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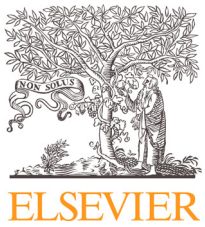

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Sentinel lymph node biopsy in high-risk cutaneous squamous cell carcinoma of the head and neck

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KEYWORDS
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Summary *Introduction:* Cutaneous squamous cell carcinoma (cSCC) shows malignant behaviour in 3–4% of patients with locoregional metastases and a poor prognosis, metastases that are difficult to predict clinically. Therefore, sentinel lymph node biopsy (SLNB) has been assessed, with contradictory findings thus far. We aimed to clarify the prognostic value of SLNB in high-risk cSCC patients.

Patients and methods: We completed a retrospective clinical study amongst 63 patients, preoperatively classified as N0 with a high-risk primary cSCC of the head and neck who underwent SLNB between 2001 and 2014 at Helsinki University Hospital (Finland). Considered high risk, the inclusion criteria comprised at least two of the following characteristics: tumour diameter $\geq$10 mm and/or thickness $\geq$4 mm and a specific tumour location, such as the lips, ear, scalp and central face. Patients were followed-up postoperatively for a median of 4.1 years (0.2–13.8 years).

Results: Only four (6.3%) patients had positive sentinel nodes. One of these patients died of cSCC, while the other three ultimately survived their disease. Five (7.9%) patients showed a negative SLNB, but developed recurrence within one year postoperatively. Recurrence appeared in the neck lymph nodes concurrently with locoregional soft-tissue invasion in all patients. Amongst these patients, three died for cSCC and the remaining two from other causes. Comparing the SLNB-positive and SLNB-negative groups with recurrence, we identified no significant differences in terms of patient or tumour characteristics.

Abbreviations: cSCC, cutaneous squamous cell carcinoma; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.

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Conclusions: SLNB appears to carry no prognostic value for identifying recurrent disease amongst high-risk cSCC in the head and neck area.

Introduction

Non-melanoma skin cancer is a common malignancy globally. Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, with an increasing annual incidence worldwide.[1-2] In Finland, 1678 new cSCC cases were recorded in 2017, a majority of which occurred in men (56%), (Finnish Cancer Registry 2017).[3]

In most cases, cSCC can be curatively treated with adequate surgery. However, approximately 3–4% of patients develop lymph node metastases during the course of disease[2,4] with distant metastases accompanying a poor prognosis, with nearly 70% mortality.[1] Immunosuppressed individuals specifically carry up to a two to three times heightened risk for metastatic disease.[5,6] As yet, no effective life-saving treatment exists for metastatic disease. Immuno-oncological treatment relying on the anti-PD-1 (programmed cell death protein 1) antibody has been introduced for metastatic disease, but does not yet enjoy widespread use.[7]

Defining high-risk cSCC remains broad and often unclearly articulated.[8,9] Numerous studies have documented high-risk factors associated with poor outcomes.[1,2,9,10] Clinical and tumour characteristics likely to lead to poor outcomes appear in cSCC staging systems. According to the American Joint Committee on Cancer's version 8 staging (2016), tumours are classified depending on the tumour size in terms of the clinical diameter and a series of associated risk factors. A tumour diameter ≥2 cm represents the distinguishing factor between T1 and T2 tumours. High-risk features resulting in upstaging to T3 include a tumour diameter ≥4 cm, minor bone erosion, perineural or deep invasion (≥6 mm or beyond the subcutaneous fat).[2] Furthermore, the National Comprehensive Cancer Network (NCNN, 2017) takes both clinical and pathologic parameters into account and provides a division into high- and low-risk tumours. A critical tumour size is defined by the anatomical location, whereas high-risk factors consist of poorly defined tumour borders, recurrence, immunosuppression, the radiotherapy site, a chronic inflammatory process, a rapidly growing tumour and neurological symptoms. Tumour-specific high-risk factors consist of perineural or vascular involvement, poor differentiation, high-risk histological subtypes, a tumour thickness of >2 mm or invasion to the deep dermis or subcutis [www.nccn.org. V1.2017].[5]

In patients with high-risk localised tumours, the successful detection of occult lymph node metastases using sentinel lymph node biopsy (SLNB) has been investigated.[5,10,11] However, the histopathological analysis of SLNB for the management and final outcome of patients remains unclear. Neither the AJCC nor NCCN staging systems consider sentinel lymph node histology as a prognostic factor.

