Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck

Sinclair M. Gore, MD, FRCS(Plast),[1,2*] Douglas Shaw, BSc, MBBS,[1] Richard C. W. Martin, FRACS,[1,3] Wendy Kelder, MD, PhD,[1,4] Kathryn Roth, MD,[1,5] Roger Uren, MD, FRACP,[6,7] Kan Gao, BEng,[1] Sarah Davies, RN, BSc,[1] Bruce G. Ashford, FRACS,[8] Quan Ngo, FRACS,[9] Kerwin Shannon, FRACS,[1] Jonathan R. Clark, MBiostat, FRACS[1,7,9]

[1]Sydney Head and Neck Cancer Institute, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia, [2]Blenheim Head and Neck Cancer Centre, Oxford University Hospitals, Oxford, United Kingdom, [3]Melanoma Unit, Waitemata Health and Auckland Regional Head and Neck Service, University of Auckland, Auckland, New Zealand, [4]Department of Surgery, Martini Hospital, Groningen, The Netherlands, [5]Department of Otolaryngology – Head and Neck Surgery, St. Joseph's Health Care, London, Ontario, Canada, [6]Nuclear Medicine and Diagnostic Ultrasound, Royal Prince Alfred Hospital Medical Centre, Newtown, New South Wales, Australia, [7]Sydney Medical School, University of Sydney, New South Wales, Australia, [8]Wollongong Hospital, Wollongong, New South Wales, Australia, [9]Liverpool Hospital, Liverpool, New South Wales, Australia.

Accepted 6 May 2015
Published online 15 July 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.24120

ABSTRACT: *Background.* Nodal metastasis from cutaneous squamous cell carcinoma (SCC) is poorly predicted clinically and is associated with a high mortality rate.

Methods. From 2010 to 2013, patients with high-risk cutaneous SCC were assessed with sentinel node biopsy (SNB) either at the time of primary cutaneous tumor resection or at secondary wide local excision.

Results. Of 57 patients, 8 (14%) had nodal metastasis. Significant predictors of metastasis are the number of high-risk factors ($p = .008$), perineural invasion (PNI; $p = .05$), and lymphovascular invasion (LVI; $p = .05$). During a mean of 19.4 months, 9 patients developed recurrence and 6 died of cutaneous SCC, indicating that over 1300 patients would be required for a randomized controlled trial with 80% power to detect a significant difference in disease-free survival.

Conclusion. Lymph node metastasis occurs in 14% of patients with high-risk cutaneous SCC. Larger studies will be required to identify which "high-risk" factors should be considered as an indication for surgical assessment of the nodal basin. © 2015 Wiley Periodicals, Inc. *Head Neck* **38**: E884–E889, 2016

KEY WORDS: squamous cell carcinoma, metastasis, skin cancer, head and neck, sentinel node biopsy

INTRODUCTION

The incidence of lymph node metastasis from cutaneous squamous cell carcinoma (SCC) has been reported as 4.9% for trunk and limb SCC, with an overall survival of 96.6%. Lower survival rates are seen after metastasis of head and neck cutaneous SCC with the worst outcomes in those with nodal extracapsular spread or extranodal deposits of SCC.[1–3] "High-risk" cutaneous SCC has a reported lymph node metastasis rate of up to 37%, depending on the risk criteria used.[4–7] Once patients have developed lymphatic metastasis, the recurrence rate after surgery approximates 30% and 5-year survival rates after recurrence drop below 50%.[8,9] Postoperative radiotherapy is believed to improve locoregional control, and the POST study is investigating the utility of postoperative concurrent chemotherapy and radiotherapy.[10] Many patients with metastasis present with advanced regional disease, therefore, the morbidity and mortality associated with treating metastatic cutaneous SCC should not be underestimated.

Sentinel node biopsy (SNB) has been trialed in many disciplines of surgery and has been validated as a screening tool for cancer metastasis.[11] Its use in cutaneous oncology has been mainly limited to malignant melanoma, but the technique has also been applied in small series to Merkel cell carcinoma[12] and cutaneous SCC.[13–25] The proven benefits of SNB in some (although not all) of the tumors above include improved survival, prolonged disease-free interval, reduced morbidity of disease or treatment, provision of accurate prognostic information to guide adjuvant therapies, and increased cost-effectiveness.

