SEVERITY PROFILE OF SQUAMOUS CELL CARCINOMA CASES IN A TERTIARY REFERRAL CENTER

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Summary

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer and its incidence is rising worldwide. Although most cSCC cases have an excellent prognosis, a subset of high risk cSCC is associated with increased recurrence and metastasis rates and a considerably worse outcome.

Objective

To assess the clinical and histopathologic characteristics and the severity profile of cSCCs diagnosed in a tertiary referral center during a 5 year period.

Materials and methods

Based on the medical records of patients diagnosed with cSCC in our clinic between January 2011 and December 2015, variables like age, sex, anatomic location, clinical and histopathologic features were analyzed.

Results

108 patients were identified, with a mean age of 72.28 ± 9.77 years and a gender ratio (M/F) of 1.03. 62% of cSCCs were located in the head and neck region. Tumor diameter ranged from 0.3 to 6.5 cm, the mean diameter being significantly larger in men. 41.6% were in situ SCC. 47.6% of invasive cSCCs were well differentiated and 52.4% moderately differentiated. 71.4% of invasive cSCCs involved the deep dermis, 11.1% the hypodermis, and 12.7% the musculature. Invasion of the hypodermis and musculature was more frequent in men. 86.7% of deeply invasive cSCCs were located in the head and neck region. Perineural and lymphatic invasion were uncommon. No metastatic cSCC was diagnosed. All cSCCs were surgically excised, achieving clear margins in 80.5% cases.

Conclusion

Patients often present with large and deeply invasive cSCC, posing therapeutic difficulties and carrying higher recurrence and metastatic risks.

Key words: *non-melanoma skin cancer, cutaneous squamous cell carcinoma, histopathology, prognosis.*

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Introduction

Non-melanoma skin cancers (NMSCs), comprising basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) are the most common malignancies. Despite the substantial associated morbidity and mortality and the important costs of treatment, NMSCs are not currently reported to cancer registries, and their exact incidence is not known.

Cutaneous SCC (cSCC) is the result of the malignant proliferation of suprabasal epidermal keratinocytes. It is the second most common skin

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cancer, only exceeded by BCC and its incidence is steadily rising worldwide [1]. It has an estimated incidence of 0.03-3.5 cases / 100,000 people / year, directly related to the average annual ultraviolet radiation (UVR) [2]. The incidence of cSCC is highest in regions closer to the equator [3]. Unlike BCC, which arises de novo, most cSCC develop from precursor lesions, namely actinic keratoses and Bowen's disease. Although the most important predisposing factor is cumulative lifetime UV exposure, certain inherited disorders (xeroderma pigmentosa, albinism, dystrophic epidermolysis bullosa, epidermodysplasia verruciformis, etc.), chronic immunosuppression (in organ transplant recipients, long-term glucocorticoid use, or HIV infection), exposure to ionizing radiation, chemical carcinogens (arsenic, aromatic hydrocarbons, insecticides and herbicides), and human papillomavirus (HPV) infection also contribute to the development of cSCC [4-13]. In addition, approximately 95% of skin cancers arising in sites of chronic inflammation or irritation are SCCs, referred to as Marjolin's ulcer [14].

cSCC usually affects the elderly and rarely develops before the age of 45 [15], although recent studies show an increase in the incidence of cSCC among young individuals [16]. The above mentioned genodermatoses and chronic immunosuppression predispose to the appearance of cSCC at a much younger age.

cSCC is easily managed in the early stages, but left untreated, it causes local tissue destruction, disfigurement and carries a significant metastatic potential (reported metastasis rate ranges from 0.5 to 6 %) [17, 18]. Although it accounts for only 20-25% of NMSCs, cSCC is responsible for the majority of deaths caused by NMSCs [19, 20]. While 90% of skin cancer deaths in individuals younger than 50 are attributable to melanoma, cSCC is the leading cause of skin cancer death after the age of 85 [21]. Moreover, patients diagnosed with cSCC not only have a 44-50 % risk of developing additional NMSCs [22], but are also prone to developing melanoma [23], as well as extracutaneous cancers [24, 25].