In our retrospective study, we sought to determine whether the sentinel lymph node status and early detection of nodal disease impacts survival amongst patients with high-risk cSCC. For high-risk characteristics, we used a tumour location on the lips, ear, scalp, central forehead and central cheek. In addition, a tumour thickness ≥4 mm and/or diameter ≥10 mm served as the histological inclusion parameters. In total, 63 patients with primary cSCC met the criteria leading to SLNB and underwent evaluation of the nodal status with postoperative follow-up.

Patients and methods

The Helsinki University Hospital institutional review board approved the study protocol and its plan.

It is a retrospective patient documentary study, no treatment intervention study, thus WMA declaration was not required. We performed an electronic search using the Uranus® database of Helsinki University Hospital to identify all patients who underwent surgery for primary head and neck cSCC and SLNB from 1 January 2001 through 31 December 2014. Patients were included in the study over a long period of time meeting the prevailing high-risk criteria based on both clinical and tumour characteristics. The inclusion criteria comprised at least two of the following: tumour diameter ≥10 mm and/or thickness ≥4 mm and a specific tumour location, such as on the lips, ear, scalp, central forehead and central cheek.

We identified 76 patients from whom we excluded 13 because of either missing follow-up data or a tumour histopathology different from cSCC. All primary tumour samples as well as the SLNB data were reanalysed, and diagnosis was confirmed for morphology and immunohistochemistry by the same experienced dermatopathologist (SJ).

Medical records were reviewed thoroughly and data were collected regarding each patient's age, gender, immunosuppression, cancer comorbidities, the date of SLNB surgery and excision/re-excision of the tumour, the tumour histology report, the histological tumour margins and the SLNB histopathology, the completion lymph node dissection report, oncological treatment, the date of recurrence, death and the cause of death. The tumour features included the location, diameter and thickness. The differentiation level of the tumour was classified into three categories: well, moderate or poor differentiation. Perineural invasion was reported and the histological growth pattern was reanalysed for those with metastatic disease.

Tumours

These high-risk tumours were re-excised with 10 mm clinical margins to the depth of the underlying fascia or the

deep subcutaneous soft tissue with the histological margin assessment completed.

Sentinel lymph node protocol

Patients were previously diagnosed with high-risk cSCC of the head and neck and were preoperatively evaluated as N0. Patients underwent local re-excision of the tumour and SLNB during a single procedure. On the day prior to surgery, patients received Technetium-99m-labelled colloidal albumin (Albu-Res, Nanocol) 80 MBq in 0.2 ml injected intradermally into the primary tumour site on both sides of the excision scar and then proceeded to lymphoscintigraphy with static images 30 min and 2 h following the injection. The surgeon used a gamma-detecting probe (Navigator, Tyco Health Care and Neo2000, Neoprobe Corp.) intraoperatively and harvested all radioactive nodes until no focal residual activity could be detected.

Sentinel lymph nodes

Formalin-fixed sentinel node samples were cut at 1–2 mm intervals and all tissues were examined. Routine haematoxylin–eosin stains were performed and pan-cytokeratin immunohistochemistry was used to detect smaller tumour deposits.