For "high-risk" cutaneous SCC, it is reasonable to consider that the SNB would provide important information about regional micrometastasis. On the basis of this, it may be possible to provide a more individualized, patient-tailored treatment with early lymphadenectomy in cases of occult metastatic disease, which may reduce the morbidity of treatment, improve locoregional control of the disease, and potentially improve survival. A number of smaller patient series have reported the use of SNB in cutaneous SCC and are summarized in Table 1.[13–25]

***Corresponding author:** S. M Gore, Blenheim Head and Neck Unit, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE, United Kingdom. E-mail: sinclair.gore@ouh.nhs.uk

The preliminary data of this work was presented at the Australia and New Zealand Head and Neck Cancer Society (ANZHNCS) conference, Brisbane, Australia, October 26, 2012.

TABLE 1. Results of sentinel node biopsy studies in cutaneous squamous cell carcinoma, which included more than 5 cases and comparison with results of this study.

Author, year (ref)	No. of SCC cases	Tumor location	% of node-positive patients
Altinyollar, 2002[13]	20	Lower lip	17
Cecchi, 2005[14]	5	Various	20
Civantos, 2008[15]	10	Face	10
Eastman, 2004[16]	6	Extremity	67
Kwon, 2011[17]	6	Various	0
Michl, 2003[18]	11	Various	18
Mullen, 2006[19]	14	Trunk/extremity	0
Nouri, 2004[20]	8	Face	12
Rastrelli, 2010[21]	20	Various	5
Renzi, 2007[22]	22	Foot	4.5
Reschly, 2003[23]	9	Various	44
Sahn, 2007[24]	9	Various	0
Wagner, 2004[25]	11	Face	18
TOTAL	146	Various	13
Gore et al	57	Head and neck	12.3

Abbreviation: SCC, squamous cell carcinoma.

The purpose of this study was to determine the rate of nodal metastasis in "high-risk" cutaneous SCC, to examine whether the accepted clinicopathological factors should be considered "high-risk," and to decide whether a randomized controlled trial is feasible.

MATERIALS AND METHODS

Patient selection

All patients who presented to the trial centers since early 2010 with a clinically high-risk primary or recurrent cutaneous SCC were offered wide excision of the tumor and concurrent SNB. Those patients who presented after excision of a cutaneous SCC that was pathologically confirmed to be high-risk were offered secondary SNB, either alone or along with a wider excision, if that were deemed appropriate. In all cases, clinical examination was used to assess regional lymph node basins; radiological staging was not routinely undertaken before SNB. Ethical board approval was given by the Sydney Local Health District Ethics Review Committee (protocol no. X09–0325, HREC/09/RPAH/547) and the study commenced on May 2, 2010.

Inclusion criteria comprised at least one of these characteristics in a patient with cutaneous SCC: (1) tumor size >2 cm; (2) invasion into subcutaneous fat or tumor thickness >5 mm; (3) poorly differentiated tumor; (4) perineural invasion (PNI); (5) lymphovascular invasion (LVI); (6) local recurrence in the setting of adequate prior resection margins; (7) ear or lip location; (8) immunocompromise (post-organ transplant, chemotherapy); and (9) carcinoma in a preexisting scar.

Exclusion criteria comprised: (1) clinical (physical, radiological, or pathological) evidence of distant metastasis; (2) previous surgery that may have adversely altered lymphatic drainage, such as regional nodal dissection (previous SNB-alone cases not excluded); (3) allergy to patent blue dye or radiocolloid; (4) significant cognitive or psychiatric disorder (unable to give informed consent); (5) pregnancy/lactation; and (6) inability to complete 5 years of follow-up.

Procedural detail

Preoperative lymphoscintigraphy was performed according to local nuclear medicine department protocols. Intraoperatively, patent blue dye was injected intradermally at 4 points around the center of the scar, the periphery of the tumor, or at the edge of a small skin graft or flap.