Despite the fact that most cases of cSCC promptly diagnosed and treated have an excellent prognosis, a subset of high risk cSCCs exists [26]. High risk cSCC is characterized by the presence of one or more of the following factors: recurrent tumor, location on the lips, ears, and anogenital region, or arising at a site of chronic inflammation or in a scar, tumor diameter larger than 1.5cm if located on the lips or ears and larger than 2 cm if located elsewhere on the body, poorly differentiated tumor cells, invasion of the hypodermis or subjacent musculature, and perineural or lymphatic invasion [2, 27, 28]. Chronic immunosupression has been shown to represent an extrinsic factor in high-risk cSCC [29]. High risk cSCC is associated with a markedly increased risk of recurrence, nodal or distant metastasis (usually to the lungs) and a considerably worse outcome, representing an expensive and serious public health issue [26, 30].

Therefore, education on cSCC epidemiological and clinical characteristics is of great importance in order to reduce cSCC related morbidity, mortality and economic costs. Given the lack of data on cSCC in Romania, the aim of this study was to assess the clinical and histopathological characteristics, as well as the severity profile of cSCCs diagnosed in a tertiary referral Dermatology center in Bucharest between January 2011 and December 2015.

Materials and methods

We performed a retrospective study in the Dermatology Department of Elias Emergency University Hospital, in Bucharest. The medical records of patients with histopathologically confirmed cSCCs admitted to our clinic between January 2011 and December 2015 were reviewed. Variables like age, sex, anatomic location, tumor diameter, cellular differentiation, depth of invasion, perineural and lymphatic involvement, treatment strategy and outcome were assessed.

Statistical analyses was performed using SPSS V17, STATA V10. Categorical variables were expressed as percentages and quantitative variables as mean and standard deviation. The relation between the presence of cSCC and continuous variables was analyzed using Student t-test. Two-sided *P* values less than 0.05 were considered statistically significant.

Results

A total of 108 patients were diagnosed with cSCC and treated during the mentioned time period, representing 1.08% of all hospitalized

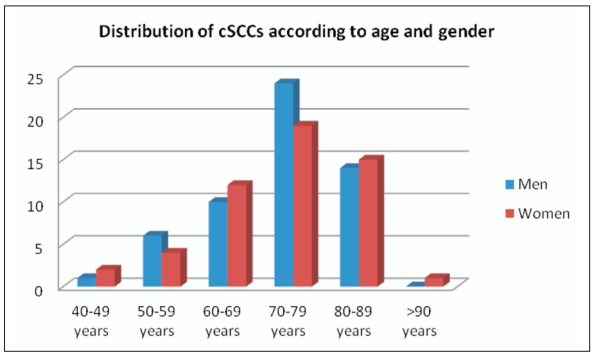

Fig. 1. Distribution of cSCCs according to age and gender

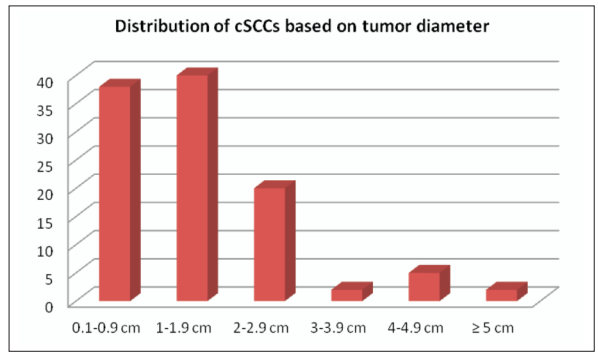

Fig. 2. Distribution of cSCCs based on tumor diameter

patients and 18.94% of patients diagnosed with skin cancer in our department. Among the 108 patients, 55 (51%) were men, the gender ratio (M/F) being 1.03.

The age of patients at the time of diagnosis ranged from 43 to 91 years, the mean age being 72.28 ± 9.77 years. The mean age at diagnosis did not differ significantly between men (71.83 ± 9.55 years) and women (72.75 ± 10.06 years) (p= 0.6269). While no case of cSCC was diagnosed under the age of 40, the highest frequency of SCC was observed in the age group 70-79 years (39.8% of cases). The distribution of cSCCs according to age and gender is illustrated in Fig.1.

