Original Article

High Prevalence of High-Risk Cutaneous Squamous Cell Carcinoma in the Thrace Region of Turkey

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Abstract

Background: The characteristics of cutaneous squamous cell carcinoma (cSCC) may show differences according to the geographic distribution and ethnicity. Although most cSCCs are treated with surgical excision or other local interventions, high-risk cSCCs may have poor outcome. In the present study, we aimed to evaluate the clinicopathological characteristics and determine the high-risk features of cSCCs in the Thrace region of Turkey where the information on cSCCs is scarce. **Methods:** We retrospectively investigated the biopsy-proven cSCCs diagnosed between the years 2014 and 2018, in a tertiary university hospital and evaluated the high-risk features. **Results:** A total of 211 cSCCs were included. Men with cSCC were significantly younger than women with cSCC (P <.001). Almost one-half of the tumors (n = 103) were located on the lower lip. Patients with a cSCC on the lower lip were younger than those with a cSCC on the other sites. All patients with a cSCC on the ears were men. Twenty-eight percent of patients had tumor size more than 20 mm and 28% had tumor thickness more than 6 mm. Immunosuppression was present in 7.6% of patients. A total of 177 (83.9%) patients had high-risk cSCC. The local recurrence rate was 6.2%, and the metastasis rate was 5.2%. **Conclusions:** The Thrace region has significant number of cSCC, and high-risk features are very frequent. Clinicians should carefully evaluate the cSCCs in terms of high-risk features.

Keywords: High-risk, histopathology, nonmelanoma skin cancer, prevalence, squamous cell carcinoma

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer (NMSC) following basal cell carcinoma.[1] The incidence of cSCC is increasing worldwide.[1,2] Although most cSCCs are treated with surgical excision or other local interventions, some have poor outcomes.[2-4] There are various reports established by different groups[4-7] defining clinical and histopathological prognostic risk factors for cSCC related to increased local recurrence and metastasis rates. Identifying these prognostic risk factors and determining which patients have high-risk cSCCs is crucial for the correct management of cSCC.[4-7]

We conducted a retrospective study to determine the characteristics of cSCCs diagnosed in a 5-year period at a tertiary university hospital in the Thrace region, which is located in the European (north-western) part of Turkey [Figure 1]. In Turkey, there are no definitive statistics on Fitzpatrick skin types, but the Turkish population primarily has Fitzpatrick skin types 3 and 4. However, unlike the general population, most people in the Thrace region have fair skin, green or blue eyes, and light-colored hair. Moreover, a significant portion of the people living in this region is engaged in agricultural activities, mostly without sun protection. Therefore, in this region, clinicians see a lot of cSCC in their daily practice, and data on cSCC may have some peculiar characteristics. We aimed to analyze the demographic, clinical, and histopathological features of cSCCs as well as the rates of local recurrence, metastasis, and high-risk cSCCs in a single center in the Thrace region of Turkey and to compare our results to previously published studies from other geographical regions of Turkey [Figure 1].

Submission: 18-10-2020 **Acceptance:** 15-12-2020
Web Publication: 31-12-2020

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_103_20

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How to cite this article: Solak SS, Yöndem H, Urun YG, Cezik M, Can N. High prevalence of high-risk cutaneous squamous cell carcinoma in the thrace region of Turkey. Turk J Dermatol 2020;14:83-9.

Methods

An electronic search of the database of the Trakya University Medical Faculty was performed, and records of biopsy-proven cSCCs at any site on the body diagnosed between January 1, 2014, and December 31, 2018, were extracted. Lower and upper lip SCCs were included. *In situ* tumors (e.g., Bowen's disease, actinic keratosis, and actinic cheilitis), keratoacanthoma, and mucosal tumors (genital, nasal, buccal, and labial mucosae) were excluded. In cases of multiple primary cSCCs, the patients who had a cSCC diagnosed before 2014 were excluded. If multiple primary cSCCs were diagnosed in the study period, analyses were performed based on only the first cSCC of each patient. The prognostic risk factors were examined for each cSCC according to the European guidelines.[5]

