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ORIGINAL PAPERS

# Skin Cancers of the Head and Neck Region: the Real World Epidemiological and Therapeutic Data from the Cancer Registry of Dolj County

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## Abstract

The majority of skin cancers of the head and neck are represented by basal cell carcinoma (BCC) and cutaneous squamosal cell carcinoma (CSCC), both non-melanoma skin cancers. Identified in the early stages, the cure rate is considered high. Sun protection and early identification of suspicious lesions are the optimal strategies for these cancers to be associated with higher response rates and favorable cosmetic results. Even if the incidence is lower, 10% to 25% of melanomas could also be identified in the head and neck region. For advanced stages or for cases ineligible for optimal surgical treatment, the multimodal approach including adjuvant radiotherapy, chemotherapy, biological therapy or immunotherapy must be decided in a multidisciplinary team.

We set out to retrospectively evaluate the data of patients with skin tumors in the head and neck region included in the cancer registry of Dolj county between January 2000 and December 2019. Seventy-three patients were subsequently identified who met the inclusion criteria.

The median age of the patients was 73 years (46 to 98). Forty-six cases of these were BCC, 15 CSCC cases, 1 adenoid cystic carcinoma case, 1 malignant melanoma case and one case without histopathological confirmation. The ratio between BCC and CSCC in our study is 3:1, in concordance with the ratio identified in the literature. The vast majority of cases come from the urban environment, surgery being the main treatment, especially for the early stages. Adjuvant radiotherapy was administered both in cases of BCC and epidermoid carcinoma. Adjuvant poly-chemotherapy, interferon therapy and re-irradiation have also been used.

Considering the main risk factor, exposure to the sun, it is possible that the predominance of cases from cities is caused by underreporting of these types of cancer in rural communities where the main occupation is agriculture, associated with sun exposure, but also by a lower addressability or non-compliance with the inclusion in the oncological monitoring programs. The current existence of some modern oncological therapies, including immunotherapy for CSS and malignant melanoma, justifies a better monitoring and inclusion of these cases in multidisciplinary evaluation. Superficial radiotherapy, which has now become less accessible in our country, due to the implementation of radiological safety rules and the conversion of equipment from the former Soviet Union cobalt and superficial X-ray radiotherapy device to modern liniac accelerators focused on modern techniques radiotherapy is necessary to reduce the risk of recurrence in the case of resection with inadequate margins of non-melanoma skin tumors.

**Keywords:** head and neck, BCC, CSCC, basal cell carcinoma, scuamos cell carcinoma, malignant melanoma, chemotherapy, superficial radiotherapy, immunotherapy, sun exposure.

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## Rezumat

Majoritatea cancerelor de piele ale capului și gâtului sunt reprezentate de carcinomul bazocelular (BCC) și carcinomul scuamocelular (CSCC), ambele cancere de piele non-melanom. Identificate în stadiile incipiente, rata de vindecare este considerată ridicată. Protecția solară și detectarea precoce a leziunilor suspecte sunt strategiile optime pentru ca aceste tipuri de cancer să fie asociate cu rate de răspuns terapeutic mai mari și rezultate cosmetice favorabile. Chiar dacă incidența este mai mică, 10% până la 25% din melanoamele maligne pot fi identificate și în regiunea capului și gâtului. Pentru stadiile avansate sau pentru cazurile neeligibile pentru tratamentul chirurgical optim, abordarea multimodală care include radioterapia adjuvantă, chimioterapia, terapia biologică sau imunoterapie trebuie decisă într-o echipă multidisciplinară.

Ne-am propus să evaluăm retrospectiv datele obținute de la pacienți cu tumori cutanate în regiunea capului și gâtului incluși în registrul de cancer al județului Dolj în perioada ianuarie 2000 – decembrie 2019. Ulterior au fost identificați 73 de pacienți care au îndeplinit criteriile de includere.

Vârsta medie a pacienților incluși în studiu a fost 73 de ani (între 46 și 98ani). Dintre acestea, 46 cazuri au fost BCC, 15 cazuri CSCC, 1 caz carcinom adenoid chistic, 1 caz melanom malign și un caz a fost declarant caz oncologic fără confirmare histopatologică. Raportul dintre BCC și CSCC în studiul nostru este de 3:1, în concordanță cu raportul identificat în literatură. Marea majoritate a cazurilor provin din mediul urban, chirurgia fiind principalul tratament, mai ales pentru stadiile incipiente. S-a administrat radioterapie adjuvantă atât în cazurile de BCC, cât și în carcinom epidermoid. De asemenea, au fost utilizate polichimioterapia adjuvantă, terapia cu interferon și reiradierea.

