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Original Article

SQUAMOUS CELL CARCINOMA OF THE SKIN: EPIDEMIOLOGY, DIAGNOSIS, MANAGEMENT, RECURRENCE AND MORTALITY RATES FOR THE BULGARIAN POPULATION

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Summary

Squamous cell carcinoma of the skin (SCCs) accounts for 20-30% of non-melanoma skin cancers, resulting in 1 million cases in the United States annually. The risk of developing SCCs increases annually, and this process will likely be continued because of the aging population. We investigated 355 patients with histopathologically confirmed SCCs. We rated the age- and sex-related incidence, risk factors, localisation, pathological features, staging systems and treatment, and the recurrence and mortality rates of the tumours. Staging and risk stratification for recurrence and metastases is significant. Most SCCs are successfully treated surgically, with a small subset of carcinomas leading to recurrence, metastasis, and death. Patients with advanced and metastatic disease are often inappropriate for surgical and radiation therapy. We present the first study on squamous cell carcinoma of the skin conducted for the population of the Pleven and Lovech regions of Bulgaria.
Keywords: squamous cell carcinoma of the skin, epidemiology, treatment, recurrence, mortality

Introduction

Non-melanoma skin cancers, known as keratinocyte carcinomas, are a group of skin diseases which start their development from the epidermis. Squamous cell carcinoma of the skin (SCCs) accounts for 30% of non-melanoma skin tumours. It is the second most common tumour in the human organism, with more than 1 million cases per year in the USA [1]. A comparative study of the incidence of SCCs between 1976 – 1984 and 2000 – 2010 from Mayo Clinic showed an increase of 263% in the second period [2]. Karia et al. reported that 5604 to 12 572 patients suffering from SCCs developed metastasis in lymph nodes, and between 3932 and 8791 patients died from the disease in 2012 in the USA population [3]. It is estimated that the rates of SCCs are higher in southern and central USA, where the mortality of SCCs is identical to kidney and oropharyngeal carcinoma and

Melanoma malignum [4]. The number of patients with SCCs has increased by 50 – 300% in the different regions during the last three decades, and it is estimated that by 2030, the incidence of SCCs in Europe will double [5]. The most significant risk factors for SCCs are sun exposure, age, fair skin (Fitzpatrick skin types I-II), and immunosuppression [6]. Immunosuppression plays a critical role in SCCs, with solid organ transplant recipients (SOTR) having an 80 to 250 times higher risk of developing SCCs than the general population [7, 8]. Rare familial syndromes like Bloom syndrome, Gorlin syndrome, Muir–Torre syndrome, Rothmund-Thomson syndrome and Werner syndrome are associated with photosensitivity or defective DNA repair and predispose patients to multiple SCCs at a young age [9]. SCCs are characterised by asymmetric extension of the tumour cells beyond the clinically visible edges of the lesion [10]. The National Comprehensive Cancer Network (NCCN) guidelines recommend standard excision with a 4- to 6-mm margin of uninvolved skin around the tumour to a depth of the mid-subcutaneous tissue with histologic margin assessment for low-risk primary SCCs [11, 12]. Primary SCCs with perineural invasion or high risk for regional lymph node or distant organ metastasis may be considered for adjuvant radiation therapy to the local tumour site following surgical treatment [13].

Materials and methods

Our retrospective and prospective study involved 355 patients with SCCs. The cases were selected for six years (2016-2022) and registered with histologically verified SCCs in the Oncological Registry in Pleven and Lovech regions. The study was carried out through interviews, clinical examination and reviewing patients' medical records. A detailed questionnaire was designed and filled out by a doctor. It included patient history, sun exposure information, localisation and macroscopic diameter of the carcinoma, specific localisation in the facial area, histopathological characteristics, staging of the SCCs according to the TNM classification and American Joint Committee on Cancer - Cancer Staging Manual 8th version (AJCC 8), and treatment types. The survey data was processed with IBM specialised software SPSS (Statistical Package for Social Sciences) version 20.0. The following statistical methods were used:

Descriptive statistics: Quantitative variables represented by summarising statistical characteristics - arithmetic mean (Mean) and standard deviation (SD); Categorical variables summarised by absolute (n) and relative (%) frequencies;

Chi-square test – examining dependencies between descriptive (categorical) data with two or more categories;

Kaplan-Meier analysis – to evaluate the curve (function) of survival until the occurrence of the studied events;

Log Rank test – for comparison of survival curves in two or more independent groups;

The threshold level of significance adopted is α=0.05. Statistical significance is assumed when the p-value is less than α.

