Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/medici

Original Research Article

Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma: Analysis of recurrence-free survival

Donatas Samsanavičius [a,*], *Vygintas Kaikaris* [a], *Simonas-Jonas Norvydas* [b], *Rokas Liubauskas* [c], *Skaidra Valiukevičienė* [c], *Jurgita Makštienė* [d], *Kęstutis Maslauskas* [a], *Rytis Rimdeika* [a]

[a] *Department of Plastic and Reconstructive Surgery, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[b] *Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[c] *Department of Skin and Venereal Diseases, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[d] *Department of Pathological Anatomy, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*

ARTICLE INFO

Article history:
Received 21 June 2015
Received in revised form
21 June 2016
Accepted 8 September 2016
Available online 28 September 2016

Keywords:
Sentinel lymph node biopsy
Cutaneous squamous cell carcinoma
Relapse
Recurrence-free survival

ABSTRACT

Background and aim: Cutaneous squamous cell carcinoma (CSCC) is a malignant epithelial cell tumor. CSCC has a tendency to spread via lymphogenic pathway. Metastases are found in 2%–6% of cases. Prognosis of patients with CSCC is directly related to the morphology and localization of primary tumor.

The aim of this study was to evaluate the recurrence-free survival of patients with CSCC after tumor excision and SLNB as well as to analyze morphologic CSCC features related to patient recurrence-free survival.

Materials and materials: A retrospective analysis of 51 patients with CSCC, who underwent surgical treatment between January 1, 2012, and December 31, 2014, in the Clinic of Plastic and Reconstructive Surgery, Hospital of the Lithuanian University of Health Sciences, was done. The diagnosis of CSCC was verified on a histological examination, and all patients had no clinical evidence of nodal or distant metastases on a physical examination or imaging studies. Sentinel lymph node biopsy (SLNB) was performed for low- and high-risk CSCC patients.

Results: A total of 51 patients were enrolled into the study (34 women and 17 men). Total of 68 lymph nodes were removed during sentinel lymph node biopsy. No micrometastases were identified. Until April 1, 2015, no relapse event was documented. The mean time after operation was 27.5 months. During the follow-up period, no distant metastases were identified.

Conclusions: No patient who had no micrometastases in sentinel lymph nodes developed local and distant CSCC metastases during the follow-up period. Our report supports the concept that SLNB can be applied for CSCC. It is obvious that larger prospective studies with

* *Corresponding author at*: Department of Plastic and Reconstructive Surgery, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50161 Kaunas, Lithuania.
E-mail address: dsamsanavicius@gmail.com (D. Samsanavičius).
Peer review under the responsibility of the Lithuanian University of Health Sciences.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.medici.2016.09.002

longer follow-up period are needed to establish the efficacy of SLNB and define the optimal treatment of occult nodal metastasis for CSCC.

1. Introduction

Cutaneous squamous cell carcinoma (CSCC) is a malignant epithelial cell tumor whose prevalence among Whites increased more than twice in the past decade [1–5]. Most of CSCC cases are diagnosed in Australia and New Zealand. According to data, the prevalence ranges from 10 to 20 cases per 10,000 population in Europe and to 400 cases per 10,000 population in Australia [1–5]. In Lithuania, the prevalence of nonmelanocytic malignant skin tumors during 1993–2009 increased from 21.0 to 58.1 and from 31.0 to 78.5 per 10,000 population in men and women, respectively [6]. The mean age of patients ranges from 64 to 68 years [1]. Scandinavian countries have the highest prevalence rate among European countries [7]. In Lithuania, this rate is similar to other European countries. CSCC is the second most prevalent malignant skin tumor, which accounts for 20% of nonmelanocytic tumors [6].