Follow-up protocol

Follow-up care was provided at Helsinki University Hospital, which included a clinical examination focused on the operative site and lymph node basins supplemented with ultrasound examination of the lymph node basins every six months for the first two years and, thereafter, once a year for up to five years. Needle samples were taken of suspicious lymph nodes, and, when verified as metastatic, complete lymph node dissection was performed. An oncologist was consulted for recurrent disease.

Statistical analysis

The distribution of parameters was characterised using standard descriptive methods. cSCC-related recurrence-free survival was calculated as the time interval between diagnosis and the first recorded sign of disease progression following the primary operation. Patients with no signs of progression at their last follow-up visit were censored at the time of their last visit. Overall survival was defined as the time interval between diagnosis and death. We used the Kaplan–Meier survival analysis to analyse recurrence-free survival and overall survival. Statistical analyses were performed using NCSS 12 Statistical Software ((2018), NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss).

Results

The specific inclusion criteria resulted in a sample of 63 patients: 41 (65%) males and 22 (35%) females, with a median age at diagnosis of 73.2 years (range, 40.1–91 years). Table 1 provides the detailed demographic characteristics of patients. Given other comorbidities, 17 (27%) patients were immunosuppressed. In addition, 24 (38%) had other skin malignancies, such as basal cell carcinoma or precancerotic tumours including previously treated actinic keratosis, actinic cheilitis or MbBowen. Furthermore, nine (14%) patients had another malignancy amongst the comorbidities. One patient presented with a long-lasting ulcer preceding the formation of the squamous cell cancer.

The preoperative local lymph node status was evaluated clinically in 46 (73%) patients, an ultrasound was used for

Table 1 Patient and tumour characteristics.

Patients, *n* = 63	
Gender	Male 41 / Female 22
Age, years (range)	Mean 71.7 (40.1–91)
Immunosuppression, n	17 (27%)
kidney transplant	4
Liver transplant	1
B-cell lymphoma	1
Waldenstrom macroglobulinaemia	1
Autoimmune disease	
Rheumatoid arthritis	3
Sarcoidosis	1
Polymyalgia rheumatica	1
Werner syndrome	1
Epidermodysplasia verruciformis	1
Autoimmune hepatitis	1
Discoid lupus erythematosus	1
Multiple myeloma	1
Follow-up, years mean (range)	4.2 y (0.2–13.8)
Tumour recurrence	7 (11%)
Survival	
Alive	29 (46%)
Death, squamous cell carcinoma	4 (6%)
Death from other causes	30 (48%)
Tumours, *n* = 63	
Location, – (%)	
Lower lip	25 (40)
Upper lip	6 (9)
Ear (Auricle)	10 (16)
Forehead	8 (13)
Scalp	8 (13)
Cheek	6 (9)
Largest diameter, mean mm (range)	16.4 (3–40) 15 mm median
Tumour thickness, mean mm (range)	6.7 (2.2–31) 6 mm median
Differentiation level, n (%)	
Well	29 (46)
Moderate	30 (48)
Poor	4 (6)
Invasion, n (%)	
Perineural	12 (19)

Table 2 Sentinel lymph node operations and sentinel lymph node status.

Patients *n* = 63	
Number of removed sentinel nodes/patient, mean (range)	4.4 (1–10) median 4
Location, n (%)	
Ipsilateral neck	24 (38)
Bilateral neck	18 (28)
Parotid gland	7 (11)
Ipsilateral neck and parotid gland	13 (21)
Occipital region and ipsilateral neck	1 (2)
Sentinel lymph node status, n (%)	
Positive	4 (6.3)
Negative	59 (93.7)

16 and a computed tomography (CT) scan was performed in one case. All patients were classified as N0 preoperatively. Table 1 also provides the anatomical location of the tumour, as well as the measured absolute thickness and diameter. The lower lip was the primary tumour site in 25 (40%) patients, representing the most common location. The median thickness of tumours was 6 mm, while the median diameter was 15 mm. Those with a well or moderate differentiation level represented the majority. Perineural invasion was detected in 12 (19%) samples. All tumours were excised with clear histological margins, with a mean radial skin margin of 7.7 mm (range, 1.8–19) with a median of 7 mm, while the mean margin at the base of the tumour was 8.2 mm (range, 0.2–20) with a median of 10 mm.