The results were described by tables, graphs, and numerical values (percentages, coefficients, average values, standard deviation, etc.).

Ethical aspects

The study was conducted following the national and international requirements for clinical studies, including the preservation of the anonymity of the participants and the non-disclosure of their personal information. Each participant signed an informed consent form before the excision of the suspected lesions during their hospital stay.

Results

Within the study framework, 355 patients aged 40 to 96 were investigated. The average age of the patients suffering from SCCs was 75.02 years (± 10.74 SD). The male patients were 185 (52.1%) with a mean age of 74.11 years (±10.57). The female patients were 170 (47.9%) with an average age of 76.01 (± 10.87). The results for the sex- and age-related incidence are shown in Fig. 1. No statistical differences were registered regarding the age and sex of the patients, p>0.05(actual value p=0.057). Depending on the time needed to get the SCCs excised and histologically confirmed, the patients were divided into the following four groups: up to 1 year – 182 patients (51.3%), up to 2 years –

212 patients (34.1%), up to 3 years – 42 patients (11.8%) and up to 5 years – 10 patients (2.8%). Data analysis showed a statistical significance of the time of diagnosis and the overall survival of the patients: p<0.05 (actual value p=0.001). The later the time to diagnosis, the lower the survival was. We also assessed the development of other skin cancers – SCCs, basal cell carcinoma (BCCs), and malignant melanoma (MM) – 21 patients (5.9%) developed other SCCs; 15 patients (4.3%) had previous BCCs, and five patients (1.4%) developed MM. We rated sun exposure and immunosuppression as risk factors: 239 patients (67.3%) practised outdoor activities as a daily routine (plant and animal husbandry/ sports), and 260 patients (73.3%) admitted having severe sunburns in their lives. According to the medical documentation. we observed four patients (1.13%) under immunosuppression for concomitant diseases. We analysed the localisation of primary SCCs of the body (Table 1).

It is noteworthy to emphasise the rate of facial localisation (a total of 206 patients – 58.02%). In Table 2, we present the distribution of SCCs on the face. Measuring the macroscopic diameter of the tumour, we observed a Mean Diameter of SCCs 19.86 mm (SD 14.34mm).

The minimum value was 4 mm, and the maximum was up to 100 mm. Statistical analysis showed that the difference in the diameter of SCCs in the different age groups was statistically significant – p<0.05 (actual p-value 0.028). The data analysis showed that the differences between the diameter of the lesions and the time to get the surgical treatment were also significant: p<0.05 (actual p-value <0.001). A statistically significant difference between the macroscopic diameter of the tumours and the overall survival was also noted: p<0.05 (actual p-value <0.001). The analysis of causes of death in the retrospective group showed that 70 patients (19.7%) lost their lives. Two patients (0.56%) died from severe Covid-19 infection, 42 patients (11.83%) – died from acute vascular accidents, 13 patients (3.66%) died because of cardiovascular diseases, six patients (1.69%) lost their lives because of other malignant diseases, and seven patients (1.97%) died because of advanced metastatic SCCs. The overall survival

Table 1. Distribution of patients with SCCs according to topographic localisation of the tumour

Topographic localisation of the tumour	N	%	Topographic localisation of the tumor	N	%
Lips	33	9.3	Lower limb	9	2.5
Eyelids	6	1.7	Unspecified	1	0.3
Ear	24	6.8	Labia major	14	3.9
Face	168	47.3	Labia minor	4	1.1
Head and Neck	27	7.6	Vulva	2	0.6
Thorax	24	6.8	Glans penis	19	5.4
Upper limb	20	5.6	Corpus penis	4	1.1
Total 355 100.0%					

