Ann Surg Oncol (2019) 26:4481–4488
https://doi.org/10.1245/s10434-019-07865-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Sentinel Node Biopsy in 105 High-Risk Cutaneous SCCs of the Head and Neck: Results of a Multicenter Prospective Study

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ABSTRACT

Background. Regional nodal metastases from cutaneous squamous cell carcinoma (cSCC) is strongly associated with a poor prognosis, but these metastases are difficult to predict clinically. Sentinel node biopsy (SNB) has been used for a wide range of malignancies to assess for regional nodal metastasis, but is not widely used for cSCC.

Methods. Patients presenting with high-risk cSCC of the head and neck with clinically N0 necks were offered SNB at the time of primary cSCC excision or secondary wide local excision. Patients with positive sentinel nodes were offered completion lymph node dissection, and all the patients were followed up at regular intervals for up to 5 years.

Results. In this study, 105 lesions underwent SNB, and 10 sentinel nodes (9.5%) were positive. In an additional five patients, regional recurrence developed after a negative sentinel node, with a total subclinical nodal metastasis rate of 14.3%. Nodal metastases were significantly associated with reduced disease-specific survival. The significant predictors of metastasis were four or more high-risk features or tumors with a concurrent invasion deeper than 5 mm and PNI.

Conclusion. For high-risk cSCC, SNB is a safe and feasible staging technique. The total number of high risk features and certain combinations of high-risk features predicted metastasis better than individual high-risk features.

Non-melanoma skin cancer is one of the most common cancers in the Western world, with an incidence varying markedly according to the two predominant risk factors: skin type and ultraviolet (UV) sun exposure.[1]

Cutaneous squamous cell carcinoma (cSCC) constitutes approximately 20% of non-melanoma skin cancer, making it the second largest subgroup after basal cell carcinoma.[2] The cSCC incidence rates in Australia are reported to be as high as 387 per 100,000/year,[3] with SCC diagnosed for approximately 700,000 patients per year in the United States,[4] and the incidence is continuing to rise worldwide.[5,6]

Regional (nodal) metastases are the most important predictor of prognosis for patients with cSCC, but occur in less than 5% of patients. The majority of the tumors are

First Received: 14 January 2019;
Published Online: 3 October 2019

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cured by simple excision or other local techniques.[2] Several high-risk clinical and pathologic features have been reported in retrospective studies including locally recurrent tumors, perineural and lymphovascular invasion, poor differentiation, immunosuppression, invasion into subcutaneous tissues, and larger size.[7–9] The regional nodal metastasis rates for certain high-risk groups are reported to be as high as 47.3%,[10] but this could not be verified in any prospective studies. Currently, there is poor concordance among a range of clinical guidelines on what characteristics constitute high-risk features, with a number of additional high-risk features such as histologic subtypes (e.g., adenosquamous, desmoplastic), lesions in the previous radiotherapy field, and growth rate also included.[11]

Sentinel node biopsy (SNB) has been validated as an accurate technique for assessment of regional nodal metastasis in a range of malignancies. The procedure is reported to increase staging accuracy, improve local disease control, and provide prognostic information.[12] However, the recently published The Dermatologic cooperative oncology group (DeCOG) and Multicenter selective lymphadenectomy trial II (MSLT-II) results show no survival benefit from CLND compared with ultrasound surveillance.[13,14]

Sentinel node biopsy has been assessed only in small, mostly retrospective studies of cSCC (Table 1), and its use remains controversial. Interest in SNB for detecting occult nodal metastasis appears to be growing, as is evident by the increasing number of studies and review articles in recent years.[15–17] A recent meta-analysis of 23 studies observed that no studies have reported on the prognostic value or predictors of a positive sentinel lymph node and noted the need for further studies to address these issues.[18] Further uncontrolled studies are required to identify the high-risk characteristics of metastasis and to define a high-risk population that would be suitable for controlled trials.

The primary aim of this study was to prospectively determine the rate of subclinical nodal metastases in high-risk cSCC using SNB combined with long-term follow-up evaluation. The secondary aims were to determine whether reliable clinicopathologic predictors of nodal metastases could be verified and whether a randomized prospective study was feasible.