Demographic and clinical data, including patient age, sex, and birthplace, anatomical localization of the tumor, associated diseases, presence of immunosuppression, recurrence, and metastasis, were extracted from electronic patient files. Histopathological features of the tumors, including tumor size (measured by the pathologist), tumor thickness, histologic subtype, degree of differentiation, and presence of perineural invasion were provided in pathology reports. The degree of differentiation was classified as well differentiated, moderately differentiated, or poorly differentiated. We excluded any records in the absence of any of the above variables. Patient follow-up data were obtained from the electronic patient files.

Analyses were carried out using IBM SPSS Statistics, version 24 (IBM, New York, USA). The results were expressed as mean, median, and range for the continuous variables. Mann–Whitney U-test was used to compare the differences between the continuous variables. Pearson Chi-square test or Fisher's exact test was used for the differences between the categorical variables. $P < 0.05$ was considered statistically significant. Ethics approval was obtained from the Trakya University Research Ethics Board to conduct this study.

Results

A total of 231 patients diagnosed with cSCC within the study period were identified. Twenty patients were excluded from the analysis because of missing data, leaving 211 patients available for review. There were 162 (76.8%) men and 49 (23.2%) women (male-to-female ratio: 3.3:1). The annual number of patients with cSCC is presented in Figure 2a. The mean age was 71.05 ± 13.33 (69.25 ± 13.28 for men and 77 ± 11.79 for women; range 30–102 years). Men with cSCC were significantly younger than women with cSCC ($P < 0.001$). Overall, 170 (80.6%) patients were aged > 60 years. Of these patients, cSCC occurred most often ($n = 63$) in the 70–79 age group [Figure 2b]. The overwhelming majority of affected patients (95.3%) were born in the Thrace region.

Tumor characteristics are summarized in Table 1. Head and neck were the most common sites for cSCCs (93.9%), and almost one half of the tumors ($n = 103$) were located on the lower lip [Figure 3a]. Patients with a cSCC on the lower lip were younger than those with a cSCC on the other sites (mean age 66.8 and 75.0, respectively, $P < 0.001$). Face and ears were the second and third most common sites for cSCC, respectively. All patients with a cSCC on the ears were men. Twenty-eight percent of the tumors were >20 mm in size and 28.9% were >6 mm in depth.

Immunosuppression was present in 16 (7.6%) patients, caused by chemotherapy for extracutaneous malignancies ($n = 9$), immunosuppressive drugs for autoimmune diseases ($n = 4$), and renal transplantation ($n = 3$). Seven immunosuppressed patients had more than one cSCC. All cSCCs in immunosuppressive patients were in the head and neck region. According to all clinical and histopathological prognostic risk factors, a total of 177 (83.9%) patients had high-risk cSCC [Figure 3b].

Median follow-up time for the patients was 15 months (range 2–71 months); however, information on the follow-up was available in only 67% of the cases. During the follow-up period, the local recurrence rate was 6.2% ($n = 13$) with a mean time of 20 months (range 5–48 months), and

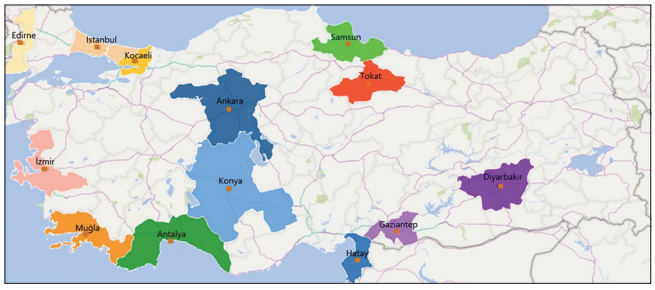

Figure 1: Cities in Turkey where cutaneous squamous cell carcinoma studies were performed