SNB was typically performed immediately before primary tumor site (re)excision, unless the location of the primary tumor hampered the detection of the sentinel node field. Incisions for SNB were made in appropriately planned sites for inclusion in potential completion lymph node dissections (CLNDs). Sentinel nodes were identified by the combination of the preoperative lymphoscintigram, the visually identified "blue" node, and the use of a handheld gamma probe.

Primary tumor resection margins were individualized according to clinicopathological criteria, in all cases aiming for macroscopic tumor clearance and histologically clear margins. Wound closure was at the discretion of the operating surgeon.

Pathology protocol

All sentinel nodes were cut along their longitudinal axis in 3-mm thick slices and embedded entirely in paraffin blocks after tissue processing. Four sequential 5 μm tissue sections were cut from each block and stained with hematoxylin-eosin and with cytokeratins. Each section was examined microscopically for the presence of metastatic tumor cells by the lead skin cancer histopathologist in each enrolled center.

Post-sentinel node biopsy management

Patients who were shown to have micrometastatic disease were offered CLND. Patients who were discovered at the time of SNB to have occult macroscopic disease

underwent immediate therapeutic selective lymphadenectomy after intraoperative confirmation of the diagnosis with frozen section analysis. After a negative SNB, patients were followed clinically at 4 monthly intervals for the first 2 years, and then 6 monthly intervals thereafter.

Statistical analysis

Patient data recorded included patient demographic data, tumor data, nodal tissue data, and patient outcome data. This information was summarized using descriptive statistics. Continuous data were analyzed using a *t* test and categorical data using a chi-square test. Adjusted odds ratios (ORs) were calculated using logistic regression. Statistical analyses were performed using Stata version 11 (StataCorp, College Station, TX). Sample size calculations were performed using ACCorD version 1 (Boffin, Sydney).

RESULTS

Between January 2010 and April 2013, 57 patients were enrolled. The mean age was 67 years (range, 29–90 years) with a male preponderance (male:female = 47:10). SNB was undertaken in 45 patients (79%) at the time of cutaneous tumor resection, of which 17 (30%) were recurrent tumors. In 12 cases (21%), pathological analysis of the excised cutaneous tumor (primary:recurrent = 10:2) prompted SNB and further wide local excision was performed to achieve adequate margins.

Tumor location, diameter, depth, differentiation, invasion, and metastasis are described in Table 2. The mean tumor diameter was 25 mm (range, 6–65 mm) and mean depth of invasion was 9.2 mm (range, 1.0–22 mm). In 44 cases, the tumor was over 5-mm thick or was at least invading to Clark level 4. The mean number of sentinel nodes identified on preoperative lymphoscintigraphy was 2.2 (range, 0–6). In 1 case, there was a failure of the SNB technique because of no identifiable sentinel node being found on lymphoscintigraphy and no identifiable sentinel node upon nodal basin exploration. In all other cases ($n = 56$), at least 1 sentinel node was found. Two cases underwent immediate selective neck dissection because of the intraoperative finding of macroscopic tumor, whereas the remaining 55 cases had only sentinel nodes resected.

In total, 7 patients (12.3%) had subclinical nodal metastasis detected at the time of planned SNB. In 5 cases (8.8%), micrometastatic SCC was detected on pathological examination, and in 2 cases (3.5%) macroscopic tumor was discovered at the time of SNBexploration. All 7 patients proceeded to therapeutic lymphadenectomy; the 5 SNB cases were performed as completion lymphadenectomies after histopathology results, whereas the 2 patients with macroscopic disease proceeded to immediate selective neck dissection. In these 2 patients, the number of nodes containing tumor was recorded. In 1 case, intraparotid macroscopic disease was found, therefore completion parotidectomy and level II neck dissection was completed: only 1 intraparotid node contained tumor. In the second case, macrometastasis was found in the submandibular nodes; immediate bilateral supraomohyoid dissections revealed 14 of 58 nodes containing tumor. Of 5 patients who had nodal micrometastasis and proceeded to CLND, 2 had further metastatic disease identified in the neck dissection specimen (one further positive node in each case).