The mean number of harvested sentinel lymph nodes was 4.4 (range, 1–10; Table 2). Most of the sentinel lymph nodes were located in the ipsilateral neck ($n = 24$; 38%), followed by bilaterally in the neck ($n = 18$; 28%), the neck and parotid gland ($n = 13$; 21%), the parotid gland ($n = 7$; 11%) and the occipital region and neck ($n = 1$; 2%).

The mean follow-up period was 4.2 years (range, 0.2-13.8 years) with a median of 4.1 years. Recurrence was detected in seven patients, amongst whom four (6%) died of squamous cell carcinoma. Two of those who died from squamous cell carcinoma developed multiple systemic metastases, both of whom were SLNB-negative. The other two patients developed aggressively spreading locoregional metastases. amongst one of these patients, who was SLNB-positive, the general physical status was too weak for further treatment. The other patient, who was SLNB-negative, recurrent cancer was treated with radical surgery and postoperative radiation, although the repeatedly recurrent cancer was no longer treatable. In total, 30 (48%) patients died from other causes and 29 (46%) patients were living at the end of the follow-up.

Sentinel lymph node-positive patients

Only four patients had positive sentinel nodes. Three of these were immunosuppressed, and three tumours were primarily in the lips and two presented with perineural invasion. One patient in this group died of squamous cell carcinoma soon after complementary surgery. The other three patients underwent selective neck dissection, one of whom also received radiotherapy. In addition, one of these three patients further developed locoregional soft-tissue recurrence which was operated on. Ultimately, all three survived their disease (see Table 3).

Sentinel lymph node-negative patients with tumour recurrence

Five patients presented as SLNB-negative but developed recurrence within one year postoperatively. Four were male and three were immunosuppressed. Two tumours originated in the lower lip, while two tumours appeared in the scalp. Three presented with an Mb Bowen-like growth pattern and two presented with perineural invasion. Recurrences appeared in the neck lymph nodes concurrently with locoregional soft tissue in all patients. Radical surgery was performed together with oncological procedures in all but one patient who refused treatment. Three patients died from cSCC, while the remaining two died from other causes (see Table 4).

Comparing the SLNB-positive group ($n = 4$) with the SLNB-negative with recurrence ($n = 5$) group, we identified no significant differences in patient or tumour characteristics.

Discussion

In this retrospective series of 63 patients with high-risk cSCC, we established that SLNB is feasible, but carries little prognostic value in this particular patient group. Although the primary tumours were considered high risk, only four patients presented with a positive sentinel node. During the course of disease, five more SLNB-negative patients developed recurrent disease and their recurrence appeared within one year. Recurrent tumours located in identical regions with sentinel lymph nodes were harvested from the neck and parotid gland lymph nodes and adjacent soft tissue. Overall, 27% of patients were immunosuppressed. In addition, 38% of patients presented with other skin malignancies previously indicating a need for regular and continuous follow-up for most of these patients.

There are various explanations for the low predictive value of the sentinel lymph node status related to cSCC outcomes in the head and neck. First, the anatomy differs vis-à-vis the lymphatic network, understood as more complex involving bilateral or contralateral drainage in up to 10% of patients.[12] This, thus, requires more accuracy in sentinel lymph node detection by the surgeon. Previous tumour surgery and scar formation can also alter and block natural lymph routes. In addition, the proximity of the primary injection site can interfere when defining the true sentinel nodes intraoperatively because of the 'shine-through effect'.[13] Furthermore, sentinel lymph nodes can be small, particularly in the parotid gland, proving technically challenging to the surgeon. However, comparable anatomical and technical difficulties remain when performing an SLNB

Table 3 Patients with positive sentinel lymph nodes.