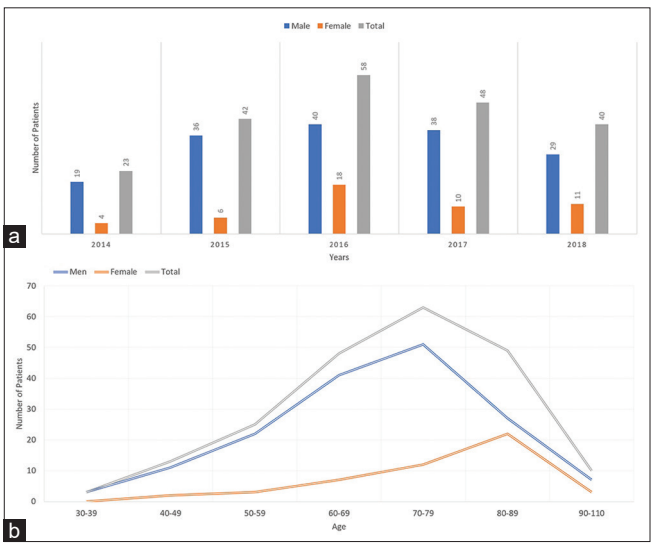

Figure 2: (a) Annual number of patients with cutaneous squamous cell carcinoma. (b) Age distribution of patients with cutaneous squamous cell carcinoma

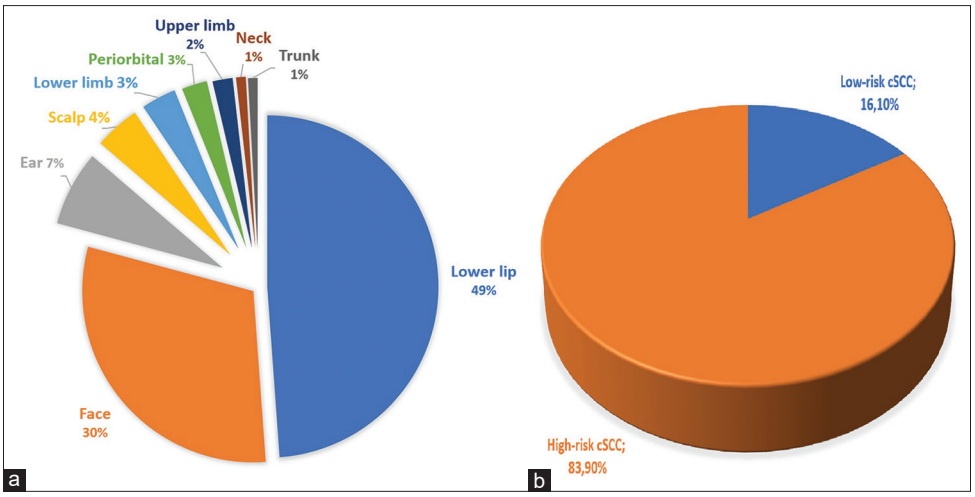

Figure 3: (a) Prevalence of cutaneous squamous cell carcinomas by anatomic localization. (b) Risk classification of patients with cutaneous squamous cell carcinoma