TABLE 2. Clinical and pathological tumor characteristics.

	No.	%
Site		
Scalp	14	24.6
Forehead/temple	8	14.0
Ear	6	10.5
Cheek	7	12.3
Nose	6	10.5
Lip	12	21.1
Neck	4	7.0
Tumor diameter, mm		
<20	21	36.8
20–50	32	56.1
≥50	4	7.0
Tumor depth, mm		
0–5	19	33.3
>5	38	66.7
Tumor differentiation		
Well	10	17.5
Moderate	27	47.4
Poor	20	35.1
Tumor invasion		
Perineural	22	38.6
Lymphovascular	3	5.3
Metastatic disease confirmed		
Micrometastasis	5	8.8
Macroscopic disease	2	3.5

Median follow-up was 19.4 months (range, 2.4–41 months). At the time of analysis, 9 patients (15.8%) had developed recurrence, of whom 3 had subclinical metastasis detected by SNB. There were 6 patients (10.5%) who had died of cutaneous SCC, of whom 2 had subclinical metastasis detected, giving a 3-year disease-specific survival rate of 82%. There were 8 local failures (SNB-positive = 2), 2 regional failures (SNB-positive = 1), and 3 distant failures (SNB-positive = 2). The 1 patient who failed SNB developed regional recurrence, increasing the true number of patients with subclinical nodal metastasis to 8 (14%). One patient developed in-field regional recurrence after positive SNB, bilateral neck dissection, and postoperative radiotherapy. This patient subsequently died of disease and was the only patient to die with established regional recurrence after positive SNB. The other 5 patients who died of disease during the follow-up period suffered local recurrence ($n = 4$) and/or distant disease ($n = 2$). No episodes of distant recurrence in the absence of local or regional recurrence have been noted. Patients with confirmed subclinical metastatic disease had a significantly higher mortality rate than those whose SNBs were negative for disease ($p = .0082$; Figure 1).

There were no major or minor perioperative or long-term complications that could be attributed to the SNB procedure. However, many patients had extensive primary tumor resections, major reconstructions, and CLND in selected cases. Complications related to these procedures were not recorded.

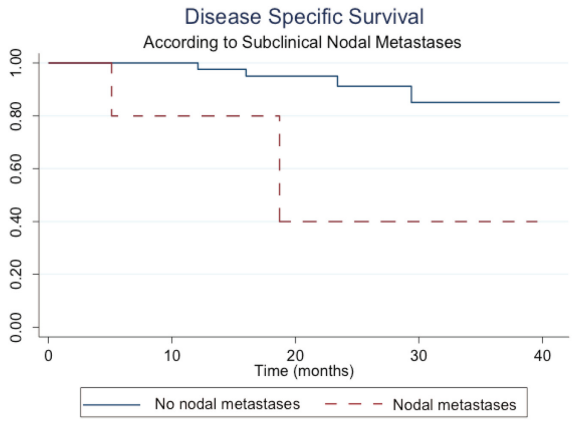

FIGURE 1. Kaplan–Meier survival analysis of patients with and without nodal metastasis. Patients with metastasis had significantly worse survival than those without ($p = .0082$).

The median number of indications for SNB was higher in patients with subclinical nodal metastasis ($n = 5$) than in nodal metastasis-negative cases ($n = 3$; $p = .04$). The number of inclusion criteria is shown in Table 3. Many of the inclusion criteria were significant predictors of nodal metastasis on single variable analysis (Table 4). Multivariable analysis using logistic regression to adjust for the effect of covariates was unstable because of the small sample size. However, using a backward elimination technique, only the number of high-risk factors remained significant ($p = .008$; OR = 10 for 4 or more factors compared to 3 or less factors). If the number of high-risk factors was removed from the regression, then PNI ($p = .05$; OR = 10) and LVI ($p = .05$; OR = 38) were significant predictors of nodal metastasis after adjusting for the effect of location, differentiation, and depth of invasion. It is important to note that all patients with nodal metastasis had depth of invasion >5 mm (hence, it could not be included in the regression) and that very few patients had LVI ($n = 3$), however, in those that did, the rate of nodal metastasis was 67%.