The majority (62%) of cSCCs in our case series were located in the head and neck area. Of these, 31% occurred in the malar region and 26% on the lower lip. Only one case of SCC on the upper lip was diagnosed. 13% of cSCCs located in the head and neck region developed in the temporal area and 11% on the external ear. Other areas of the face, the scalp and the cervical area were less frequently involved.

The second most common anatomic location of cSCCs was the trunk (15% of cases), followed by the upper limbs (12% of cases), genital area (7% of cases), and lower limbs (4% of cases).

We noted a series of significant differences between male and female patients regarding the topography of cSCCs. In women, the majority of cSCCs arising in the head and neck area were located in the malar region (46% of cases vs. 19% of cases in men), while in men the most common site was the lower lip (38% of cases vs 14% of cases in women). In addition, cSCCs involving the genital area and the upper limb were twice as frequent in women as in men.

The head and neck area was the most frequent location of cSCC in all age groups, except for the 3 cases diagnosed in patients younger than 49 years, 2 of which developed in the genital region and one on the lower limb, and the only case diagnosed in a patient older than 90, which was located on the trunk.

The diameter of the tumors ranged from 0.3 to 6.5 cm, the mean diameter being 1.61 ± 1.19 cm (Fig. 2). The mean size of cSCCs was significantly larger in male patients (1.91 ± 1.44 cm) compared to female patients (1.14 ± 0.34 cm) (p = 0.0003).

In our case series, only one patient presented with a recurrent tumor. The rest of the cSCCs diagnosed in our department were primary tumors.

The histopathologic examination revealed in situ SCC in 45 (41.6%) patients, the rest being diagnosed with invasive cSCC. 47.6% of the invasive tumors displayed well differentiated tumor cells and 52.4% moderately differentiated tumor cells.

All cSCCs diagnosed in patients younger than 50 and the majority (62.5%) of cSCCs diagnosed in patients aged 50-59 years were in situ SCCs. In situ and invasive cSCCs had similar frequencies in the age group 70-79 years, while in the age group 60-69 years and in patients older than 80, invasive cSCCs were more common than in situ SCCs (77.3% vs. 22.7% in the age group 60-69 years and 66.7% vs. 33.3% in patients older than 80, respectively).

In respect of invasive cSCCs, while in patients younger than 80 well differentiated and moderately differentiated tumors had similar frequencies, in patients older than 80 moderately

differentiated tumors were more frequently encountered than well differentiated SCCs.

50% of tumors were ulcerated. Ulceration was present more often in the moderately differentiated tumors compared to the well differentiated and in situ SCCs, but did not correlate with the depth of invasion.

We identified 2 cases of acantholytic SCC, one of which was a recurrent tumor (the only recurrent tumor in our case series). No other histologic variants of cSCC were detected.

According to the histopatologic reports, 4.8% of the invasive cSCCs only involved the superficial dermis, 71.4% of them extended into the deep dermis, 11.1% extended into the hypodermis, and 12.7% invaded the subjacent musculature. Perineural and lymphatic invasion were uncommon. Only 2 cases (1.85%) presented both perineural and lymphatic invasion. These were moderately differentiated cSCCs invading the hypodermis. One was located on the anterior torso and the other in the temporal region. Lymphatic invasion was noted in one additional case of moderately differentiated cSCC extending into the deep dermis, that was located on the upper limb.

Invasion of the hypodermis and musculature was noted in 15 cases. It varied between age groups and according to gender. The youngest patient who presented with cSCC invasive in the subjacent musculature was aged 57. As illustrated in Figure 4, invasion of the hypodermis and musculature was significantly more frequent in men than in women (10 cases were male patients and 5 cases were female patients). The vast majority of these cases (86.7%) were cSCCs located in the head and neck area, with only one case involving the upper limb and one case involving the trunk.