Table 1: Tumor characteristics of cutaneous squamous cell carcinoma

	Total (*n*=211), *n* (%)	Men (*n*=162; 76.2%), *n* (%)	Women (*n*=49; 23.2%), *n* (%)
Localization of cSCC			
Lower lip	103 (48.8)	81 (50)	22 (44.9)
Face	64 (30.3)	41 (25.3)	23 (46.9)
Ear	15 (7.1)	15 (9.3)	0 (0)
Periorbital	5 (2.4)	4 (2.5)	1 (2)
Scalp	9 (4.3)	9 (5.6)	0 (0)
Neck	2 (0.9)	1 (0.6)	1 (2)
Upper limb	4 (1.9)	4 (2.5)	0 (0)
Lower limb	7 (3.3)	5 (3.1)	2 (4.1)
Trunk	2 (0.9)	2 (1.2)	0 (0)
Tumor size (cm)			
Mean±SD (mm)	18.8±16.3	19.81±17.33	15.47±12.02
≤2	152 (72)	112 (69.1)	40 (81.6)
>2	59 (28)	50 (30.9)	9 (18.4)
Tumor thickness (mm)			
Mean±SD (mm)	6.11±5.9	6.31±5.97	5.43±5.66
≤2	55 (26.1)	41 (25.3)	14 (28.6)
3-6	95 (45)	70 (43.2)	25 (51.0)
>6	61 (28.9)	51 (31.5)	10 (20.4)
Tumor differentiation			
Well	152	115	37
Moderate	34	27	7
Poor	25	20	5
Tumor subtype			
Classical	202 (95.7)	154 (95.1)	48 (98)
Verrucous	3 (1.4)	2 (1.2)	1 (2)
Acantholytic	4 (1.9)	4 (2.5)	0 (0)
Spindle	1 (0.5)	1 (0.6)	0 (0)
Sarcomatoid	1 (0.5)	1 (0.6)	0 (0)
Perineural invasion			
Yes	8 (3.8)	6 (3.7)	2 (4.1)
No	203 (96.2)	156 (96.3)	47 (95.9)

SD: Standard deviation, cSCC: Cutaneous squamous cell carcinoma

the metastasis rate was 5.2% (n = 11) with a mean time of 9 months (range 0–48 months). The characteristics of cSCCs with local recurrence and metastasis are summarized in Tables 2 and 3. Metastasis occurred in the

Table 2: Clinical and histopathological characteristics of cutaneous squamous cell carcinomas with local recurrence

Local recurrence	Age	Sex	Localization	Tumor diameter (mm)	Tumor thickness (mm)	Differentiation	Tumor subtype	Perineural invasion	Time of event (months)	Immuno-suppression
Patient 1	94	Female	Face	40	16	Moderately	Classical	Yes	8	Yes
Patient 2	82	Male	Lower limb	55	12	Moderate	Classical	Yes	12	No
Patient 3	69	Male	Lower limb	80	15	Well	Classical	No	13	No
Patient 4	74	Male	Face	34	4	Well	Classical	No	25	No
Patient 5	93	Male	Face	16	14	Moderate	Classical	No	16	No
Patient 6	94	Male	Ear	16	3	Poor	Classical	No	27	No
Patient 7	68	Male	Hand	15	5	Poor	Classical	No	48	No
Patient 8	79	Male	Face	73	15	Well	Classical	No	29	No
Patient 9	88	Female	Face	30	24	Moderate	Classical	No	9	No
Patient 10	64	Male	Lower lip	4	2	Well	Classical	No	36	No
Patient11	88	Female	Lower lip	7	2	Well	Classical	No	5	No
Patient12	79	Male	Lower lip	8	3	Well	Classical	No	9	No
Patient13	56	Male	Lower lip	10	6	Moderate	Classical	No	26	No

Table 3: Clinical and histopathological characteristics of cutaneous squamous cell carcinomas with metastasis

Metastasis	Age	Sex	Localization	Tumor diameter (mm)	Tumor thickness (mm)	Differentiation	Tumor subtype	Perineural Invasion	Time of event (months)	Immuno-suppression
Patient 1	53	Male	Face	70	7	Well	Classical	No	13	No
Patient 2	102	Female	Face	50	6	Poor	Classical	Yes	0	No
Patient 3	78	Male	Scalp	20	6	Well	Classical	No	0	No
Patient 4	87	Male	Ear	20	13	Well	Spindle	No	8	No
Patient 5	78	Female	Face	35	25	Well	Classical	No	0	No
Patient 6	60	Male	Lower lip	25	5	Well	Classical	No	48	No
Patient 7	69	Female	Lower lip	12	3	Moderate	Classical	No	0	No
Patient 8	57	Male	Lower lip	15	5	Moderate	Classical	No	12	No
Patient 9	52	Male	Lower lip	20	6	Moderate	Classical	Yes	0	No
Patient 10	71	Male	Lower lip	35	5	Well	Classical	No	20	No
Patient 11	34	Male	Lower lip	50	40	Poor	Classical	No	3	No

regional lymph nodes: cervical ($n = 6$), parotid ($n = 5$), and submental ($n = 1$). Five of the metastases were detected at baseline.