CSCC has a tendency to spread via lymphogenic pathway [1–5]. Metastases are found in 2%–6% of cases. When the diameter of tumor exceeds 2 cm, the rate of recurrence is up to 15%, and the metastatic rate increases to 30% accordingly. For CSCC of lip and ear regions, the recurrence and metastatic rates vary from 10% to 25%. The metastatic rate for poorly differentiated tumors reaches 28.6% [1,3,5–10]. The prognosis of patients with CSCC depends on the morphology of the tumor and its spread. Patients with no regional lymph node involvement have a 96% 5-year survival rate. For advanced CSCC, which has spread to regional lymph nodes, the 5-year survival rate is 72% with adequate and 25%–35% with no treatment, respectively [1,3,5,8–12].

Prognosis of the patient with CSCC is directly related to the morphology and localization of the primary tumor; therefore, timely diagnosis, when tumor thickness (pT) and diameter is less than 2 mm and 2 cm, respectively, is essential [1]. CSCC treatment depends on tumor morphology and localization. Poor differentiation, tumor diameter greater than 2 cm, and location in the face region worsen the prognosis. Table shows risk factors for CSCC by the risk [11]. Although alternative treatment methods such as curettage, radiotherapy, and chemotherapy exist, surgical treatment remains the gold standard in the management of CSCC. Lesion excision with a margin measuring 4–6 mm reduces the recurrence rate to 3% [4]. Currently, metastasized CSCC is diagnosed when clinically regional lymph nodes are found to be enlarged and/or distant metastases are identified by noninvasive investigation methods. This shows that clinically detected metastases are the feature of advanced and spread CSCC. For more accurate evaluation of CSCC spread, sentinel lymph node biopsy (SLNB) is advocated globally. Sentinel lymph nodes are defined as one or several lymph nodes, which are primary reached by metastasizing cancer cells from a primary tumor. In the world as well as Lithuania SLNB is applied for patients with breast cancer and melanoma in order to detect a possibly metastasized tumor and administer adequate treatment immediately. SLNB could identify CSCC metastases, when they are not detected by application of noninvasive methods (clinically or ultrasound). As around 80%–85% of CSCC metastases spread via lymphogenic pathway, the examination of sentinel lymph nodes would allow to improve diagnostics of CSCC spread and administration of timely adequate treatment. Timely diagnosis of CSCC that metastasized to sentinel lymph nodes and initiated adequate treatment are associated with reduced tumor spread, improved outcome, and prolonged survival [3,5,12–19].

The aim of this study was to evaluate the recurrence-free survival of patients with CSCC after tumor excision and SLNB as well as to analyze morphologic CSCC features related to patient recurrence-free survival.

2. Materials and methods

A retrospective analysis of 51 patients with CSCC, who underwent surgical treatment between January 1, 2012, and March 31, 2015, in the Clinic of Plastic and Reconstructive Surgery, Hospital of the Lithuanian University of Health Sciences (LUHS) Kauno Klinikos, was carried out. Approval by Kaunas Regional Biomedical Research Committee was obtained.

Before hospitalization in the Clinic of Plastic and Reconstructive Surgery of the LUHS Hospital, all the patients had been given consultations and examined in the Clinic of Skin and Venereal Diseases. First, by referral of a therapist due to suspected CSCC, patients arrived for a dermatologist's consultation in the Polyclinic of Skin and Venereal Diseases. Dermatoscopic examination of the skin formation and punch biopsy were performed by a dermatologist, and CSCC was histologically confirmed by pathologists. Then, patients were further examined for CSCC metastases, i.e. ultrasonography of upper abdominal floor and regional lymph nodes as well as panoramic radiography of the chest were performed. If no remote CSCC metastases or regional lymph node metastases were found and CSCC deeper than in situ was determined, patients were included into the study upon their consent.

The patients included into the study were grouped into low-risk and high-risk CSCC groups. The patients were classified according to the guidelines of the National Comprehensive Cancer Network (NCCN). The groups of low-risk and high-risk CSCC were selected according to the risk factors for CSCC summarized in Table. If at least one high-risk criterion of CSCC was present together with low-risk CSCC criterion, the patient was included into the group of high-risk CSCC. Sentinel lymph node biopsy (SLNB) was performed for low- and high-risk CSCC patients.

Table – Risk factors for skin squamous cell carcinoma by the level of risk.