The mean tumor diameter of cSCCs invasive in the hypodermis or deeper structures was larger than that of tumors limited to the dermis (1.96 ± 1.36 cm vs. 1.36 ± 1.09 cm), but the difference did not reach statistical significance (p=0.0988).

No metastatic cSCC was diagnosed in the mentioned time period in our department.

All cSCCs were surgically excised. Clear histological margins were achieved in 87 (80.5%) cases. Re-excision was performed in cases with positive margins. Patients were referred to oncologists and radiotherapy specialists for postoperative adjuvant radiotherapy when indicated according to current best practice guidelines.

Discussions

Consistent with the available incidence data, cSCC was the second most common skin cancer diagnosed in our department during a 5 year period, accounting for 18.94% of all cases of skin cancer.

In our case series, cSCC equally affected men and women, the gender ration (M/F) being 1.03. This is in contrast with previous studies, that reported a 2-3 times higher frequency of SCC in men compared to women and explained SCC predilection for the male gender by greater cumulative lifetime UV exposure in men (especially occupational sun exposure) and to a lesser extent by exposure to other professional

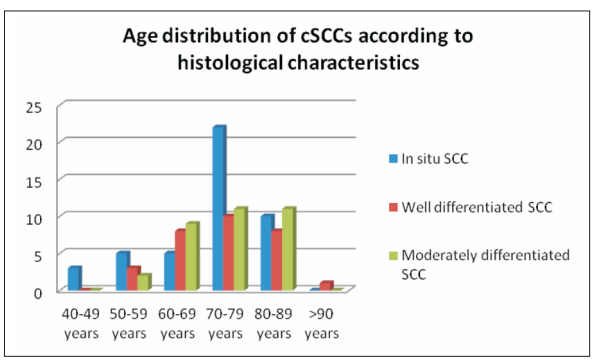

Fig. 3. Age distribution of cSCCs according to histopathological characteristics

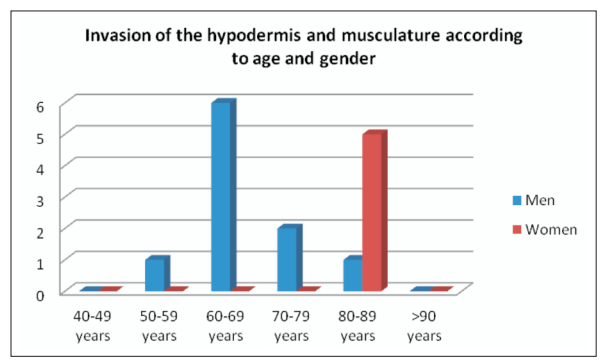

Fig. 4. Invasion of the hypodermis and musculature according to age and gender

risk factors, such as soot, oils, or tars [2, 31]. A first estimation of risk factors and diagnostic behaviors in NMSC patients in Romania has been performed in our group [32].

cSCC is a disease of the elderly, the typical age at diagnosis being 70 years [2]. The incidence of cSCC markedly increases with age. After the age of 75, the incidence of cSCC is 50 - 300 times greater than that of individuals younger than 45 [15, 33]. This is mostly due to the cumulative effects of UV exposure. UVR is a complete carcinogen that induces DNA damage through pyrimidine dimers production, resulting in mutations in the p53 tumor suppressor gene and alterations in other apoptosis regulators (Bcl-2, Bcl-XL, BAG 1) [2]. These genetic abnormalities, along with the impaired cutaneous immune response to the presence of tumor cells also caused by UVR lead to the development of skin cancer. Such genetic markers may, in the future, serve as indicators of the evolution of the disease and response to therapy [34].

cSCC may develop in younger patients suffering from certain genetic disorders, such as xeroderma pigmentosa, albinism, dystrophic epidermolysis bullosa, and epidermodysplasia verruciformis [5-8]. Moreover, chronic immunosuppression in organ transplant recipients, in patients receiving long term corticotherapy or other immunosuppressive drugs, and HIV infected individuals promotes cSCC development at a much younger age [9, 10].