Discussion

This retrospective study shows that the frequency of cSCC is high and the majority of cSCCs have high-risk features for local recurrence and metastasis in the Thrace region of Turkey, where characteristics of cSCC are scarce. The vast majority (95%) of patients included in this study were born in this region, so it is possible to say that this study represents the influence of local factors, including the skin type of the population. Most of the people of the Thrace region have Fitzpatrick skin type 1 or 2. It is clear that the light skin color plays a very important role in the development of cSCC.[1]

In Turkey, the incidence rate of cSCC is not reported separately, but is covered under the NMSCs in official cancer registries. Data on cSCC in Turkey are usually based on studies conducted in single regional institutions [Figure 1 and Table 4]. Based on all studies published in Turkey,[8-19] it is noteworthy that the Thrace region has one of the highest incidences of cSCC. Table 4 summarizes the number of cSCCs, demographic features of patients, and localization of tumors reported from different geographic areas in Turkey.[8-19]

Demographic characteristics of our study did not show a striking difference from the available literature [Table 4]. In accordance with previous studies, cSCCs were more frequent in the elderly people, and men were more commonly affected than women.[1,8-24] Men were also 8 years younger on average than women at the time of diagnosis. This seems to be a result of most men in the Thrace region being outdoor workers in agricultural occupations. It is well-known that occupational ultraviolet (UV) exposure is a strong and significant risk factor for the development of cSCC in outdoor workers.[1,25] These results may also be related to women's traditional clothing covering the head and most parts of the body. It

Table 4: Demographic features of patients with cutaneous squamous cell carcinoma and localization of tumors in Turkey

	Number of patients	Number of tumors	Duration of study (years)	Male/ female ratio	Mean age/most common age range	Most common localization on head and neck	SCC of lip (%)	SCC of ear (%)	SCC of trunk (%)
Eroğlu *et al*. 1996, Turkey (Ankara)[9]	1039	1039	10	1.8	60.6	NM	NM	15.19	3.3
Ulkur *et al*. 2005, Turkey (Istanbul)[10]	138	138	11	3.31	60-70	NM	NM	NM	14.4
Akturk *et al*. 2006, Turkey (Kocaeli)[11]	74	77	8	2.7	> 70 (%39)	Lip	24	NM	1.29
Ceylan *et al*. 2006, Turkey (Izmir)[12]	817	847	10	2.86	60-70	Lip	42	7.4	1.9
Turkmen *et al*. 2010, Turkey (Gaziantep)[13]	156	213	10	1.4	NM	Lip	23	NM	NM
Koyuncuer 2014, Turkey (Hatay)[8]	31	33	3	1.58	72.4	NM	NM	NM	NM
Bas *et al*. 2014, Turkey (Tokat)[14]	106	106	5	2.11	70-79	NM	NM	NM	1.1
Guneren *et al*. 2014, Turkey (Samsun)[15]	317	317	NM	3.59	60-69	Lip	34.06	14.51	NM
Agırgol 2017, Turkey (Muğla)[16]	36	36	4	1.4	70-80	NM	NM	NM	NM
Ozalp *et al*. 2018, Turkey (Diyarbakır)[17]	45	45	5	NM	72.9	Lip	17.1	NM	NM
Uslu *et al*. 2019, Turkey (Antalya)[18]	85	91	4	NM	NM	Nose	19.7	12.08	NM
Findik *et al*. 2019, Turkey (Konya)[19]	114	117	10	1.59	70-80	Lip	22,2	10.25	7.6
Current Study, Turkey (Edirne)	211	211	5	3.3	71.05, 70-80	Lip	48.8	7.1	0.9

NM: Not mentioned, SCC: Squamous cell carcinoma

is therefore important to focus on education regarding UV protection measures, particularly for male outdoor workers in this region.[25]