Characteristic	Low risk	High risk
Tumor location and size	Area L, <20 mm Area M, <10 mm Area H, <6 mm	Area L, ≥20 mm Area M, ≥10 mm Area H, ≥6 mm
Borders	Well defined	Poorly defined
Disease course	Primary	Recurrent
Immunosuppression	(–)	(+)
Previous radiotherapy	(–)	(+)
CSCC histopathology		
Differentiation degree	Well differentiated	Moderately or poorly differentiated
Adenoid (acantholytic), adenosquamous (mucin producing), or desmoplastic	(–)	(+)
pT (Clark level)	<2 mm (I–III)	≥2 mm (IV and V)
Perineural or vascular invasion	(–)	(+)

Area H, central face, eyelids, eyebrows, periorbital area, nose, lips (cutaneous and vermilion), chin, mandible, ear, external genitalia, hands, feet. Area M, cheeks, forehead, scalp, and neck. Area L, trunk and extremities. (–), absent; (+), present.
*If the tumor possesses histological characteristics of sclerosing, mixed, infiltrative growth.

2.1. *Recurrence-free survival analysis of patients with CSCC*

After CSCC excision and sentinel lymph node biopsy were performed, the study subjects had check-ups by dermatologists every 6 months for the first 2 years and later once a year until the end of this study. During these consultations, ultrasonography of regional lymph nodes was performed for possible metastases.

2.2. *Radionuclide lymphoscintigraphy*

All patients underwent radionuclide lymphoscintigraphy in the Clinic of Radiology, Hospital of the Lithuanian University of Health Sciences Kauno Klinikos, either on the operation day or the day before. A volume of 0.1–0.2 mL of radiopharmacological agent (RA) 99mTc-albumin nanocolloid (Nanocoll, Amersham Health) was injected into the skin and spread evenly around the primary tumor (total of 50–250 MBq). Dynamic lymphoscintigraphy using a planar gamma camera (Siemens e.cam) was performed following the injection of RA in order to register lymph drainage from the tumor and to detect peak accumulation of RA in the sentinel lymph node. Lymphatic pathways leading from the marker injection site to one or several sentinel lymph nodes were observed. Static lymphoscintigrams were performed 20 min after the injection of RA. Projections of sentinel lymph nodes, which had RA accumulation detected, were marked on the skin. Surgery was started <4 h after the injection of RA, before distant lymph nodes filled with radionuclide.

2.3. *Operative technique*

All patients underwent tumor excision and SLNB. Audio radiometer (Neoprobe Neo 2000®) signal radiated from the injection of radioactive material accumulated on the primary tumor or scar areas and obscured the finding of SLNB. In such case, the tumor or scar was removed and then SLNB was performed. Blue dye injections were not used for sentinel lymph node identification.

2.4. *Pathological evaluation*

Skin, subcutaneous tissue fragments, and lymph nodes removed during surgery were examined in the Clinic of Pathological Anatomy, Hospital of the Lithuanian University of Health Sciences. All sentinel lymph nodes were formalin fixed and embedded in paraffin. Each lymph node smaller than 5 mm was sectioned 2–4 times and each lymph node bigger than 5 mm was sectioned serial step-sectioning at 2–3 mm intervals. All lymph nodes were stained using two methods: hematoxylin-eosin and immunohistochemical staining for Cytokeratin 5. Staining of histological samples using two methods was applied in order to minimize the risk of a false negative sentinel lymph node. Based on the findings of histological examination, the thickness of CSCC according to Breslow and Clark was evaluated [1,5].

2.5. *Statistical analysis*

SPSS 17.0 was used for statistical processing. Student *t* criteria were used to compare statistical averages of the analyzed variables. Results are presented as an arithmetic mean and standard deviation. Categorical variables were expressed as frequencies. Associations were assessed using the χ^2 criterion and Fisher criterion. Difference was statistically significant when $P < 0.05$. The recurrence rate of CSCC was investigated using Kaplan–Meier survival analysis.