The youngest patient diagnosed with cSCC in our study was 43 years old. Similar to the literature data, the mean age at diagnosis was 72.28 years, the highest frequency of cSCCs being observed among patients aged 70-79 (39.8%). The mean age at diagnosis was very slightly lower in men (71.83 ± 9.55 years) compared to women (72.75 ± 10.06 years).

In Caucasians, cSCC generally involves sun-exposed areas [35]. cSCC most commonly involves the head and neck region (in approximately 70% of cases), especially the lower lip, external ear and periauricular region [2]. In accordance with the results of previous studies, the head and neck region was the most common anatomic location in our patients (62% of cases). The second most common anatomic location of cSCCs was the trunk (15% of cases), followed by the upper limbs (12% of cases), genital area (7% of cases), and lower limbs (4% of cases). We noted important differences between male and female patients regarding the topography of cSCCs. In women, the majority of cSCCs arising in the head and neck area were located in the malar region, while in men the most common site was the lower lip. In addition, cSCCs involving the genital area and the upper limb were twice as frequent in women as in men. The retrospective design of our study did not allow for the evaluation of risk factors that promoted cSCC development. We can only hypothesize that smoking, which, apart from UVR, is an important risk factor for lower lip SCC may explain the frequent localization of SCC on the lower lip in our male patients. On the other hand, genital HPV infection and precursory lesions such as lichen sclerosus and atrophicus might account for the higher frequency of genital SCC observed in our female patients compared to our male patients. The location of cSCC has important prognostic and therapeutic implications. SCCs arising on the lip and external ear portend the poorest prognosis, SCC of the lip carrying the highest metastatic potential (13.7%) and that of the ear the highest recurrence rate (18.7%) and a high metastatic risk (11%) [26]. Moreover, reconstruction after excision is more difficult in these areas and the cosmetic results of surgery are often unsatisfactory.

Tumor diameter ranged from 0.3 to 6.5 cm, the mean diameter being 1.61 ± 1.19 cm. The mean size of cSCCs was significantly larger in men (1.91 ± 1.44 cm) compared to women (1.14 ± 0.34 cm) (p = 0.0003). A possible explanation for this finding resides in women's increased attention to skin problems, particularly in the head and neck region, leading them seek medical advice sooner than men [32]. The diameter of cSCC is also an important prognostic factor, as tumors larger than 1.5cm if located on the lips or ears and larger than 2 cm if located elsewhere on the body have been shown to have a worse outcome and a higher rate of metastatic spread [2]. While the metastatic rate of cSCCs with a diameter of less than 2 cm is estimated at approximately 1%, it significantly increases with tumor diameter, reaching 9.2% for tumors 2-5cm

in diameter and as much as 14.3% for tumors larger than 5cm [26, 36].

The histologic differentiation grade is another essential aspect for establishing prognosis and treatment planning. Poorly differentiated cSCCs behave more aggressively, having reported recurrence rates of 28.6-54% and a reported metastatic rate of 32.8%, as opposed to 11.8-13.6% and 9.2%, respectively, for well-differentiated cSCCs [2, 26, 28]. In our study, 41.6% of cases were in situ SCCs. As expected, in situ SCCs were more frequent than invasive cSCCs in patients younger than 60 and invasive cSCCs predominated among older patients. 47.6% of the invasive cSCCs were well differentiated and 52.4% were moderately differentiated. While in patients younger than 80 well differentiated and moderately differentiated tumors had similar frequencies, in patients older than 80 moderately differentiated tumors were more frequently encountered than well differentiated cSCCs.

Ulceration was a frequent finding (50% of tumors). It was observed more often in moderately differentiated tumors, but did not correlate with the depth of invasion.

Histologic variants of cSCC were very uncommon. 2 cases of acantholytic SCC were the only cases of SCC variants identified among our patients. One of the acantholytic SCCs was the only recurrent tumor detected among our patients. The histologic variants of SCC, such as acantholytic SCC and spindle cell SCC have been shown to be more aggressive and to have a worse outcome.

