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REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

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DOI: 10.5603/rpor.99904

Article type: Research paper

Published online: 2024-03-27

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Abstract

Background: The behavior of cutaneous squamous cell carcinoma (cSCC) of the head and neck remains poorly understood. There is much controversy regarding the risk of local and nodal recurrences, as well as individual/environmental factors that increase the risk, such as tumor size, perineural invasion, and the state of the immune system.

The objective was to analyze factors influencing local and/or regional lymph node recurrence in patients with cSCC in the head and neck region.

Material and Methods: This retrospective single-centre study included 521 patients with cSCC of the head and neck region, with local recurrence observed in 11% and nodal recurrence in 5%. Various potential risk factors were analyzed.

Results: Statistically significant risk factors for both local and nodal recurrence include: tumor recurrence ($p < 0.0001$, $p < 0.0001$ respectively), tissue inflammation confirmed histopathologically ($p < 0.0001$, $p = 0.0019$, respectively), tumor size ≥ 10 mm ($p = 0.018$, $p = 0.0056$, respectively), invasion depth > 2 mm ($p = 0.0238$, $p = 0.0031$, respectively). Risk factors significant only for local recurrence include: surgical margins ($p = 0.0056$), tumor differentiation grade ($p = 0.0149$). No risk factors were found to be significant solely for nodal recurrence.

Conclusion: The authors argue that, in addition to classically recognized risk factors for local and nodal recurrence, attention should be paid to the presence of tissue inflammation confirmed histopathologically. It is also suggested to consider a tumor size of 10 mm as a threshold, increasing the risk of recurrence, instead of the frequently proposed 20 mm.

Key words: cutaneous squamous cell carcinoma; local recurrence; nodal recurrence; risk factors

Introduction

Squamous cell carcinoma of the skin (cSCC) accounts for 20% of all malignant skin tumors. Due to high exposure to ultraviolet radiation, the head and neck region is among the most common locations for this type of cancer. Studies conducted over the last 30 years have indicated a 50–300% rise in the occurrence of primary cSCC [1, 2]. cSCC is the second most prevalent cause of skin cancer-related deaths, following melanoma. The etiology of the carcinogenesis process of cSCC is multifactorial and involves genetic and epigenetic variations, as well as numerous extrinsic factors such as tobacco smoking, alcohol consumption, ultraviolet exposure, and environmental pollutants [3, 4].

Conventional surgery is the preferred treatment for patients with cSCC in the head and neck region. However, there are patient groups for whom this therapy is ineffective, where cSCC appears to be significantly more aggressive, leading to local and regional recurrences. The risk of local recurrence ranges between 3.0% and 4.6%, as reported in two large studies involving early-stage cSCC patients [5, 6], in contrast to advanced cSCC, where the 5-year risk of local recurrence is approximately 30% [7, 8]. The risk of nodal recurrence varies from 3.7% in the study by Schmults et al. [5] through 16.4% in the study by Haisma et al. [9] and up to 20.7% in the study by Moore et al. [10].

The most commonly mentioned risk factors for local/nodal recurrence comprise low histopathological differentiation, tumor diameter exceeding 20 mm, location on the cheek or ear, perineural invasion (PNI), and immunosuppression [5, 11, 12]. Tumors manifesting these characteristics are classified as “high-risk cSCC”. However, there are still many controversies, for example, regarding tumor diameter — according to the the National Comprehensive Cancer Network® (NCCN) 2.2019, for tumors located in the intermediate-risk area (skin of the head and neck excluding the ears, temples, eyes, nose, lips, chin), the factor is a size ≥ 10 mm, while for tumors in the high-risk area (ears, temples, eyes, nose, lips, chin), any size [13]. The association with immunosuppression remains contentious. Two comprehensive meta-analyses did not indicate that this variable affects the risk of local recurrence [14, 15].

It should be noted that a low survival rate in patients with metastatic cSCC indicates the need to identify individuals at increased risk of local recurrence and/or lymph node metastasis. This group of patients should be under special supervision with more frequent monitoring.