	Gender/ age	Immu no-suppressed	Tumour location	Tumour diameter/ thickness (mm), growth pattern	Tumour differenti-ation	Perineural invasion of the tumour	Positive sentinel lymph nodes (n), anatomical location	Secondary surgery, dissection report, oncological treatment	Alive at the end of follow-up	Dead; squamous cell ca/other	RFS OS (y) (y)
1.	M/65 y	No	Upper lip	20/5 Conventional	Well	No	1/3 Upper neck	Neck dissection LI-III, N 0/23	No	Other	5.6 5.6
2.	M/79 y	Yes	Forehead	30/7 Conventional	Low	Yes	1/1 Parotid gland	Subtotal parotidectomia, N 2/2 and diffuse spread of cancer in parotid gland	No	Squamous cell ca	0.03 0.16
3.	F/78 y	Yes	Lower lip	30/7 Conventional	Moderate	Yes	1/5 Bilateral neck, positive in left	I. Neck dissection LI-V l.sin, N 0/31 and radiotherapy II. Neck dissection LI-III l.dx, N 0/6 and spread of cancer in soft tissue	No	other	1.76 5.77
4.	F/78 y	Yes	Lower lip	20/11 Conventional	Low	No	1/4 Upper neck	Neck dissection LI-III, N 1/13	No	Other	1.93 1.93

L: neck dissection level.
N: nodal status.
RFS: recurrence-free survival.
OS: overall survival.

of the primary melanoma in the head and neck, for which SLNB represents a standard of care procedure. All of these factors give cause for consideration of the various biologically spreading mechanisms of cSCC and melanoma.

Perineural invasion of cSCC to the surrounding soft tissue has been demonstrated in various studies.[1] This indicates that the cancer spread mechanisms depend less on the lymphatic network, thereby differing from, for instance, melanoma. We found the simultaneous detection of metastatic tissue in adjacent soft tissue and locoregional lymph nodes in all five patients with primary SLNB-negative results who later presented with recurrence. Koler et al.'s findings were similar, whereby they showed metastatic spread proceeding via lymphatics, but were also able to metastasise through a direct extension to the adjacent soft tissue.[14]

In our study, 6.3% patients were SNLB-positive, similar to reports of 8-15.1% from other studies on cSCC. [9,10,15] The definition for high-risk cSCC varied from one study to the next, thereby explaining some of this wide variability.

We found a greater proportion of patients (7.9%) who progressed to recurrent disease following a negative SLNB, with corresponding rates varying from 4.6 to 7.1% in other studies.[8,13,15] In our whole patient population, nodal disease developed in 14.3% of all patients. In 11.1% patients, recurrent disease occurred both in the lymph nodes and adjacent soft tissue.

In our rather long follow-up with a mean of 4.2 years, all recurrences presented within two years postoperatively. Thus, regular and close follow-up visits are extremely important following primary surgery.

Clinical studies on SLNB as an option for diagnosing lymph node metastases of cSCC have been small, whereby the inclusion criteria for high-risk cSCC differ and follow-up times remain unequal, thereby explaining the heterogonous results on the prognostic merit. Kwon et al. reported a study of 51 patients from literature and Wu et al. amongst 83 patients where SLNB carried a negative predictive value of 95-100%, that is, there were no regional nodal recurrences in any patient found to have a negative SLN amongst head and neck cSCC cases.[16,17]

According to a study by Jansen et al. amongst 114 patients, a positive predictive value of 50% was noted amongst patients with SLNB positivity in developing distant metastases. However, SLNB-negative patients ($n = 7$) also developed distant metastases during the follow-up period. Thus, they concluded that the SLNB result did not represent a prognostic tool for the development of distant metastases.[18] Furthermore, Lhote et al. studied 37 cSCC patients who underwent SLNB alongside 290 cases from the literature. Their findings suggested that the relapse-free survival or overall survival were unaffected by the sentinel lymph node status.[11]