TABLE 1 Published studies on sentinel lymph node biopsy (SLNB) in cutaneous squamous cell carcinoma (cSCC) with 5 or more patients

References	Study design	Tumor locations	No. of tumors	% of SLN-positive patients
Altinyollar et al.[23]	Prospective	Lip	20	16.6
Michl et al.[24]	Retrospective	Various	11	18.2
Reschly et al.[25]	Retrospective	Various	9	44
Eastman et al.[26]	Prospective	Extremities	6	66.7
Nouri et al.[27]	Prospective	Head and neck	8	12
Wagner et al. [28]	Retrospective	Various	17	29.4
Cecchi et al.[29]	Unknown	Various	5	20
Civantos et al.[30]	Retrospective	Head and neck	15	6.7
Mullen et al.[31]	Retrospective	Trunk/extremities	14	0
Renzi and Caggiati[32]	Retrospective	Various	22	4.5
Sahn and Lang[33]	Retrospective	Various	9	0
Rastrelli et al.[34]	Retrospective	Various	20	5
Kwon[35]	Retrospective	Various	6	0
Hokkam et al.[36]	Prospective	Lip	18	11.1
Matthey-Gie et al.[37]	Retrospective	Various	8	12.5
Fukushima et al.[38]	Retrospective	Various	54	7.4
Takahashi et al.[39]	Retrospective	Various	26	23.1
Krediet et al.[40]	Retrospective	Various	17	11.7
Sollamo et al.[41]	Retrospective	Lip	26	11.5
Gore et al.[19]	Prospective	Head and neck	57	14.0
Durham et al.[42]	Retrospective	Head and neck	53	11.3
Samsanavicius[43]	Retrospective	Various	51	0
Maruyamae et al.[44]	Retrospective	Various	49	18.4
Total			521	8.9
Mooney et al.	Prospective	Head and neck	105	9.5

SLN sentinel lymph node

MATERIALS AND METHODS

Patient Selection

Patients presenting to trial centers with a clinically high-risk cSCC were offered primary SNB during wide local excision of the tumor. Patients with a pathologically high-risk cSCC shown by histology were offered secondary sentinel biopsy with or without a wider local excision as deemed required. The patients underwent clinical examination for regional nodal metastases, but routine radiologic assessment was not undertaken unless the primary tumor warranted computed tomography (CT) or magnetic resonance imaging (MRI) to assess the extent of local invasion.

Inclusion Criteria

The inclusion criteria specified a tumor with at least one of the following recognized high-risk features: size larger than 2 cm, invasion into subcutaneous fat (Clark level 5) or depth of invasion (DOI) greater than 5 mm, poorly differentiated tumor, perineural invasion (PNI), lymphovascular invasion, local recurrence in the setting of adequate prior resection margins, ear or lip location, immunocompromise (after organ transplantion, chemotherapy), and carcinoma in a preexisting scar.

Exclusion Criteria

The exclusion criteria ruled out clinical (physical, radiologic, or pathologic) evidence of regional or distant metastasis, previous surgery such as regional nodal dissection that may have adversely altered lymphatic drainage (previous SNB-alone cases were not excluded), allergy to patent blue dye or radiocolloid, significant cognitive or psychiatric disorder (inability to give informed consent); pregnancy or lactation, and inability to complete 5 years of follow-up evaluation.

Ethical board approval was given by the Sydney Local Health District Ethics Review Committee (protocol no. X09–0325, HREC/09/RPAH/547).

Procedure Detail

The patients underwent preoperative lymphoscintigraphy according to local nuclear medicine department protocols that varied between sites. Intraoperatively, patent blue dye was injected at four sites along the periphery of the tumor or along the edge of the scar or flap/graft for previously excised tumors. Typically, SNB was performed before tumor excision or reexcision, except for patients whose primary tumor location made localization of the sentinel node difficult. The incisions for SNB were planned so that they could be included in any further completion lymph node dissection (CLND).