The most common site for cSCC in our study was the lower lip. Approximately half of all tumors were on the lower lip. In most studies investigating cSCCs, involvement of the lower lip was not reported as a distinct anatomic site but was included in the "face" or "head and neck" regions. In studies reporting the frequency of lip involvement, rates vary between 1.9% and 42%, with a wide range.[11-13,15,17-21,23,24,26-30] Strikingly, the frequency of cSCC of the lower lip (including the current study) was found to be significantly higher in published Turkish studies (17%–42%)[11-13,15,17-19] in comparison with the studies conducted in most other countries (1.9%–10.7%).[21,23,24,26-30] This difference may be explained by two different factors. First, some studies include vermillion of the lower lip as cSCC whereas it is excluded in other studies.[5,6,26] Second, this result may be related to smoking habits. The prevalence of smoking in Turkish men is reported to be higher than in many European countries.[31] Supporting the latter possibility, patients with a cSCC on the lower lip were 9 years younger on average than those with a cSCC at another site in the body.

Of the cSCCs in this study, 7.1% were located in the ears, which is similar to the frequencies reported by colleagues in different geographic regions of Turkey[9,12,15,18,19] (7.4%–15.1%) [Table 4] and other countries (4%–15%).[21-24,26-28,32] It is interesting to note that ears were a location exclusive to men in our study. In results reported by Korhonen *et al*.[21] and Hayes *et al*.,[23] males had significantly more cSCCs in the ears with a male/female ratios of 5–14.2:1. These results imply that shorter hair on men is possibly associated with the development of cSCC on the ears, as is suggested in previous studies.[20-22,32] This may also be attributed to the fact that women in the Thrace region, especially those who live in the rural areas, wear traditional headscarves that cover the ears. People often forget to protect the ears with sun protection cream and do not wear hats that cover the ears. However, it is essential to raise the awareness regarding sun protection on the ears, especially in men. Localization of cSCC on the trunk was found to be 0.9% in our study, with similar frequencies found in some other regions of Turkey.[11-14] However, in studies from some of the largest cities of Turkey (Ankara,[9] Istanbul,[10] and Antalya[18]) and in studies from Finland,[21] Norway,[22] the UK,[30] Brazil,[33] and Sweden,[34] the frequency of cSCC on the trunk was significantly higher. This may reflect the sociocultural behavior of the population living in the Thrace region. The older generation that forms the vast majority of our study group does not have the habit of sunbathing or using tanning beds.

Table 5: Tumor size and thickness of cutaneous squamous cell carcinoma in studies reported from different countries

	Mean/most common			
	Tumor diameter, *n* (%)		Tumor thickness, *n* (%)	
Korhonen *et al*. 2019, Finland[21]	NM		<1 mm	45 (4)
			1-2 mm	313 (28)
			2.1-4 mm	203 (18)
			>4 mm	112 (10)
			Unknown*	458 (40)*
Nelson and Ashton 2017, UK[30]	15 mm*		4.5 mm*	
Brougham *et al*. 2012, New Zeland[26]	11.1 mm		NM	
Brantsch *et al*. 2008, Germany[27]			3.9 mm	
	≤20 mm	425 (69)	≤2 mm	207 (34)
	21-50 mm	160 (26)	2.1-6 mm	318 (52)
	>50 mm	30 (5)	>6 mm	90 (15)
Roozeboom *et al*. 2013, Netherland[28]	13.3 mm		3.5 mm	
	≤20 mm	NM (83)	≤4 mm	155 (69)
Eroğlu *et al*. 1996, Turkey (Ankara)[9]	≤20 mm	472 (45)	NM	
	20.1-50 mm	359 (34)		
	>50 mm	135 (12)		
	NM	73 (7)		
Ceylan *et al*. 2006, Turkey (Izmir)[12]	11-20 mm (most commonly)		NM	
Koyuncuer 2014, Turkey (Hatay)[8]	8.48 mm		NM	
Current study, Turkey (Edirne)	18.8±16.3		6.11±5.9	
	≤20 mm	152 (72)	≤2 mm	55 (26)
	>20 mm	59 (28)	2.1-6 mm	95 (45)
			>6 mm	61 (29)