3. Results

Analysis of subjects. A total of 51 patients were enrolled into the study (34 women and 17 men). The mean age of female and male patients was 74.87 ± 11.34 years (range, 48.61–92.51 years) and 76.29 ± 10.89 years (range, 66.00–85.00 years), respectively.

Nearly two-thirds (65%) of the patients had CSCCs of the head and neck (Fig. 1), while 39% were localized on the cheek (Fig. 2). The women were more frequently diagnosed with CSCC of the lower extremities than the men ($P < 0.05$). Distribution in other regions was the same.

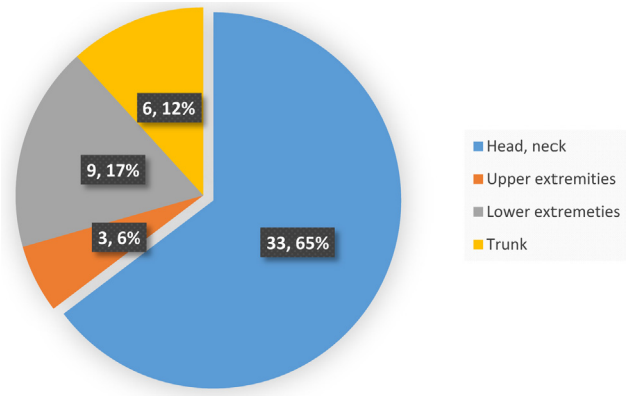

Fig. 1 – Distribution according to the anatomical region.

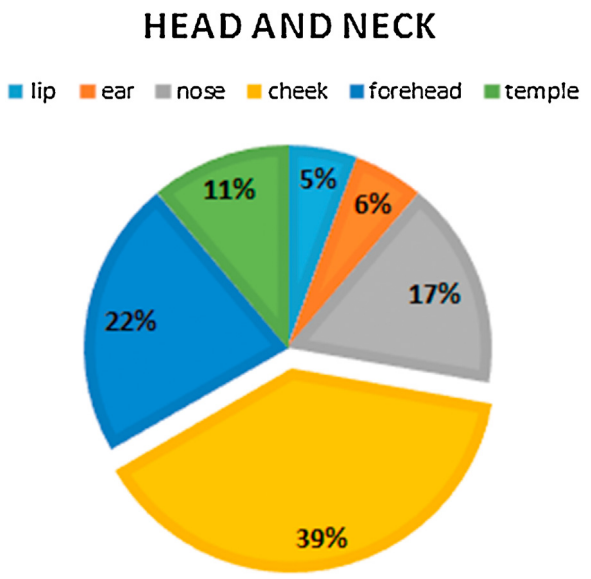

Fig. 2 – Distribution according to the head and neck region.

One of the risk factors of CSCC is the size (diameter). The research results showed that the diameter of CSCC did not statistically significantly differ between men and women ($P = 0.394$). The mean diameter of CSCC in men and women was 2.18 ± 4.17 cm (range, 0.4–25 cm) and 2.23 ± 4.16 cm (range, 0.5–30 cm) ($P = 0.681$), respectively (Fig. 3). CSCC diameters did not statistically significantly differ between CSCC localizations ($P = 0.008$). The biggest CSCCs were detected when they were localized in the anatomical locations on legs and the smallest ones were found to be localized on the anatomical locations of the head and the neck.

CSCC thickness according to Breslow's staging varied from 0.3 mm to 10.1 mm. CSCCs were found to be thicker in the lower extremities as compared with other body parts; however, the difference was not significant ($P = 0.698$). Analysis of CSCC thickness according to Breslow's staging between genders showed that men and women were matched by this characteristic (2.50 ± 1.89 mm and 2.07 ± 1.39 mm, respectively). Analysis of CSCC thickness according to Clark revealed that Clark's level IV lesions predominated and accounted for 70.51% of all the patients. Clark's level V lesions made up 18.19%, while CSCCs of Clark's level lower than IV accounted for just 11.3%. The Clark's level of invasion was similar between men and women.