Intraoperative sentinel node location was identified by a combination of a handheld gamma probe, visual identification of a "blue" node, and review of the preoperative lymphoscintigram. Tumor resection margins were individualized to individual tumor clinicopathologic characteristics, with the aim to have histologically clear margins. Wound closure was at the discretion of the operating surgeon.

Pathology Protocol

All sentinel nodes were submitted for analysis. Each node was cut along its longitudinal axis into 3-mm-thick slices and entirely embedded in paraffin after tissue processing. Four sequential 5-μm tissue sections then were cut from each block and stained with hematoxylin–eosin and cytokeratins. The lead skin cancer histopathologist at each center microscopically examined each section to determine the presence of metastases.

Post-sentinel Node Management

Patients identified as having macroscopic evidence of metastasis at the time of SNB and confirmed in the intraoperative frozen section analysis, proceeded directly to immediate therapeutic selective lymph node dissection. Patients identified as having microscopic metastasis via a formal pathologic examination were offered CLND. Patients with a negative SNB were followed up clinically for 5 years at 4-month intervals for the first 2 years and then at 6-month intervals thereafter. Clinical suspicion of nodal metastasis was initially investigated by ultrasound and further imaging at the discretion of the treating surgeon.

Statistical Analysis

Patient data including individual demographics, tumor clinicopathologic characteristics, and outcome data were collected and summarized using descriptive statistics. Categorical data were analyzed using a two-tailed Chi-square test, and logistic regression models were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Survival analysis was performed using the Kaplan–Meier method, and comparisons between groups were made using the log-rank test. Statistical significance was set at a p value lower than 0.05. Statistical analysis was performed using IBM SPSS version 25.0 (IBM Corp, Armonk, NY, USA), and GraphPad Prism (GraphPad Software) 7.02 was used to generate Kaplan–Meier curves.

RESULTS

Between February 2010 and September 2017, 105 SNB procedures were performed for 104 patients, with one patient undergoing two SNBs for metachronous lesions 32 months apart. The average patient age at the time of SNB was 65 years (range 27–90 years), and the series had a strong male preponderance (male:female, 90:14). On 41 occasions (39%), the SNB was performed at the initial lesion excision after pathologic examination of the lesion, with or without further excision, to achieve adequate margins on 31 occasions (30%) or at the time of recurrent lesion resection on 33 occasions (31%).

Pathologic features of the lesions such as location, tumor diameter, DOI, tumor differentiation, PNI, and lymphovascular invasion are described in Table 2. The mean tumor diameter was 23.3 mm (range 2.9–65 mm; $n = 101$), and the mean DOI was 8.5 mm (range 1–25 mm; $n = 101$). The mean number of nodes excised at the time of SNB (excluding 4 patients who underwent immediate CLND for macroscopic disease) was 3.6 (range 0–18; $n = 101$).

TABLE 2 Clinical and pathologic tumor characteristics

Clinicopathologic characteristic	*n*	%
Site		
Scalp	18	17.1
Forehead/temple	18	17.1
Ear	12	11.4
Cheek	16	15.3
Nose	8	7.6
Lip	24	22.9
Neck	9	8.6
Tumor diameter (mm)		
< 20	45	42.9
20–50	50	47.6
> 50	6	5.7
Not reported	4	3.8
Tumor depth (mm)		
0–5	27	25.7
> 5	74	70.5
Not reported	4	3.8
Tumor differentiation		
Well	21	20
Moderate	38	36.2
Poor	45	42.9
Unknown	1	0.9
Tumor invasion		
Perineural	42	40
Lymphovascular	7	6.6

A sentinel node could not be identified in six patients (5.7%), including one patient with an intra-parotid sentinel node that would have required a superficial parotidectomy. In one patient with a ventriculo-peritoneal shunt, a lymphoscintigraphy-guided neck dissection was part of the radical excision performed for a recurrent auricular SCC rather than an SNB due to concern that previous surgery may have altered lymphatic drainage patterns, and all 31 lymph nodes were negative for SCC.