Având în vedere principalul factor de risc, expunerea la soare, este posibil ca predominanța cazurilor în mediul urban să fie cauzată de subraportarea acestor tipuri de cancer în comunitățile rurale unde ocupația principală este agricultura, asociată cu expunerea la soare, dar și de o mai mică adresabilitate sau nerespectarea recomandărilor de dispensarizare oncologică. Existența actuală a unor terapii oncologice moderne, inclusiv imunoterapia pentru CSS și melanomul malign, justifică o mai bună monitorizare și includere a acestor cazuri în evaluarea multidisciplinară. Radioterapia superficială, devenită acum mai puțin accesibilă în țara noastră, datorită implementării regulilor de siguranță radiologică și datorită înlocuirii echipamentelor din fosta Uniune Sovietică (aparate de cobaltoterapie și unități de radioterapie superficială cu raze X) cu acceleratoare liniare moderne axate pe tehnici moderne) este necesară pentru a reduce riscul de recidivă în cazul rezecției cu margini inadecvate ale tumorilor cutanate non-melanomice.

**Rezultate:** cancerele capului si gâtului, BCC, CSCC, carcinom bazocelular, carcinom scuamocelular, melanom malign, chimioterapie, radioterapie superficială, imunoterapie, expunere la soare.

## INTRODUCTION

Since the 2000s, Hochman and Lang have noted that the incidence of skin cancers is increasing at a higher rate than other types of cancer, mentioning the need for immediate investigation of a suspicious skin lesion even by the primary care physician. From that moment, the role of the multidisciplinary approach in the management of these cancers is it is mentioned and highlighted. Basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (CSCC), but also malignant melanoma can be identified in the head and neck region and sometimes the prognosis is more severe than in other anatomical regions of the body. Currently, the horizons opened up by molecular target therapies and immunotherapy, but also the classic treatments by radiotherapy and topical or systemic chemotherapy add an extra therapeutical value to surgery, the basic treatment especially in the early stages. Modern oncological treatments also offer to recurrent and metastatic disease the opportunity to be transformed from disease with a severe prognosis in a chronic disease with the potential of a long-term evolution. In this context, a periodic monitoring of these cases in the oncology departments and a multimodal approach becomes a necessity, the treatment guidelines in dermato-oncology being a method to standardize the approach of these cases[1-4].

## MATERIALS AND METHODS

The study included patients with skin tumors in the head and neck region included in the cancer registry of Dolj county between January 2000 and December 2019. The inclusion criteria covered all types of malignant skin tumors in the head and neck region. Patients with synchronous or metachronous tumors were not excluded. Patients with skin metastases from primary scuamos tumors originating in the head and neck mucosa were excluded. Patients without histopathological confirmation were accepted only in cases with a limitation or risks associated with performing a biopsy.

## RESULTS

Seventy-three patients who met the inclusion criteria were identified. The median age of the patients was 73 years (46 to 98). 46 cases of these were BCC, 15 cases epidermoid carcinoma, 1 case adenoid cystic carcinoma, 1 case malignant melanoma and one case without histopathological confirmation. Only 1 case out of the 73 included in the study comes from the countryside, 72 of the cases live in the urban area. It should be mentioned that the cases of adenocarcinoma and adenoid cystic carcinoma were synchronous with BCC in the head and neck region. 19 cases were early cancers staged TNM as T1N0M0, one case was staged T2N0M0, one case T3N0M0 and one case was included in the T4 category without being able to specify the nodal extension and the status of distant metastases. Most of the cases located in the left nasal wing (10 cases), nasal pyramid (8 cases), frontal region (8 cases), left temporal region (4 cases), left ear (4 cases), right auricular region, left auricular region and left temporal region, 3 cases each in each of these locations and in other locations including left nasogenian sulcus, right nasogenian sulcus, left zygomatic, right zygomatic, scalp two cases were identified in each mentioned region. For other anatomical locations mentioned in table 1, one case being identified in each situation.