Based on the histological examination results, CSCC differentiation was analyzed. It was determined that CSCC

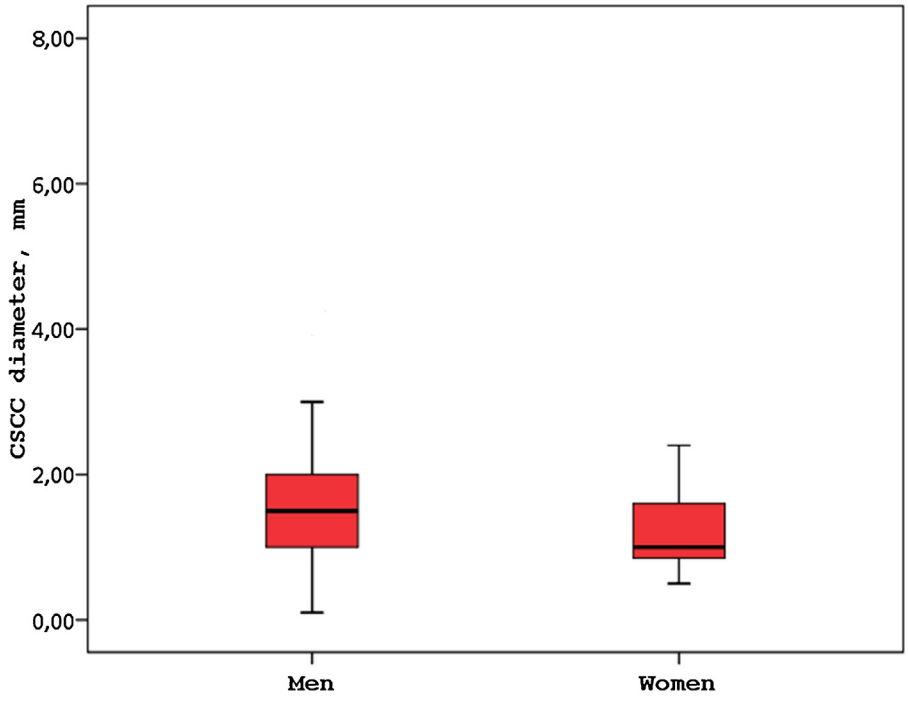

Fig. 3 – CSCC diameter by gender.

tumor was well differentiated (G1) in 37 patients (73%). There were no undifferentiated CSCC tumor in our study.

Analysis of patient groups. According to the NCCN recommendations for CSCC risk determination, the patients were divided into two groups: low-risk (20 patients) and high-risk (31 patients).

The homogeneity of low-risk and high-risk groups was compared in terms of patient age, sex, place of residence, tumor localization, and ulceration.

In both groups, the age of the subjects did not statistically significantly differ ($P = 0.514$). The mean age of the patients in the low-risk group was 72.98 ± 12.36 years; the mean age of the patients in the high-risk group was 76.25 ± 8.92 years. The risk groups were homogeneous in terms of sex, i.e. the distribution of men and women in the groups did not differ ($P = 0.255$). Both groups were also homogeneous in terms of the place of residence, i.e. the distribution of the patients living in town and country between the high- and low-risk groups did not statistically significantly differ ($P = 0.224$).

The mean thickness of CSCC according to Breslow in the low-risk group was 1.17 ± 0.41 mm. In the high-risk group, it was 2.85 ± 1.32 mm. The values of CSCC thickness according to Breslow were statistically significantly different between the high- and low-risk groups ($P < 0.001$).

The distribution of ulcerated and non-ulcerated tumors statistically significantly differed between the groups ($P = 0.035$). There were 65.2% patients with ulcerated CSCC in the high-risk group and 42.9% patients in the low-risk group.

The diameter of CSCC was statistically significantly different in the compared risk groups ($P < 0.001$). The mean diameter of CSCC in the low-risk group was 0.94 ± 0.44 cm; meanwhile, in the high-risk group, it was 2.14 ± 1.62 cm.