TABLE 3. Frequency of numbers of inclusion criteria cases proven to be negative and positive for nodal metastasis.

No. of inclusion criteria	Frequency in N-negative cases	Frequency in N-positive cases
1	6	0
2	15	0
3	18	1
4	7	2
5	3	3
6	1	1
Median number of inclusion criteria	3	5

Mean number of sentinel node biopsy indications was higher in cases proven to have nodal metastasis (N-positive).

TABLE 4. Univariable analysis (Pearson chi-square tests) of nodal metastasis or recurrence by sentinel node biopsy indication.

	Nodal metastasis *p* value	Nodal metastasis or nodal recurrence *p* value
LVI	.003	.007
Poor differentiation	.154	.281
PNI	.006	.023
Ear, nose, or lip	.093	.042
>4 indications	.001	.003
>5 mm depth	.125	.097
>10 mm depth	.043	.105

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion.

DISCUSSION

The overall rate of metastasis from all cutaneous SCCs is low, but particularly high-risk tumors of the head and neck have been shown to have an elevated metastatic risk of up to 37%.[6] Our prospective data suggest, however, that occult metastasis occurs in only 14% of patients with a broad spectrum of high-risk factors, although this may increase as follow-up continues. The high local recurrence rate (14%) and mortality rate (10.5%) in this study confirm the "high-risk" nature of the primary tumors included in this study population.

In this study, clinical examination was used as the principal assessment of whether regional or systemic metastasis was present when SNB was considered. Given the broad spectrum of high-risk factors included in this study, it was considered that the true-positive rate of systemic metastasis, as indicated by CT scanning, would be sufficiently small that regional surgical management would not be enhanced.

Frozen section analysis was only used for intraoperative confirmation of suspected macrometastasis, permitting immediate selective neck dissection. It was not used for analysis of true sentinel nodes; as in commonly used melanoma protocols, the authors believe that traditional paraffin-embedded sections are the gold-standard method of assessing such tissue. Minimal delay to definitive treatment was incurred by those who proceeded to definitive nodal basin dissection.

The majority of cases in this series underwent SNB at the time of definitive tumor excision ($n = 45$) with the remainder being treated at the time of wider excision ($n = 12$). No correlation was found between immediacy of SNB and accuracy of the technique. It would be ideal to only perform SNB at the time of primary tumor excision but, given that some of our inclusion criteria were pathological rather than clinical, 12 of 57 cases were performed after the tumor had been excised. Later studies may have enough recruiting power to include only cases in which SNB is performed concurrently with primary excision.

In 1 patient (1.7%), SNB failed as a technique because of there being an absence of identifiable sentinel nodes on lymphoscintigraphy and no identifiable radioactive or dyed nodes on surgical exploration. In no cases did a negative sentinel node lead to subsequent regional failure; the only regional failures were in 1 sentinel node-positive

patient (who had aggressive disease and recurred despite maximal surgical and radiotherapy treatment) and the patient who failed SNB. Although the follow-up duration of this cohort is not optimal, this reflects a 0% false-negative rate for SNB as a technique when performed; it is possible that later analyses of this cohort will show later recurrences that will raise the false-negative rate of SNB in this setting.

The strongest predictors of metastasis were the number of high-risk tumor factors present and pathological diagnosis of PNI and LVI. In this study, individual clinical factors were not strongly predictive of metastasis. Schmitt et al[26] have confirmed that the number of high-risk factors has an impact on SNB-positivity in cutaneous SCC. Beyond PNI and LVI, depth of invasion does remain an important consideration as all patients in our study with metastasis had primary tumors more than 5-mm thick. Univariable analysis shows that increasing tumor thickness has a significant effect on likelihood of nodal metastasis (Table 3) with tumors >10-mm in depth being significantly more likely to suffer nodal metastasis ($p = .043$) than thinner tumors but, interestingly, this was not borne out when assessing later nodal recurrence or survival ($p = .105$). It is clear from Australian series that the majority of nodal metastases do not arise from aggressive primary cancers and most are curable.[2,3,7,9] Therefore, using high-risk primary features as inclusion criteria may exclude those patients who are most likely to benefit from the SNB technique (ie, those with easily treated primary cancers who present with advanced nodal disease).