A total of 15 patients (14.3%) had subclinical nodal metastases, including 10 patients with a positive sentinel node (9.5%) and an additional five patients (4.8%) who had nodal recurrence at the follow-up assessment. Macroscopic disease was identified at the time of SNB in four cases, and CLND was undertaken during SNB. Microscopic disease was identified on pathologic examination of the sentinel nodes in six cases, with three patients having CLND as per protocol. The remaining two patients underwent postoperative radiotherapy, and one patient declined any further intervention. This patient experienced recurrence 11 months after SNB and subsequently underwent levels 2–5 neck dissection with 3 of 26 nodes shown to be positive.

Of the seven patients who underwent either immediate or staged neck dissection as per protocol, the median number of nodes removed was 35.4 (range 6–60; $n = 7$), and the mean number of involved nodes was 3.4 (range 1–14; $n = 7$), including nodes removed with the SNB. The negative predictive value of SNB was 94.7%. The overall sensitivity for SNB was 66.7%, and the specificity was 100%.

Recurrence and Survival

The median follow-up period was 26.2 months (range 1–60 months; $n = 105$). At the time of analysis, the findings comprised 13 local recurrences (4 SNB-positive), eight regional recurrences (3 SNB-positive), and four distant metastases (3 SNB-positive). Nodal metastases developed in one patient more than 5 years after SNB in the context of multiple subsequent cutaneous SCC excisions, and this was not believed to be associated with the index lesion for which the SNB was performed. Another patient experienced distant disease (L2 vertebra deposit) in the absence of local or regional recurrence.

A total of ten patients died of cSCC during the follow-up period. The 5-year disease-specific survival rate was 83.1% ± 5.2%. The patients with subclinical nodal metastases had a significantly higher mortality rate than those without nodal metastases ($p < 0.0001$; Fig. 1). Death

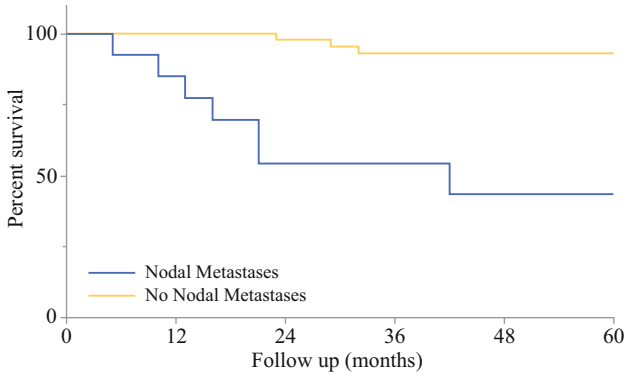

FIG. 1 Disease-specific survival of patients with and without nodal metastases calculated using Kaplan–Meier estimates. Nodal metastases were significantly associated with reduced survival ($p < 0.0001$)

was due local failure in three cases, regional failure in two cases, distant failure in two cases, local and regional failure in one case, and both local and distant failure in one case. One patient died of local, regional, and distant failure.

Predictors of Nodal Metastases

In the univariate analysis, the only significant predictor of subclinical nodal metastases was DOI. The rate of nodal metastases for the patients with a DOI of 5 mm or greater was 19.7% (15/76) compared with 0% (0/23) for the patients with a DOI of less than 5 mm ($p = 0.01$). The rate of nodal metastases in the patients with a DOI of 10 mm or greater was 25% (8/32) compared with 0% (0/67) for the patients with a DOI of less than 5 mm ($p = 0.001$). However, for the patients with both a DOI of 5 mm or greater and PNI, the rate of nodal metastases was 28.1% (9/32) compared with 9% (6/67) for the patients who did not fulfil both criteria ($p = 0.02$; Table 3). The median number of inclusion criteria for the patients with subclinical nodal metastases was four compared with three for the patients without nodal metastases ($p = 0.036$; Table 4).