**Table 1.** Characteristics of patients diagnosed with skin cancers in the head and neck region included in the cancer registry of Dolj county between January 2000 and December 2019.

| **Patients' characteristics** | |
|---|---|
| | Number (percent) |
| **Age** | |
| Median | 73 |
| Range | 46-98 |
| **Geographic area** | |
| Urban | 72 (98.6) |
| Rural | 1 (1.4) |
| **Sex** | |
| Male | 42 (57.5) |
| Female | 31 (42.5) |
| **Histology** | |
| Basal cell carcinoma | 46 (63) |
| Epidermoid carcinoma | 15 (20.6) |
| Adenoid cystic carcinoma | 1 (1.4) |
| Adenocarcinoma | 1 (1.4) |
| Malignant melanoma | 1 (1.4) |
| Not reported | 1 (1.4) |
| **Topography** | |

| | |
|---|---|
| Left nasal wing | 10 (13.6) |
| Nasal pyramid | 8 (11) |
| Right ear | 4 (5.5) |
| Left ear | 3 (4) |
| Right auricular region | 3 (4) |
| Left auricular region | 3 (4) |
| Left nasogenian sulcus | 2 (2.7) |
| Right nasogenian sulcus | 2 (2.7) |
| Left temporal region | 4 (5.5) |
| Right temporal region | 3 (4) |
| Frontal region | 8 (11) |
| Left zygomatic | 2 (2.7) |
| Right zygomatic | 2 (2.7) |
| Left genian region | 3 (4) |
| Right genian region | 1 (1.4) |
| Left eyelash | 1 (1.4) |
| Right parietal region | 1 (1.4) |
| Left submandibular region | 1 (1.4) |
| Scalp (unspecified other region) | 2 (2.7) |
| Mental region | 1 (1.4) |
| Interbrow area | 1 (1.4) |
| Left eye internal angle | 1 (1.4) |

The high percentage of non-advanced TNM stages justifies the extensive use of surgery. Surgery was the only treatment modality used in most cases, for curative purposes, especially in early TNM stages. In 8 cases, surgery was followed by adjuvant radiotherapy, 4 of these cases being BCC. The ratio between BCC and SCC in our study is 3:1. For one case, salvage surgery is mentioned after the disease progression 3 months after the curative surgery. The association between an adenoid cystic carcinoma and a BCC of ear should be mentioned in this case without a clear specification of the recurrent tumor histology. A case of squamous cell carcinoma benefited from re-irradiation of the tumor recurrence at 6 months, the re-irradiation dose being 30Gy in 15 daily fractions, the cumulative radiation dose being in that case 80Gy delivered in a standard fractionation regimen. Chemotherapy was administered with adjuvant role in 1 case and for palliative purpose in 2 cases. Carboplatin and 5-fluorouracil were delivered in an association regimen with adjuvant radiotherapy in a case of nodal recurrence after primary surgery treatment for an epidermoid carcinoma. Dacarbazine, Vincristine and Cispatin were administered in 7 cycles in the case of malignant melanoma with unfavorable prognosis (Clark Level IV). Interferon (IFN) was also administered in this case. The local and systemic treatments used in the study group were summarized in table 2.

**Table 2.** Treatment management for patients diagnosed with skin cancers in the head and neck region included in the cancer registry of Dolj county between January 2000 and December 2019.

| Cases management | |
|---|---|
| Aim of treatment | |
| Curative/not specified | 69 (9.5) |
| Palliative/salvage | 4 (5.5) |
| **Surgery** | |
| Curative/not specified | 69 (94.5) |
| Salvage | 1 (1.4) |
| Cytoreductive | 2 (2.7) |
| **Radiotherapy** | |
| Adjuvant | 8 (11) |
| Reirradiation | 1 (1.4) |
| **Chemotherapy** | |
| Adjuvant | 1 (1.4) |
| Palliative | 2 (2.7) |

## DISCUSSION

With a ratio of approximately ~3 to 4:1 BCC and CSCC are considered the most frequently encountered non-melanoma skin cancers of the head and neck region. The cumulative amount of ultraviolet radiation in the wavelength range 290 to 320 nm is considered the main risk factor. Exposure to arsenic, fair skin, but also genetic syndromes such as xeroderma pigmentosum and nevoid basal cell carcinoma syndrome are considered risk factors[5-7].

Only 10% to 25% of malignant melanomas originate in the head and neck region. They are most frequently located on the face, scalp, neck and ear. It is considered that melanoma in the head and neck region has a worse prognosis, especially the one located in the scalp and ear, followed by the cheek and neck[8].

