiological or laboratory testing [15]. There is no standard method for detecting

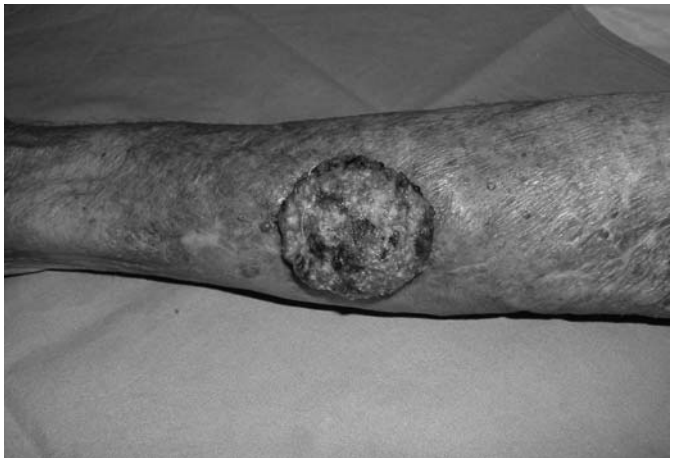

Fig. 1: A large esophytic and ulcerated SCC of the dorsal aspect of the left forearm in a 84 ys old lady (case 4).

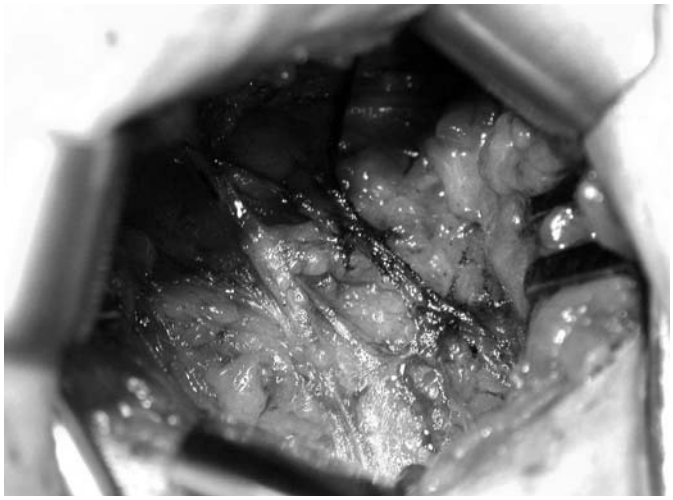

Fig. 2: After vital stain inoculation, the lymphatic pathways of the elbow showing to be positive.

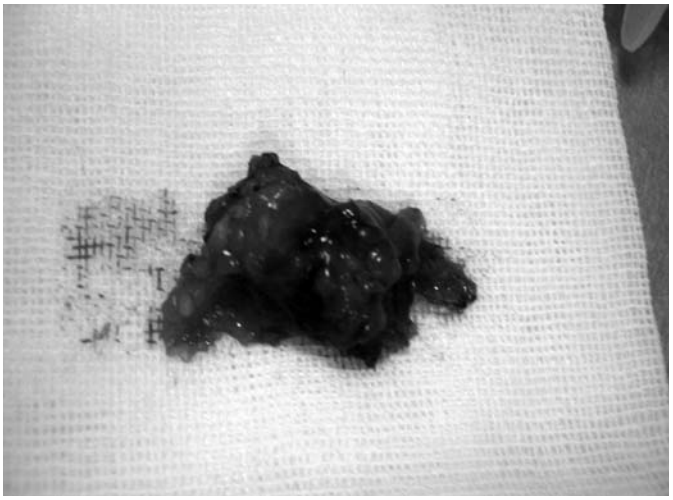

Fig. 3: The removed epithroclear node mass.

sub clinical metastases. Elective Lymph Node Dissection (LND) can be performed to evaluate for sub clinical nodal metastatic disease; however, is not advocated because of the high morbidity-to-benefit ratio [7-10-15]. The use of preoperative lymphoscintigraphy and SLN biopsy may help to identify patients with sub clinical metastases and thus theoretically at higher risk for overt metastatic disease. In this series there were no sub clinical metastasis, however in a previous study Reschly reported 44% of sub clinical metastasis of SLNB of cutaneous SCC of different anatomical sites [16].