The low- and high-risk groups were also compared according to the differentiation level of CSCC. The prevalence of differentiated and moderately-differentiated (G1, G2) CSCCs were 100% and 89% in the low- and high-risk groups, respectively.

Analysis of detected and excised sentinel lymph nodes. A total of 68 lymph nodes were removed during SLNB. All the lymph nodes removed accumulated RA. No micrometastases were identified.

Analysis of recurrence-free survival of patients. There were no patients for radical lymphadenectomy, radiation therapy or chemotherapy who were treated under CSCC excision and SLNB. Until April 1, 2015, no single relapse event was observed giving the recurrence-free survival of 100%. One patient developed CSCC in other part of the body at 8-month follow-up; however, it was not considered as CSCC relapse case (Fig. 4). The mean time after operation was 30.4 months (95% CI, 16–39 months). During the follow-up period, no distant metastases were identified.

4. Discussion

Recurrence-free survival of patients with CSCC is closely related to the administered treatment (radical or non-radical tumor excision) and risk factors (CSCC size ≥2 cm, tumor thickness ≥4 mm, poor tumor differentiation, perineural tumor invasion, immunosuppression, tumor location) [12,20]. Metastases from CSCC firstly spread to regional lymph node basins and clinically manifest within 2 years of follow-up [1]. Aggressive surgical treatment has been shown to benefit selected patients with locoregionally confined advanced CSCC

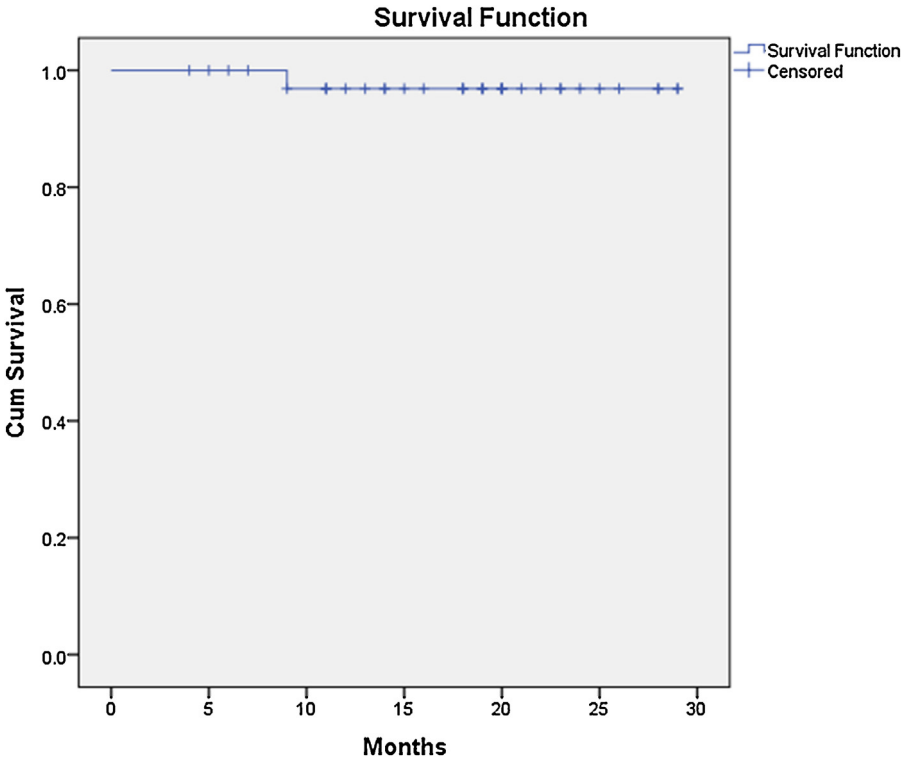

Fig. 4 – Survival until recurrence.

and long term survivors have been reported following radical salvage resection and therapeutic lymphadenectomy. The role for elective lymphadenectomy in high-risk CSCC remains undefined with most studies limited to head and neck primary sites. For these reasons, SLN biopsy is an unproven and yet theoretically appealing surgical technique to accurately stage CSCC with minimal morbidity, identify early occult nodal disease and select patients that might benefit from therapeutic lymphadenectomy or other adjuvant therapy [1].