The aim of the study was to analyze factors that may influence the occurrence of local recurrence and/or metastasis to regional lymph nodes in patients with cSCC in the head and neck region.

Materials and methods

A retrospective single-center analysis was conducted between August and October 2023 on patients diagnosed with cSCC of the head and neck. A total of 521 patients were included in the study. The following demographic and clinical characteristics were analyzed: age, gender, tumor location, primary/recurrent tumor, tumor size (≥ 10 mm), tumor stage [American Joint Committee on Cancer (AJCC) 8^{th} edition], immunosuppression, smoking habit, cell differentiation grade (G), depth of invasion (> 2 mm), perineural invasion (PNI), perivascular invasion (PVI), the presence of tissue inflammatory infiltrate, and surgical margins (positive - at the incision line or below 1mm/clear). These factors were analyzed for the risk of first or subsequent local recurrence and/or nodal recurrence. Due to the retrospective nature of the study the approval from the ethics committee was not required.

Statistics

All calculations and statistical analyses were performed using MedCalc® Statistical Software version 20.027 (MedCalc Software Ltd, Ostend, Belgium). Categorial variables are presented using frequency and percentages. The percentages of people with or without local recurrence

at a specific frequency such as: recurrent tumor, inflammatory conditions, tumor size > 1 cm, depth of invasion > 2 mm, surgical margin status, differentiation and smoking were determined. The significance of intergroup differences was determined using the χ^2 test. Analogous calculations were performed for recurrence in lymph nodes. Additionally, Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for primary tumor and inflammation to investigate the risk of local recurrence or lymph node recurrence. For this purpose, logistic regression was performed. All results were considered significant if p-value was less than 0.05.

Results

The characteristics of the entire study group

The characteristics of the study group are presented in Table 1.

Clinical assessment

The average age was 75.8 years (25–97; median 78). The majority of patients were males (347; 67%). The most common locations were the ear (n = 165; 32%) and nose (n = 140; 27%), accounting for over 50% of the entire studied group. Subsequently, cSCC was observed on the skin of the cheek, temple, forehead, orbital area, and scalp. Four hundred fifteen patients (79%) presented with the primary tumor, and 106 (21%) due to recurrence. Tumor size ≥ 1 cm was observed in 305 patients (56%). The most common stage of advancement was T2 (n = 224; 43%), followed by T1 (n = 206; 40%) and T3 (n = 91; 17%). There were no patients with T4. Immunosuppression was confirmed in 46 patients (9%).

Treatment procedure

All patients underwent surgical tumor removal. Moreover, 82 patients (16%) underwent postoperative brachytherapy, 75 (14%) received radiotherapy for the primary loci, and 27 (5%) received radiotherapy for both the primary loci and metastatic lymph nodes. Chemotherapy was not administered to any patient. Additionally, lymph node dissection was performed in 99 patients (19%).

Histopathological assessment

Tumor differentiation was G1 in 76 patients (15%), G2 in 407 (78%), and G3 in 38 (7%). The invasion depth was assessed as > 2 mm in 295 cases (57%), PNI was present in 23 cases

(5%), and PVI in 19 cases (4%). Tissue inflammation confirmed histopathologically was found in 175 patients (34%). Positive margins were found in 95 patients (18%). Lymph node metastases were confirmed in 54 patients (10%).

The follow-up ranged from 24 to 180 months (mean 56.04 months). Local recurrence was observed in 55 patients (11%) after 4–42 months postoperatively (mean 12.35 months). Lymph node recurrence was noted in 26 patients (5%) 3-34 months postoperatively (mean 8.85 months).

Characteristics of the group with local and nodal recurrences

The influence of selected factors on the occurrence of local/nodal recurrence are presented in Table 2.

The number of local recurrences for tumors in the specific locations was as follows: ear (n = 19, 35%), nose (n = 12, 22%), cheek (n = 10, 18%), temple (n = 6, 11%), scalp (n = 4, 7%), forehead (n = 2, 3.5%), orbital area (n = 2, 3.5%). Recurrences were significantly more frequently observed when the tumor was located on the skin of the ear ($p < 0.0001$) or nose ($p = 0.0036$) than in other areas of the head and neck region.