Regarding the depth of invasion, 4.8% of the invasive cSCCs in our case series only involved the superficial dermis, 71.4% of them extended into the deep dermis, 11.1% extended into the hypodermis, and 12.7% invaded the subjacent musculature. Invasion of the hypodermis and musculature was significantly more frequent in men than in women. The vast majority of these cases (86.7%) were cSCCs located in the head and neck area and had a mean diameter larger than that of tumors limited to the dermis. Thus, these lesions were characterized by several intrinsic high risk factors. The depth of invasion greatly influences the risk of local recurrence and metastasis [2]. In cSCCs less than 2 mm deep metastasis is very rare. With a depth of invasion of 2-4 mm, the reported recurrence rate is 5.3% and the metastasis rate is 6.7% [2]. Some authors report metastatic rates of up to 50% for cSCCs with a depth of invasion greater than 4 mm [36, 37]. Bone, nerve, or muscle involvement is associated with greater metastatic potential.

Perineural invasion is reported to occur in 5-10% of cSCCs and considerably worsens the prognosis, being associated with a metastatic rate of up to 47% [2, 38, 39]. Survival rates depend on the diameter of involved nerves. In a study conducted by Ross AS *et al*., no fatalities associated with SCC occurred when nerves less than 0.1 mm in diameter were involved, but 32% of patients with involvement of nerves 0.1 mm in diameter or larger died from SCC [40]. The outcome is substantially improved with complete resection of the tumor and removal of the involved nerve, especially by Mohs micrographic surgery [2]. We noted both perineural and lymphatic invasion in 2 of our patients (1.85%) and lymphatic invasion alone in only one patient.

No metastatic cSCC was diagnosed during the mentioned time period in our department, confirming cSCC has a far better prognosis than mucosal or internal organ SCC. Efforts are made to enhance diagnostic methods for SCCs affecting the mucosa or internal organs [41-45]. These are associated with much greater morbidity and mortality and therefore early detection is critical.

The gold standard for the treatment of cSCC is complete surgical removal of the tumor, either by standard surgical excision with post-operative histological control of excision margins or by Mohs micrographic surgery. Current guidelines recommend a minimal lateral surgical margin of 5 mm for low risk tumors and 10 mm for high risk cSCCs and a deep margin that involves the hypodermis (sparing the aponeuroses, perichondrium and periosteum if not invaded) [46]. In patients who refuse or have contraindications for surgery, radiotherapy is the best alternative. A series of locally destructive procedures (cryotherapy, curettage & electrodessication, photodynamic therapy) can also be employed, as well as topical treatments, such as imiquimod 5 and 3.75%, 5- fluorouracil 0.5%, 1% and 5%, diclofenac 2.75%, ingenol mebutate 0.05% and 0.015%, and chemical peels [46]. All these treatment modalities often fail to remove the tumor

completely and are associated with a high rate o recurrence. All cSCCs diagnosed in our clinic were surgically excised. Clear histologic margins were achieved in 87 (80.5%) cases. Re-excision was performed in cases with positive margins. Patients were referred to oncologists and radiotherapy specialists for postoperative adjuvant radiotherapy when indicated according to current best practice guidelines [46].

In summary, patients in our setting often present with large and deeply invasive cSCCs which pose therapeutic difficulties and are associated with higher local recurrence rates and greater metastatic potential and hence with higher economic costs. This is especially relevant in a low resources country like Romania. These findings correlate with earlier reports of more advanced skin tumors in Eastern European countries [47, 48]. In the same time, although cSCCs are more common in the elderly, they are becoming increasingly frequent in younger individuals, especially due to chronic immunosupression.

Conclusions

This retrospective study highlighted the severity of the NMSC problem in the Romanian population. As NMSC incidence is expected to increase continuously, fueled by population aging, persistence of risk behaviors and increasing iatrogenic immunosupression, this public health problem will likely continue to grow.

Therefore, our work emphasizes the urgent need for national skin cancer screening programs and educational campaigns on the risk, prevention, and early detection of skin cancers, the implementation of efficient strategies for the early diagnosis and treatment of these tumors and the improvement of their registration and epidemiological surveillance in order to decrease the medical, social and economic burden of cutaneous malignancies in Romania.

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Conflict of interest
NONE DECLARED

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