In our study, CSCC occurred most commonly in the facial area (65%). A significantly greater percentage of women than men had CSCC in the area of lower extremities. For other sites, there was no significant difference in tumor prevalence between the genders. Based on the findings of our study, CSCC was found mostly in the head/neck area. Relatively frequent development of CSCC in this area could be interpreted as the impact of increased UV exposure on the defined area compared to the rest of the body. Tumor size and localization are important prognostic factors. According to recent literature, CSCC is considered high-risk when it measure more than 2 cm on the upper/lower extremities and trunk; >1 cm on the forehead, scalp, cheek, and neck; and >0.6 cm on the ears, lips, genitals, hands, and feet [1]. Analysis of CSCC size showed that the mean tumor size was 2.21 ± 4.14 cm in our study and this corresponds to the results published by other authors [1,5]. In our study, the ratio of CSCC measuring less than 2 cm to CSCC greater than 2 cm was 1:1. We tried to evaluate the relation of tumor size and localization with the risk of recurrence and disease-free survival, but there were no associations between tumor size, localization, tumor depth, and recurrence.

Studies evaluating the recurrence-free survival time between patients with positive and negative SLNB findings are scarce. The evaluation of relapse risk is complicated. The majority of studies that have been conducted recently had a small sample size and found no benefit in performing SLNB in order to evaluate CSCC spread [12,21–23]. Our study showed no local relapse among 51 patients. Micrometastases and distant metastases were not found. The data on the metastatic rate of CSCC in other studies vary greatly. Mullen et al. in their study found no micrometastases in patients with CSCC and reported a metastatic rate of 0% [17]. The same results were reported by Kwon et al. [1]. However, the sample size in these studies was small ($n < 14$) and this resulted in nonsignificant results. Studies that included a higher number of patients present a greater rate of CSCC metastases. In the study by Renzi et al., which enrolled 22 patients with CSCC, one patient had micrometastasis in the SLN, giving a metastatic rate of 4.5% [23]. Fukushima et al. reviewed the clinical data obtained from 54 patients, and 4 patients were found to have micrometastases in the SLNs (metastatic rate of 7.4%) [21].

In any case, all patients with high risk CPaSCC should be followed-up closely. Studies have shown that the majority of recurrences and metastases take place within two years after treatment, with 95% of recurrences and metastases being observed within five years. Thus, close follow-up is essential during this period of time to detect recurrences, metastases and also new primary skin cancers [23].

The possibility of false-negative sentinel lymph node cannot be rejected. There are three main reasons for this problem: error of an operating surgeon, error of a pathologist, and biological error [24]. The error of surgeon is influenced by learning curve and is determined by inexperience. Literature suggests that wide excision margins increases the probability of false-negative SL. The error of a pathologist can be influenced by the micropreparation slice count. A higher count of serial slices and immunohistochemical staining increases the number of detected positive nodes [24,25]. A biological error can be due to obstruction of lymphatic vessels with cancer cells or inadequate excision of the primary tumor, when the remaining cancerous cells spread via different lymphatic pathways to distant nodes. However, in our study, the analysis of patient recurrence-free survival revealed that no one patient who had no micrometastases in sentinel lymph nodes developed local and distant CSCC metastases during the follow-up period. The 3-year recurrence survival rate was 100%. Such a false-negative rate documented in our study is reported by other authors as well [22,26]; therefore, in case of CSCC, SLNB is an accurate and appropriate diagnostic procedure, which could have an impact on better patient outcome.

All these problems encourage to perform multicenter research and to evaluate the importance of SLNB further.

5. Conclusions

No patient who had no micrometastases in sentinel lymph nodes developed local and distant CSCC metastases during the follow-up period. Our report supports the concept that SLNB can be applied for CSCC. It is obvious that larger prospective studies with longer follow-up period are needed to establish the efficacy of SLNB and define the optimal treatment of occult nodal metastasis for CSCC.