Although elective neck dissection has become routine in mucosal SCC, this is a less attractive approach for cutaneous SCC because of the unpredictable nature of cutaneous lymphatic drainage and high sensitivity associated with the pathological processing of sentinel nodes. Currently, the presence of micrometastasis is an indication for nodal basin dissection and lymphadenectomy; although the MSLT-II trial in melanoma aims to answer whether SNB is adequate without definitive nodal basin clearance, such refinements of surgical treatment have not been trialed in cutaneous SCC and 20% of patients in this series had additional disease on completion neck dissection. The use of lymphoscintigraphy is critical to guide therapeutic nodal dissections because the pattern of drainage is not predictable from cutaneous sites unless the first nodal echelon is known.[8]

Other authors have described their experience with SNB for cutaneous SCC (Table 1). The overall micrometastatic rate in these 146 cases was 13% but included tumors from a wide range of locations. Of the 82 head and neck primary tumor cases within these studies, 80 SNB procedures were technically successful with 8 positive cases (10%). The current series describes 57 head and neck cutaneous SCCs with a rate of nodal positivity that is consistent with pooled data from the aforementioned articles. These data suggest that SNB for cutaneous SCC of the head and neck is a procedure with a low false-negative rate and high negative predictive value (0.98). Longer term follow-up of this cohort will be required to strengthen these data and ascertain the full effect of SNB (and nodal basin dissection if positive for disease) on survival outcomes.

Taking disease-free survival as a primary endpoint, assuming a 25% dropout rate and based on an estimated 20% nodal relapse at 5 years in the observation group and 5% relapse (local + distant) rate in the treatment arm after early lymphadenectomy (ie, a hazard ratio of 0.25), a randomized controlled study with 204 patients (102 per arm) would have 80% power to detect a difference in recurrence (given a 2-sided test at the 5% level of significance). However, based on the present data, 8 patients (14%) would have failed regionally without SNB compared to 8 (3.5%) in this cohort, and 13 patients (23%) would have developed any type of recurrence compared to 9 (16%) in this cohort. This translates into a hazard ratio of 0.67. Using the same criteria, 1352 patients would have 80% power to detect a difference in recurrence at 5% level of significance.

This is the largest published study of SNB in head and neck cutaneous SCC and highlights the problems of using risk factors that not only predict for nodal metastasis but also local failure. Further studies of SNB in cutaneous SCC should focus on defining which subgroup of patients may benefit from this procedure, namely patients with a high risk of nodal disease but low risk of local recurrence. We emphasize the need to continue this prospective study in order to better define which clinicopathological features are useful predictors of nodal metastasis until primary tumor molecular factors are identified that can more reliably predict metastatic disease potential.

REFERENCES

1. D'Souza J, Clark J. Management of the neck in metastatic cutaneous squamous cell carcinoma of the head and neck. *Curr Opin Otolaryngol Head Neck Surg* 2011;19:99–105.
2. Forest VI, Clark JJ, Veness MJ, Milross C. N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases: results of 2 Australian Cancer Centers. *Cancer* 2010;116:1298–1304.
3. Kelder W, Ebrahimi A, Forest VI, Gao K, Murali R, Clark JR. Cutaneous head and neck squamous cell carcinoma with regional metastases: the prognostic importance of soft tissue metastases and extranodal spread. *Ann Surg Oncol* 2012;19:274–279.
4. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol* 2008;9:713–720.
5. Moore BA, Weber RS, Prieto V, et al. Lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. *Laryngoscope* 2005;115:1561–1567.
6. Peat B, Insull P, Ayers R. Risk stratification for metastasis from cutaneous squamous cell carcinoma of the head and neck. *ANZ J Surg* 2012;82:230–233.
7. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. *Cancer* 2006;106:2389–2396.
8. Ch'ng S, Pinna A, Ioannou K, et al. Assessment of second tier lymph nodes in melanoma and implications for extent of elective neck dissection in metastatic cutaneous malignancy of the parotid. *Head Neck* 2013;35:205–208.
9. Oddone N, Morgan GJ, Palme CE, et al. Metastatic cutaneous squamous cell carcinoma of the head and neck: the Immunosuppression, Treatment, Extranodal spread, and Margin status (ITEM) prognostic score to predict outcome and the need to improve survival. *Cancer* 2009;115:1883–1891.
10. Trans-Tasman Radiation Oncology Group. Post-operative concurrent chemo-radiotherapy versus post-operative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck. Post-Operative Skin Trial, POST study. 0501 Trans-Tasman Radiation Oncology Group, TROG; 2009.
11. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006;355:1307–1317.
12. Gupta SG, Wang LC, Peñas PF, Gellenthin M, Lee SJ, Nghiem P. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: the Dana–Farber experience and meta-analysis of the literature. *Arch Dermatol* 2006;142:685–690.