Table 2. Distribution of SCCs in the facial area

Specific localisation of SCCs on the face	N	%
Lower lip	42	20.4
Upper lip	7	3.4
Buccal	82	39.8
Lower eyelid	10	4.9
Upper eyelid	3	1.5
Forehead	36	17.5
Nose	26	12.6
Total	206	100.0

did not show significant differences in the different sex groups: p>0.05 (actual p-value =0.216). The pathological classification of the tumours was made according to the TNM classification and the Staging (AJCC 8) [14]. The distribution of the patients according to their tumour diameter (T) was the following: T1 – 214 (60.3%); T2 – 107 (30.1%), T3 – 25 (7.0%); and T4 – 9 (2.5%). Depending on the presence of lymph node metastasis (N), the patients were divided into groups as follows: N0 – 343 (96.6%); N1 – 8 (2.3%); N2 – 2 (0.6%) and N3 – 2 (0.6%). Distant metastasis in internal organs (M): M0 – 351 (98.9%); M1 – 2 (0.6%) and M3 – 2 (0.6%). The Staging according to the AJCC 8 is presented in Table 3.

Statistical analysis showed a significant difference between the stage of the SCCs and the overall survival of the patients: p<0.05 (actual p-value <0.001). The microscopic depth of the SCCs was evaluated using the Breslow level of invasion. The distribution of the tumours according to their microscopic thickness is presented in Table 4.

Surprisingly, data analysis showed significant differences between the microscopic depth of the tumour in the different age groups: p<0.05 (actual p-value 0.001) with thicker tumours in the group of 71-80-year-olds. Comparing the macroscopic diameter of SCCs and microscopic depth also showed statistical significance: p<0=05 (actual p-value <0.001). Of the investigated 355 patients diagnosed with SCCs, 302 (85.1%) had an invasive carcinoma and 53 (14.9%) – had an *in situ* carcinoma. In the group of *in situ* carcinomas, one patient (2.0%) had actinic keratosis, four patients (7.8%) were diagnosed with Morbus Bowen, and 46 patients (90.2%) suffered from keratoacanthoma. In the group of invasive SCCs, 11 patients (3.8%) had a superficial tumour; 129 patients (44.0%) had ulcerous-infiltrative carcinoma, and 153 patients (52.2%) were diagnosed with nodular SCCs. We assessed the histological characteristics of the tumours and found 345 (97.2%) common well-differentiated SCCs; 1 (0.3%) adenosquamous carcinoma, 1 (0.3%) spindle-cell carcinoma, and 8 (2.3%) acantholytic tumours. The cell differentiation of the tumours was analysed in 159 patients (100%): 83 (52.2%) SCCs had well-differentiated (G1); 64 (40.3%) G2 carcinomas; 11 (6.9%) had poorly differentiated tumours (G3), and one patient (0,6%) had a very poorly differentiated (G4) SCCs. The keratinisation of 349 tumours was assessed, of which 309 (88,5%) were keratinising, and 40 (11,5%) were non-keratinising. The treatment of each SCCs was also examined. Three hundred-two patients (85.1%) were treated with surgical excision, and 53 patients (14.9%) received a combined treatment (surgical excision + radiotherapy). In 303 cases (85.4%), the surgical excision led to the full tumour removal. In the other 52 patients (14.6%), radiotherapy was applied after surgery in addition to clearing the rest of the tumour cells. We analysed the local recurrences and

Table 3. Staging of the patients with SCCs according to the American Joint Committee on Cancer Staging Manual 8 (AJCC 8)

Stage of the SCCs	N	%
Stage I	214	60.3
Stage II	125	35.2
Stage III	10	2.8
Stage IV	6	1.7
Total	355	100.0