The number of lymph node recurrence for tumors in specific locations was as follows: nose (n = 12, 46%), ear (n = 12, 46%), cheek (n = 2, 14%). Recurrences were significantly more frequently observed when the tumor was located on the skin of the nose ($p = 0.0118$) or ear ($p = 0.0118$) than in other areas of the head and neck region.

The primary tumor reduced the risk of local recurrence by 95% (OR = 0.047; 95% CI: 0.023–0.096; $p < 0.0001$) and decreased the risk of lymph node recurrence by 80% (OR=0.19; 95% CI: 0.08–0.44; $p = 0.0001$) (Tab. 3). Recurrent tumors significantly influenced the risk of both local and lymph node recurrence ($p<0.0001$ in both cases). There was a statistically significant dependence between the size of the tumor above 10 mm in the case of local recurrence ($p = 0.0018$) and recurrence in lymph nodes ($p = 0.0056$).

Tissue inflammation confirmed histopathologically significantly influenced the risk of local ($p < 0.0001$) and lymph node recurrence ($p=0.0019$). It increased both the risk of local recurrence by 2.5 times (OR = 2.6; 95% CI: 1.38–5.05; $p = 0.0035$) and the risk of lymph node recurrence by 2.5 times (OR = 2.7; 95% CI: 1.15–6.16; $p = 0.0221$) (Tab. 3).

There was a statistically significant dependence between the depth of infiltration > 2 mm of influence and the occurrence of local recurrence ($p = 0.0238$) and recurrence in lymph nodes ($p = 0.0031$). Additionally, there was a dependence between the occurrence of local recurrence and differentiation (G) ($p = 0.0149$), positive margins ($p = 0.0056$) and smoking (p

= 0.004). There was no statistically significant dependence between local/nodal recurrence and age, gender, immunosuppression, PNI, PVI and side effects.

Discussion

The majority of head and neck cSCC are curable, but there is a certain number of patients belonging to the high-risk group for local and nodal recurrence.

Risk factors for local recurrence

In the analyzed material, local recurrence was observed in 11% of patients (3% with primary cSCC and 8% with recurrent cSCC). Literature suggests that the incidence of local recurrence in early stages and all locations varies between 3.0% and 4.6% [5, 6], while advanced cSCC may have a recurrence rate of approximately 30% [7, 8]. The authors' results are influenced by the fact that their center handles all cases of skin cancer, both at early and advanced stages.

In the analyzed material, the most significant risk factors for local recurrence were recurrent tumor ($p < 0.0001$) and tissue inflammation confirmed histopathologically ($p < 0.0001$). Resection of the primary tumor reduced the risk of local recurrence by 95%, while inflammatory findings in histopathological examination increased the risk by 2.5 times. Other significant factors included invasion depth above 2 mm ($p = 0.0238$), tumor size above 10 mm ($p = 0.0018$), low tumor differentiation ($p = 0.0149$), smoking ($p = 0.0465$), and tumor's location on the skin of the ear ($p < 0.0001$) and nose ($p = 0.0036$). It is worth noting that most of these factors are confirmed in the literature, but the role of inflammation is rarely discussed. However, the assessment of its presence seems valuable in histopathological examination since inflammation has a documented impact on angiogenesis, significantly modifying the course of the cancer process, as discussed in a recent review by Li et al. [16]. The significance of underlying chronic inflammatory conditions as a classifying factor for high-risk cSCC was emphasized in the NCCN 2.2019 recommendations [13]. It is known that an inflammatory infiltrate can be present and can surround the tumor cells of cSCC [17]. Moreover, the presence of accompanying infiltration is considered a sign of malignancy in cases of pigmented lesions or mesenchymal tumors [17]. In the context of other variables, a meta-analysis covering 36 studies and 17,248 patients with 23,421 cSCCs found that significant factors for local recurrence included invasion depth > 2 mm, subcutaneous tissue invasion, PNI, tumor size > 20 mm, location on the temple, and low differentiation grade [15]. Another meta-analysis based on 7 prospective and 36 retrospective studies involving 21,530