Tumor size is a prognostic criterion for head and neck skin tumors. Derebaşınlıoğlu identifies a larger

average size for CSCC than for BCC, the location on the nose being the most common for BCC, CSCC being more frequently found in the oral region. CSCC was located less often than BCC in the orbital region. Malignant melanoma of the head and neck seems to be more frequently identified on the forehead and scalp[9].

Mohs micrographic surgery (MMS), surgical excision, cryoablation, radiotherapy, topical application of 5-flurouracil, but also systemic chemotherapy is used in the treatment of BCC. Vismodegib, a selective inhibitor of the Hedgehog pathway, is approved in the United States of America (USA) for cases of metastatic BCC, relapsed after surgery, inoperable or ineligible for radiotherapy[10,11].

Superficial radiotherapy became accessible to dermatologists in the treatment of BCC and SCC using portable devices, but with the widespread implementation of MMS, the role of radiotherapy decreased significantly. Even if a fractionation scheme with a total dose of 45Gy in daily fractions of 3Gy, 3 weeks, alternative fractionation schemes that propose 2 or 3 fractions per week are agreed. A dose of 35Gy in 7 fractions of 5Gy each fraction is proposed in the case of elderly patients, the regimen being a hypo-fractionated one, but also a standard fractionated irradiation up to the total dose of 60Gy in 30 daily fractions is considered an option for young patients with large lesions[12,13]. Re-irradiation of head and neck skin cancers is considered feasible and with the most favorable results if the Biological Effective Dose (BED) delivered in an initial radiotherapy was less than 55Gy at 5mm in the skin depth and cumulative BED was less than 110Gy[14].

However, we cannot ignore the fact that radiotherapy could increase the risk of radiation-induced cancer in different organs included in the irradiation field, even in areas not exposed to the sun (for example, lung cancer induced by breast irradiation)[14-15].

The use of IFN in the treatment of malignant melanoma had a historical role, being administered as an adjuvant in high-risk cases independently or in association with irradiation. Currently, malignant melanoma benefits from modern therapies including BRAF pathway inhibitors such as Vemurafenib, Dabrafenib and Encorafenib in association with MEK inhibitors such as Trametinib and Cobimetinib. This class of therapies are active in BRAF- and NRAS-mutant melanoma. Immunotherapy including programmed death-ligand 1 (PD-L1), programmed cell death protein 1 (PD-1) and anti-Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) therapies are revolutionary therapies in melanoma therapy even in metastatic stages, requiring a multimodal approach to the disease[15-18].

Fluoropyrimidines including 5-Fluorouracil, but also Cisplatin, Bleomycin, Doxorubicin are chemotherapeutic agents used in the treatment of CSCC. Target molecular therapies including Erlotinib, Gefitinib, Cetuximab are proposed in phase II studies which evaluates the therapeutical options for advanced CSCC. The study by Wollina et al. proposes the use of a fluoropyrimidine analogue (Capecitabine) and subcutaneous interferon alpha in the treatment of CSCC, the treatment being considered feasible. Retinoids including 13-cis-retinoic acid (13-CRA) in combination with Cisplatin or IFN-alpha have also been included in clinical trials that included CSCC[20-23].

Cemiplimab (Libtayo®), an antibody that modulates the anticancer programmed cell death protein-1 (PD-1) blockade response, was approved in the USA and Europe for patients with locally advanced or metastatic CSCC who do not benefit from curative surgery or radiotherapy. An intravenous regimen of Cemiplimab 3 mg/kg once every 2 weeks or 350 mg once every 3 weeks was validated by the phase II EMPOWER-CSCC 1 trial and demonstrated a durable and clinically significant response with a favorable safety profile. The low rates of adverse effects including a 7% treatment discontinuation and a 3% toxic death also justify the use of this modern immunotherapeutic agent[24-26].

## CONCLUSION

Considering the main risk factor, exposure to the sun, it is possible that the predominance of cases from cities is caused by underreporting of these types of cancer in rural communities where the main occupation is agriculture, associated with sun exposure, but also by a lower addressability or non-compliance with the inclusion in the oncological monitoring programs. The current existence of some modern oncological therapies, including immunotherapy for CSS and malignant melanoma, justifies a better monitoring and inclusion of these cases in multidisciplinary evaluation. Superficial radiotherapy, which has now become less accessible in our country, due to the implementation of radiological safety rules and the conversion of equipment from the former Soviet Union cobalt and superficial X-ray radiotherapy device to modern liniac accelerators focused on modern techniques radiotherapy is necessary to reduce the risk of recurrence in the case of resection with inadequate margins of non-melanoma skin tumors.

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