No individual high-risk feature (i.e., inclusion criterion) was significant in predicting subclinical nodal metastasis in the multivariable analysis using logistic regression. Using a backward elimination method, only the number of inclusion criteria (≥ 4 vs ≤ 3) was statistically significant (OR 3.3; 95% CI 1.1–10.2; $p = 0.035$). When the number of inclusion criteria was excluded from the model and the depth criteria was set deeper than 10 mm (because all positive SNB lesions were > 5 mm), the only significant predictor of subclinical nodal metastases was a depth greater than 10 mm (OR 3.2; 95% CI 1.0–10.1; $p = 0.043$).

Complications

Two patients had SNB wound-site infections requiring oral antibiotics, but this did not prolong their hospital stay, and one patient had a postoperative hematoma managed conservatively, bringing the rate of minor complications to 2.9%. Complications attributed to primary tumor resection, reconstruction, or CLND were not recorded.

DISCUSSION

This study, which represents the largest cohort of SNB for cSCC of the head and neck to date, demonstrated that subclinical nodal metastases occur in 14.3% of high-risk lesions. The significant predictors of nodal metastases were DOI, PNI, and number of high-risk factors.

The SNB-positive rate of 9.5% and the occult metastasis rate of 14.3% in this cohort were comparable with the cumulative reported rate of 8.9% in the current literature for cSCC of the head and neck (Table 1). The preliminary results from this prospective clinical trial were reported in 2015, with 57 patients and a mean follow-up period of 19.4 months.[19] In this study of 105 patients (including the previous 57 patients), the mean follow-up period was 28.3 months, and 16 patients reached 5 years of follow-up evaluation.

TABLE 3 Statistical significance of positive sentinel node biopsy (SNB) and subclinical nodal metastases by indication(s) for SNB

	SNB-positive p value[a]	Subclinical nodal metastases p value[a,b]
> 5-mm depth	0.113	0.020
> 10-mm Depth	0.001	0.001
PNI	0.085	0.150[c]
> 5-mm depth with PNI	0.008	0.020
> 3 indications	0.007	0.073

PNI perineural invasion

[a] p values are for Fisher's exact test unless otherwise marked

[b] SNB-positive patients and SNB-negative patients in whom metastasis subsequently developed

[c] Pearsons Chi-square

TABLE 4 Number of inclusion criteria for subclinical nodal metastases-negative and metastases-positive patients

No. of inclusion criteria	Frequency in SNB-negative cases	Frequency in SNB-positive cases	% Positive
1	13	0	0
2	25	4	13.8
3	29	3	9.4
4	16	5	23.8
5	7	2	22.2
6	0	1	100

SNB sentinel node biopsy

Although SNB is a safe procedure, in the current study, the regional failure rate was 7.6%, which was considerably higher than that reported previously (1.7%), reflecting the longer follow-up period. Regional recurrence developed in five patients after a negative sentinel node (Table 5), giving a negative predictive value of 94.7%. This may be artificially low because one of the patients did not have the sentinel node resected considering that it would have required a formal parotidectomy, and another patient had a high-risk local recurrence in the interval between the negative SNB and regional recurrence. Exclusion of these cases for the aforementioned reasons would have resulted in a false-negative rate of 23.1% (i.e., 3 false-negatives in 13 patients with subclinical nodal metastasis).

Other factors that had an impact on the negative predictive value included some large primary tumors that potentially crossed several lymphatic drainage pathways and some patients with multiple synchronous and metachronous lesions, making it difficult to define the index lesion for a given nodal metastasis. This was illustrated by one patient in this cohort who presented with metastasis more than 5 years after a negative SNB. Future studies may need to consider controlling for such factors to differentiate better between true false-negatives and regional recurrences from synchronous or metachronous lesions. Finally, it would be ideal to perform the SNB at the time of the initial lesion excision to avoid disturbing the lymphatic drainage, but this was not possible because several inclusion criteria were pathologic.