patients with 28,627 cSCCs showed that low tumor differentiation, PNI, and invasion depth > 2 mm had a significant impact on tumor recurrence [14]. However, it is essential to note that the results of a systematic review by Lubova et al., encompassing 8,535 patients from 40 studies across various countries, were not as conclusive. Only 2 out of 6 studies showed a significantly higher risk of recurrence in specific locations, 3 out of 6 for recurrent tumors, 11 out of 15 for immunosuppression, 3 out of 6 in relation to invasion depth, 7 out of 15 for low tumor differentiation, 5 out of 11 in relation to tumor size, and 10 out of 15 in relation to margin width [18]. Nevertheless, low tumor differentiation is widely considered an independent significant risk factor for local recurrence, increasing the risk 2.5-3.3 times [5,11]. As mentioned, in the analyzed material tumor differentiation had a significant impact on the occurrence of local recurrence ($p = 0.0149$). However, no increased risk of local recurrence was observed with the coexistence of PNI and/or PVI. It should be noted that the cited meta-analysis by Zeng et al. did show such a relationship [14]. Additionally, in the examined material, no statistical significance was found between tumor differentiation and the risk of nodal recurrence. Similar results were presented by Harris, although it is important to note that his study only concerned highly advanced tumors [19].

Risk factors for lymph node recurrence

In the analyzed material, nodal recurrence was observed in 5% of patients (2% with primary cSCC of the head and neck and 3% with recurrent cSCC of the head and neck). Schmults et al. [5] reported a similar percentage of nodal recurrence. However, there are centers where the percentage of nodal recurrences was as high as 16.4% [9] or even 20.7% [10]. In the analyzed material, the most significant risk factors for nodal recurrence were recurrent tumor ($p < 0.0001$) and tissue inflammation confirmed histopathologically ($p = 0.0019$). Resection of the primary tumor reduced the risk of nodal recurrence by 80%, while tissue inflammation confirmed histopathologically increased the risk by 2.5 times. Regarding the tumor location that led to nodal recurrence, it was observed when cSCC was located on the skin of the ear, nose, and cheek. However, significantly more recurrences were associated with the ear ($p = 0.0118$) and nose ($p = 0.0118$). These findings are partially confirmed by data from the Zeng et al. meta-analysis, where the location of cSCC on the ear, lips, and temple had a significant impact on metastasis, while the location on the cheek was not associated with an increased risk of metastasis [14]. In the analyzed material, the depth of invasion above 2 mm ($p = 0.0031$) and tumor size ≥ 10 mm ($p = 0.0013$) were also significant risk factors for nodal recurrence. Thompson's meta-analysis confirmed that invasion depth above 2 mm is the most

significant and independent risk factor for nodal recurrence [15]. Additionally, the studied material indicated an increased risk of nodal recurrence if tissue inflammation was confirmed by histopathology, similar to the case of local recurrences ($p = 0.0019$). Nevertheless, no significant impact of immunosuppression on the risk of nodal recurrence was observed (analogously to the case of local recurrence), which is consistent with the two previously cited meta-analyses [14, 15] and the retrospective study by Haisma et al. [9]. However, many authors point out the increased risk of head and neck cSCC and its more aggressive nature with the duration of immunosuppression [6, 20]. The study follow-up ranged from 24 to 180 months (average 56.04 months), which could have an impact on the obtained results. There was also no influence of PNI and/or PVI on the risk of nodal recurrence, although it should be noted that the meta-analysis by Zeng et al. did show such a relationship [14]. Additionally, no statistical significance was found between the tumor differentiation grade and the risk of nodal recurrence in the study group. Similar results were presented by Harris, although it is important to note that his study only concerned highly advanced tumors [19]. The statistical analysis also did not indicate that the age of the patient was a risk factor for nodal occurrence, consistent with earlier publications [5, 19].

Strong and weak points of the study

The single-center nature of the study may be regarded as a limitation; however, it is essential to emphasize that this allowed for the patients to be operated on by a consistent, highly specialized team of head and neck surgeons. Simultaneously, the authors' center is recognized as having the highest reference standards in Poland, offering a wide range of procedures from managing early cancers to cases requiring reconstructive surgery. It should be added that the analysis was limited solely to head and neck cSCC, but, on the other hand, this location itself is considered to increase the risk of cSCC occurrence [1].