13. Altinyollar H, Berberoğlu U, Celen O. Lymphatic mapping and sentinel lymph node biopsy in squamous cell carcinoma of the lower lip. *Eur J Surg Oncol* 2002;28:72–74.
14. Cecchi R, Buralli L, de Gaudio C. Lymphatic mapping and sentinel lymphonodectomy in recurrent cutaneous squamous cell carcinomas. *Eur J Dermatol* 2005;15:478–479.
15. Civantos FJ, Moffat FL, Goodwin WJ. Lymphatic mapping and sentinel lymphadenectomy for 106 head and neck lesions: contrasts between oral cavity and cutaneous malignancy. *Laryngoscope* 2006;112(3 Pt 2 Suppl 109):1–15.
16. Eastman AL, Erdman WA, Lindberg GM, Hunt JL, Purdue GF, Fleming JB. Sentinel lymph node biopsy identifies occult nodal metastases in patients with Marjolin's ulcer. *J Burn Care Rehabil* 2004;25:241–245.
17. Kwon S, Dong ZM, Wu PC. Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma: clinical experience and review of literature. *World J Surg Oncol* 2011;9:80.
18. Michl C, Starz H, Bachter D, Balda BR. Sentinel lymphonodectomy in nonmelanoma skin malignancies. *Br J Dermatol* 2003;149:763–769.
19. Mullen JT, Feng L, Xing Y, et al. Invasive squamous cell carcinoma of the skin: defining a high-risk group. *Ann Surg Oncol* 2006;13:902–909.
20. Nouri K, Rivas MP, Pedroso F, Bhatia R, Civantos F. Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Arch Dermatol* 2004;140:1284.
21. Rastrelli M, Soteldo J, Zonta M, et al. Sentinel node biopsy for high-risk cutaneous nonanogenital squamous cell carcinoma: a preliminary result. *Eur Surg Res* 2010;44:204–208.
22. Renzi C, Caggiati A, Mannooranparampil TJ, et al. Sentinel lymph node biopsy for high risk cutaneous squamous cell carcinoma: case series and review of the literature. *Eur J Surg Oncol* 2007;33:364–369.
23. Reschly MJ, Messina JL, Zaulyanov LL, Cruse W, Fenske NA. Utility of sentinel lymphadenectomy in the management of patients with high-risk cutaneous squamous cell carcinoma. *Dermatol Surg* 2003;29:135–140.
24. Sahn RE, Lang PG. Sentinel lymph node biopsy for high-risk nonmelanoma skin cancers. *Dermatol Surg* 2007;33:786–792; discussion 792–793.
25. Wagner JD, Evdokimow DZ, Weisberger E, et al. Sentinel node biopsy for high-risk nonmelanoma cutaneous malignancy. *Arch Dermatol* 2004;140:75–79.
26. Schmitt AR, Brewer JD, Bordeaux JS, Baum CL. Staging for cutaneous squamous cell carcinoma as a predictor of sentinel lymph node biopsy results: meta-analysis of American Joint Committee on Cancer criteria and a proposed alternative system. *JAMA Dermatol* 2014;150:19–24.