*There are unknown cases. NM: Not mentioned

Tumor size is a significant parameter in identifying high-risk cSCCs.[5,6,28] Roozeboom *et al*.[28] emphasized that tumor diameter and tumor thickness were the independent prognostic factors for local recurrence as well as for metastasis. The prevalence of tumors larger than 20 mm was reported to be 46% in Ankara[9] and 31% in Germany[27] [Table 5]. In our study, although it is not as high, the percentage of tumors larger than 20 mm (28%) is remarkable. Our result is significantly higher than the prevalence of tumors larger than 20 mm reported in Izmir, Turkey[12] (11.4%) and in the Netherlands (16.5%)[28] [Table 5]. This could be related to the fact that patients with cSCCs in the Thrace region have a low level of knowledge and awareness of skin tumors and do not seek medical care until tumors expand. Thus, this result indicates that not only primary prevention but also secondary prevention with early detection is crucial to decrease the burden of cSCC.

The tumor thickness is another prognostic factor for cSCC. Guidelines agree that tumors with ≤2 mm thickness are at low risk for metastasis.[3,5-7] No published data regarding tumor thickness in Turkey exists. In our study, 26.4% of tumors had tumor thickness <2 mm and none of them metastasized. cSCCs that metastasized were categorized as 3–6 mm or more than 6 mm in thickness. Data on tumor thickness was also not stated in many of the reports from other countries. In studies from Finland[21] and Germany,[27] the proportion of tumors <2 mm were 32% and 34% respectively, similar to our findings [Table 5]. It is very important to report the thickness as well as the size of cSCCs in all pathology reports.[5,21,27,28] If one of these parameters is missing, the prognosis cannot be determined correctly.[27,28]

The recurrence rates were reported to be 3.2%, 7.2% and 16.7% in studies from Ankara,[9] Istanbul,[10] Antalya,[18] respectively. Metastasis rates were reported to be 1.9% in the study from Istanbul[10] and 3.5% in the study from Ankara.[9] The data in our study showed a recurrence rate of 6.2% and a metastasis rate of 5.2%. These variable results could be related to different follow-up durations. A 5-year minimum follow-up period is recommended for NMSCs.[5] However, the follow-up period was short in our study (mean 18 months) which serves as an important limitation.

When all clinical and histopathological prognostic factors of the cases were evaluated, a striking percentage (83.9%) of the tumors were high-risk cSCCs. The high rate of high-risk cSCCs is a remarkable statistic. Clinicians working in this region should have a high index suspicion for high-risk features in patients with cSCC to follow-up with patients more carefully and achieve favorable outcomes.

Our study had several limitations. First, the retrospective nature of the study prevented us from accessing some parameters; 9% of the cases were excluded because of missing data, mostly on clinical prognostic risk factors. Moreover, etiological risk factors such as skin type, sun protection habits, exposure to chemicals (e.g., arsenic) and tobacco and alcohol use were not able to be assessed for the same reason. Second, the percentage of high-risk features might be higher as a result of referral bias because our study was conducted

in a tertiary university hospital. Third, a small number of patients with some features like perineural invasion, histological subtype, immune status, recurrence, and metastasis precluded the evaluation of any associations.

Conclusions

Our study revealed several characteristics of cSCC in the Thrace region. cSCC affects men more than women and arises in men at an earlier age. cSCCs show involvement of different locations between sex; ear involvement is significantly higher in men. cSCC of the lower lip is seen in younger people. Overall, our study highlights that the Thrace region has remarkably high numbers of cSCC and high-risk tumor features are very frequent. Clinicians should thoroughly investigate the presence of high-risk features.

Acknowledgement

We thank Prof. Can Baykal (Istanbul Medical Faculty, Department of Dermatology) for comments that improved the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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