Conclusions

In summary, the assessment of the risk of local and/or nodal recurrence is an extremely crucial element in managing patients with cSCC. In our material, the most significant variables increasing the risk of both local and nodal recurrence were: recurrent tumor, tissue inflammation confirmed histopathologically, tumor size ≥10 mm, invasion depth >2 mm, location on the skin of the nose and ear; variables increasing the risk of local recurrence but not nodal recurrence were: positive margins, low tumor differentiation, smoking. No factors were identified that solely increased the risk of nodal recurrence. The authors suggest

adopting tumor size ≥ 10 mm (instead of > 20 mm) and incorporating the criterion of inflammation in histopathological imaging into the classification for high-risk head and neck area cSCC.

Conflict of interests

Author declare no conflict of interests.

Funding

None declared.

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Table 1. The characteristics of the entire study group

Feature	**n = 521**
Clinical characteristics	
Age Mean (range) [years]	75.8 (25–97)
Sex Male	347 (67%)

Female	174 (33%)
Tumor location	
Ear	165 (32%)
Nose	140 (27%)
Cheek	98 (19%)
Temple	50 (10%)
Forehead	24 (4,5%)
Scalp	22 (4%)
Periorbital	20 (3%)
Chin	2 (0.5%)
Primary tumor	415 (79%)
Recurrent tumor	106 (21%)
Tumor size ≥ 10 mm	
Yes	305 (56%)
No	216(44%)
T classifications	
T1	206 (40%)
T2	224 (43%)
T3	91 (17%)
T4	0
Immunosuppression	
Yes	46 (9%)
No	475 (91%)
Smoking	
Yes	152 (29%)
No	369 (71%)
Histopathological characteristics	
Differentiation	
G1	76 (15%)
G2	407 (78%)
G3	38 (7%)
Depth of invasion > 2 mm	
Yes	295(57%)
No	226 (43%)
Perineural invasion (PNI)	
Yes	23 (5%)
No	498 (95%)
Perivascular invasion (PVI)	
Yes	19 (4%)
No	502 (96%)
Tissue inflammation	
Yes	175 (34%)
No	346 (66%)
Surgical margin status	
Clear	426 (82%)

Positive	95 (18%)
Lymph node metastases Yes No	 54 (10%) 467 (90%)

Table 2. The influence of selected factors on the occurrence of local/nodal recurrence

		Local recurrence			**Nodal recurrence**		
		Yes (n = 55)	**No (n = 466)**	**p**	**Yes (n = 26)**	**No (n = 495)**	**p**
Recurrent tumor		13 (24%)	402 (86%)	< 0.0001	11 (42%)	404 (82%)	< 0.0001
Tumor size > 1 cm		43 (78%)	262 (56%)	0.018	22 (85%)	283 (57%)	0.0056
Smoking		22 (42%)	132 (28%)	0.0465	8 (31%)	146 (31%)	0.9004
Differentiation	1	4 (7%)	72 (15%)	0.0149	2 (7.5%)	74 (15%)	0.5928
	2	54 (93%)	356 (77%)		22 (85%)	385 (78%)	
	3	0 (0%)	38 (8%)		2 (7.5%)	36 (7%)	
Depth of invasion > 2 mm		39 (71%)	256 (55%)	0.0238	22 (85%)	273 (55%)	0.0031
Tissue inflammation		33 (60%)	142 (30%)	< 0.0001	16 (62%)	159 (32%)	0.0019
Surgical margin status		33 (60%)	359 (77%)	0.0056	20 (77%)	372 (75%)	0.8384

Table 3. Statistically significant risk factors for local/nodal recurrence

	Local recurrence			**Nodal recurrence**		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Primary tumor	0.047	0.023–0.096	< 0.0001	0.19	0.08–0.44	0.0001
Tissue inflammation	2.6	1.38–50.5	0.0035	2.7	1.15–6.16	0.0221

OR — odds ratio; CI — confidence interval