This study reinforced our preliminary data showing that DOI is an important predictor of nodal metastases in that no patient with a DOI less than 5 mm experienced nodal metastases and the rate of nodal metastasis increased for tumors 10 mm or larger (25%) compared with tumors 5 mm or larger (19.7%). When combined with PNI, a DOI of 5 mm or greater increased the rate of nodal metastases to

TABLE 5 Characteristics of patients with negative sentinel node and regional recurrence

Age/ Gender[a]	Lesion location	SNB timing	Differentiation	Sentinel node excised	Time to regional recurrence (months)	Follow-up length (months)	Status	PNI	Number of inclusion criteria
34F	Lip	Rec[b]	Moderate	Y	24.5	68.4	Alive without disease	Present	6
58M	Temple	Primary[c]	Moderate	N	7.3	13.0	Deceased due to metastatic SCC	Present	2
34M	Lip	WLE[d]	Moderate	Y	5.1	66.1	Alive without disease	Absent	2
76M	Scalp	Primary	Poor	Y	11.4	16.0	Deceased due to locally advanced SCC	Absent	3
76M	Cheek	WLE	Moderate	Y	9.9	44.0	Alive without disease	Absent	2

[a]Age at time of SNB

[b]Excision of recurrent lesion

[c]Initial lesion excision

[d]Wider local excision

28% compared with 9% for the patients who did not fulfil both criteria ($p = 0.02$). Although we were also able to show that the number of high-risk factors also was a significant predictor, the clinical value of comparing four or more high-risk factors versus fewer than four high-risk factors is questionable.

The high-risk nature of the current cohort was demonstrated by the 5-year disease-specific survival rate of 83.1% ± 5.2% and the 2-year local control rate of 88.6% ± 3.1%. Survival for the patients with nodal metastasis was significantly lower than for the patients without nodal metastasis, with 7 of the 15 patients who experienced nodal metastases dying of disease, confirming the prognostic importance of metastatic cSCC.

The high local failure and mortality rates represent a major challenge for the designing of a randomized study with disease progression or mortality as end points. Although SNB has the potential to identify patients with occult nodal metastasis, its value diminishes for patients with early local recurrence.

Currently, no consistently reproducible clinical or pathologic indicators of metastasis are reported in the literature other than DOI and PNI, which also predict strongly for local recurrence. Recently, those performing molecular analysis of cutaneous SCCs hope to identify mutations that may predict tumor behavior better than currently used clinicopathologic features.[20] In their studies, epidermal growth factor receptor (EGFR), E-cadherin, B-catenin, and DNA methylation in the primary tumor are showing promise together with other mutations.[21,22] If specific tumor genotypes capable of regional metastasis can be identified, then SNB could be targeted to patients at high risk of nodal metastasis before the development of incurable local disease.

CONCLUSION

Sentinel node biopsy is a safe and feasible staging technique for high-risk cSCC. Thick tumors (DOI > 5 mm), especially those with PNI, have a significantly higher chance of developing nodal metastasis. In the current study, nodal metastases were significantly associated with reduced disease-specific survival. Further studies of SNB in cSCC should focus on defining a subgroup of patients at intermediate risk for cSCC but not at high risk for early local failure and mortality who may benefit from early diagnosis and management of nodal metastases.

AUTHOR CONTRIBUTIONS CPM: data curation, formal analysis, writing—original draft, writing—review and editing. RCWM: conceptualization, data curation, investigation, methodology, supervision, writing—review and editing. RD: data curation, formal analysis, supervision, writing—original draft, writing—review and editing. BGA: data curation, investigation, writing—review and editing. KS: data curation, investigation, writing—review and editing. CEP: data curation, investigation, writing—review and editing. QN: data curation, investigation, writing—review and editing. JW: data curation, investigation, writing—review and editing. SD: data curation, project administration, resources, writing—review and editing. KG: data curation, formal analysis, project administration, resources, writing—review and editing. SC: investigation, supervision, validation, writing—review and editing. T-HL: data curation, formal analysis, investigation, supervision, validation, writing—review and editing. RG: conceptualization, investigation, methodology, project administration, supervision, validation, writing—review and editing. JRC: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualization, writing—original draft, and writing—review and editing.

FUNDING No specific funding.

DISCLOSURES There are no conflicts of interest.

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