Conflict of interest

The authors have no conflicts of interest to declare and no funding was received to support this study.

REFERENCES

[1] 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(19):80.
[2] Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. Adv Exp Med Biol 2014;810:120–40.
[3] Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med 2001;344:975–83.
[4] Rudolph R, Zelac DE. Squamous cell carcinoma of the skin. Plast Reconstr Surg 2004;114:82e–94e.
[5] Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: a systematic review of the English literature. Dermatol Surg 2006;32(11):1309–21.
[6] Lietuvos vėžio registras; 2011, http://www.vuoi.lt.
[7] Calzavara-Pinton P, Ortel B, Venturini M. Non-melanoma skin cancer, sun exposure and sun protection. G Ital Dermatol Venereol 2015;150(4):369–78.
[8] Dona E, Veness MJ, Cakir B, Morgan GJ. Metastatic cutaneous squamous cell carcinoma to the parotid: the role

of surgery and adjuvant radiotherapy to achieve best outcome. ANZ J Surg 2003;73:692–6.
[9] 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;29:135–40.
[10] Martinez JC, Cook JL. High-risk cutaneous squamous cell carcinoma without palpable lymphadenopathy: is there a therapeutic role for elective neck dissection. Dermatol Surg 2007;33:410–20.
[11] Garcia-Zuazaga J, Olbricht SM. Cutaneous squamous cell carcinoma. Adv Dermatol 2008;24:33–57.
[12] Kyrgidis A, Tzellos TG, Kechagias N, Patrikidou A, Xirou P, Kitikidou K, et al. Cutaneous squamous cell carcinoma (SCC) of the head and neck: risk factors of overall and recurrence-free survival. Eur J Cancer 2010;46(9):1563–72.
[13] Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol 2008;9:713–20.
[14] Veness MJ. Time to rethink TNM staging in cutaneous SCC. Lancet Oncol 2008;9:702–3.
[15] Rowe DE, Carroll RJ, Day Jr CL. Prognostic factors for local recurrence metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol 1992;26:976–90.
[16] North Jr JH, Spellman JE, Driscoll D, Velez A, Kraybill WG, Petrelli NJ. Advanced cutaneous squamous cell carcinoma of the trunk and extremity: analysis of prognostic factors. J Surg Oncol 1997;64:212–7.
[17] Mullen JT, Feng L, Xing Y, Mansfield PF, Gershenwald JE, Lee JE, et al. Invasive squamous cell carcinoma of the skin: defining a high-risk group. Ann Surg Oncol 2006;13:902–9.
[18] Goldman GD. Squamous cell cancer: a practical approach. Semin Cutan Med Surg 2008;17:80.
[19] 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(1):274–9.
[20] The National Comprehensive Cancer Network® (NCCN®), Clinical Practice Guidelines in Oncology. Squamous cell skin cancer. Version I.2016. NCCN.org.
[21] Fukushima S, Masuguchi S, Igata T, Harada M, Aoi J, Miyashita A, et al. Evaluation of sentinel node biopsy for cutaneous squamous cell carcinoma. J Dermatol 2014;41 (6):539–41.
[22] Takahashi A, Imafuku S, Nakayama J, Nakaura J, Ito K, Shibayama Y. Sentinel node biopsy for high-risk cutaneous squamous cell carcinoma. Eur J Surg Oncol 2014;40 (10):1256–62.
[23] Renzi C, Caggiati A, Mannooranparampil TJ, Passarelli F, Tartaglione G, Pennasilico GM, 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(3):364–9.
[24] De Giorgi V, Leporatti G, Massi D, Lo Russo G, Sestini S, Dini M, et al. Outcome of patients with melanoma and histologically negative sentinel lymph nodes: one institution's experience. Oncology 2007;73(5–6):401–6.
[25] Murali R, Thompson JF, Scolyer RA. Sentinel lymph node biopsy for melanoma: aspects of pathologic assessment. Future Oncol 2008;4(4):535–51.
[26] 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.