This rate of sub clinical regional metastasis is consistent with numbers found in genital and oro-pharyngeal SCCs, as well as within range of reported metastatic rates for similar high-risk cutaneous SCCs [10-13-17].

Sentinel node status may also provide prognostic information. High-risk cutaneous SCCs adequately excised before metastasis have an excellent cure rate. Conversely, metastatic disease, be it regional or distant, carries a grim prognosis with 5-year survival rates of 26% despite therapy [9-15]. Therefore, a large proportion of the tumors that will eventuate in metastatic disease likely has sub clinical regional nodal disease before lesion excision. All patients with negative SLNs are alive without disease.

Postoperative radiotherapy or LND has not been proven to increase survival rates in high-risk cutaneous SCC with clinically N0 status and is not routinely performed. If any benefit is to be gained from further therapy, however, it is more likely for those with sub clinical disease of the nodes. In our study, the three patients with negative SLNs received no further treatment.

The use of preoperative lymphoscintigraphy and sentinel lymphadenectomy may ultimately improve survival rates in patients with high-risk cutaneous SCC. Identifying sub clinical regional metastases, as well as locating the correct draining nodal basin, would guide more directed additional therapy at an earlier and theoretically more curable stage of disease progression. There is perhaps more potential for control of metastatic disease in SCC than in melanoma given SCCs propensity to metastasize predominantly to regional lymph nodes and its radiosensitivity.

Another advantage of preoperative lymphoscintigraphy and SLN biopsy is its minimal associated morbidity. In general, this procedure spares the morbidity associated with more extensive LND, including lymphedema and nerve damage, but these adverse events have been reported [18]. An additional risk is allergic or anaphylactic reactions to the injectable dye [19-20]. The procedures were well-tolerated by all patients in this study with no complications or excess recovery time.

In summary, sentinel lymphadenectomy is a low morbidity procedure that may prove to have an important role in the management of patients with high-risk cutaneous SCC and a clinical N0 status. This study, although small and with limited follow-up owing to the low rate of incidence of upper limb SCC, suggests that, the ability to reliably detect sub clinical metastases may

contribute to staging and also may improve survival by guiding additional therapy and removing small foci of disease. The evaluation and management of high-risk cutaneous SCC still await identification of multivariate-proven prognostic factors for recurrence and metastasis: in particular, further correlations between tumour spreading in thickness and /or cell dedifferentiation, and prognosis are expected. Larger studies are also needed to define further the role of SLN biopsy in the management of these high-risk malignancies.

Riassunto

Il carcinoma spinocellulare è il secondo dei tumori maligni della cute per frequenza, ma le localizzazioni agli arti sono piuttosto rare, e spesso si associano ad altre neoplasie.
Le metastasi linfatiche sono rare, tranne che nelle forme che presentano maggiore aggressività (in base alle dimensioni di T>2 cm, al grado di infiltrazione dermica, all'ulcerazione o meno, alla reazione infiammatoria e/o leucocitaria peritumorale). In questi pazienti, anche a fronte di negatività clinica e strumentale, trovano indicazione la linfoscintigrafia e la ricerca del linfonodo sentinella.
In questo studio viene analizzata una serie consecutiva di sei pazienti affetti da SCC dell'arto superiore rientranti per le carattestiche del tumore primitivo nelle categorie a rischio metastatico, anche se negativi sia clinicamente che strumentalmente per adenopatie secondarie.
La biopsia del lifonodo sentinella risultava negativa in tutti i casi, con un follow-up clinico e strumentale di negatività a 10 mesi dal primo intervento di exeresi.
Il presente studio, unico sugli SCC dell'arto superiore, costituisce la base di partenza per ulteriori analisi dalle quali possano scaturire più dettagliate linee guida di cura di queste patologie.

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