Table 4. Distribution of the tumours according to their microscopic thickness

Microscopic depth of the SCCs	N	%
Up to 1.0 mm	5	1.4
1,0-2.0 mm	40	11.3
2.0-3.0 mm	52	14.6
3.0-4.0mm	108	30.4
Over 4.0mm	150	42.3
Total	355	100.0

metastasis after the treatment. In 17 patients (4.8%), we registered local recurrence. The time for recurrence was divided into three groups – up to 1 year (7 patients – 41.2%), 1 – 2 years (8 patients – 47.1%) and more than three years (2 patients – 11.8%). We observed loco-regional lymph node metastasis in 18 patients (5.1%). We registered distant metastases in internal organs in 8 (2.25%) patients. In 6 cases, the metastatic organ was the lungs, 1 had brain metastasis, and 1 had colon metastases. The rate of these metastatic patients was tumour-diameter dependent, with statistical significance: $p<0,05$ (actual p-value <0.001). Data analysis comparing the age of the patients and the time to recurrence showed no statistical significance: $p>0.05$ (actual p-value $=0.656$).

Discussion

Our study focused on patients with SCC. We aimed to clarify the age- and sex-related incidence and risk factors and study the specific morphology of the tumours in the Bulgarian population. The age of our patients was 75.02 (±10.74 SD), which corresponds to the worldwide data – SCCs being most common in the 64-84 age group [2]. Our analysis of our results shows no statistical difference between the males and females affected by SCCs, although male patients are prevalent. This corresponds to the study by Karia et al. [3]. As for the risk factors, extensive sun damage on the skin is one of the main etiological factors leading to SCCs development. Our results confirmed the relationship between sun damage and skin cancer formation, as some patients developed more than one SCCs and even other skin malignancies – BCCs and MM, corresponding to the data from Xiang et al. [6]. In the studied group, we found that primary SCCs are more common in the head and neck region, similar to the data presented by Katalinic et al. [5]. The time of diagnosis is also crucial: we found that many patients did not have access to experienced dermatologists and suffered from a delay in the correct diagnosis and treatment. The data clearly showed that the longer it takes for the patient to get the excision, the higher the tumour stage and the worse overall survival. Also, the higher stage implied a larger tumour. This leads to major surgical excisions and adjuvant radiotherapy. Our data for local recurrence (4.8%), lymph node metastases (5.1%), distant metastases in internal organs (2,25%), and mortality (1.97%) corresponds to the data from different studies throughout the world: local recurrence rate of 5.4% and mortality rate of 1.5% - 2% in the USA, reaching up to 4% in other countries [6,15]. This leads to follow-up periods of at least four years after the initial excision of the primary tumour [16]. The data analysis also showed that the rate of metastatic tumours is tumour-diameter dependent, similar to the results of Leibovitch et al. [11]. Like in the study by Carter et al., our results demonstrated the importance of a detailed histopathological report containing important information for the degree of differentiation, aggressive pathological subtypes (acantholytic, adenosquamous, and carcinosarcomatous), tumour depth (Breslow level), presence of perineural and/or lymphatic invasion, fascia, muscle or bone invasion, presence or absence of inflammation, and margin status [17]. This information is significant for the outcome of the patient. It can change the follow-up periods and therapy after surgery (further surgical treatment, radiotherapy, or systemic treatment).

Conclusions

We present the first study of squamous cell carcinoma of the skin conducted for the Bulgarian population in Pleven and Lovech, Bulgaria. Our results correspond to the world data. In our study group, the male patients had a higher incidence rate than the females, although it was not statistically significant. The study confirmed the apparent association between sun damage (ultraviolet radiation) and SCCs development, as well as that the high-risk tumours (with macroscopic diameter >2 cm and microscopic depth > 4mm) bear a higher risk for metastases, recurrence, and mortality. The detailed histological report is a crucial part of the diagnostic process and must always be comprehensive to provide optimal treatment. The follow-up after the initial excision of the primary SCCs must be thorough and conducted for at least four years. Routine skin examination by family practitioners, especially in patients over 60, is crucial for early detection of SCCs.

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