In addition, Kofler et al. compared 101 cSCC patients who underwent SLNB with an observation group ($n = 150$) who underwent tumour excision only. They found no difference in the proportion of patients who presented with lymph node metastasis or distant metastasis during follow-up. According to them, SLNB provided no advantage in terms of survival or nodal control.[14] Our study agrees with these studies by Jansen, Lhote and Kofler and colleagues, wherein the histopathological evaluation of SLNB did not predict the final outcome of disease. In light of the present studies, we cannot confirm whether SLNB status influences the survival of high-risk cSCC patients.

The limitations of this study include its retrospective study design and a relatively small patient population. We relied on data recorded for purposes other than research and, thus, reviewing and analysing clinical diagnostic impressions from medical records can limit the findings of our work. Although we based our analysis on a single unit patient population, we had to exclude approximately 17%

Table 4 Sentinel lymph node negative patients with tumour recurrence.

	Gender/ age	Immuno sup- pressed	Tumour location	Tumour diameter/ thickness (mm), growth pattern	Tumour differentiation	Perineural invasion of the tumour	Sentinel lymph nodes (n), anatomical location	Site of tumour recurrence	Secondary surgery, dissection report, oncological treatment	Alive at the end of follow-up	Dead; squamous cell ca/other	RFS (y) OS(y)
1.	M/67 y	Yes	Auricle	23/13 MbBowen	Low	No	0/6 Parotid gland	Parotid gland and ipsilateral neck LN	Superf parotidectomia and neck dissection LI-V, N 2/28 and ECS*, radiotherapy	No	Other	0.41 10.81
2.	M/81y	No	Lower lip	22/11 Conventional	Well	No	0/5 Bilateral neck	Locoregional subcutis and ipsilateral neck LN	**	No	Other	0.24 3.26
3.	M/56 y	Yes	Scalp	10/6 MbBowen	Moderate	Yes	0/6 Parotid gland	Scar and locoregional nodes, cranial nerves, skin	Radiotherapy and setuksimabi	No	Squamous cell ca	0.64 3.80
4.	M/84 y	Yes	Lower lip	12/6 Conventional	Moderate	Yes	0/5 Bilateral neck	Locoregional skin and subcutis and ipsilateral neck LN	Neck dissection LI-III, N 2/4 and ECS*, Radiotherapy	No	Squamous cell ca	0.41 1.22
5.	F/55 y	No	Scalp	30/10 MbBowen	Moderate	No	0/7 Bilateral neck	Locoregional subcutis and ipsilateral neck LN***	re-excision and neck dissection LII-V, N 3/29, chemo-radiation	No	Squamous cell ca	0.71 1.87

L: neck dissection level.
LN: lymph node.
RFS: recurrence-free survival.
OS: overall survival.
* ECS: extracapsular spreading.
** Patient refused for further treatment.
*** Progression to systemic multiple metastases.

of the patients identified for various reasons, including erroneous diagnosis, inadequate high-risk criteria or missing follow-up data. Anyhow, the number of patients is very comparable with similar current studies. SLNB surgery was performed by a few plastic surgeons in this study, which might have resulted in a bias. However, they were all experienced with this concept and the surgical procedure.

Strengths of the study include the re-conformation for histomorphology of all primary tumours and immunohistochemistry (pancytoceratin) of the sentinel nodes by the same experienced dermatopathologist. In addition, the follow-up time was exceptionally long, median 4.1 years.

Although, according to our own research, SLNB has no prognostic value for high-risk cSCC, the role of sentinel node is still under debate. Other factors are needed to differentiate between well-behaved and aggressively behaving cSCC, TNM-based classification alone is not enough. Further studies are needed to possibly find the group the procedure benefits.

Declaration of Competing Interest

Each author declares no financial conflicts of interest with regard to the data presented in this manuscript.

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