2

Advanced Squamous Cell Carcinoma of the Skin

Vinicius Vazquez, Sergio Serrano and Renato Capuzzo
Barretos Cancer Hospital
Brazil

1. Introduction

The squamous cell carcinoma of the skin (SCCS) is one of the most common cancers around the world.(Ries, Melbert et al. 2007; 2008) It affects mostly the sun exposed areas of people with fair skin. The majority of cases are easily treatable by simple excision or radiotherapy with a good chance of achieving cure. Despite this, the aging population process associated to chronic ultraviolet radiation (U.V.) exposition is raising the SCCS incidence and consequently the number of patients with advanced tumors.(Staples, Elwood et al. 2006) This is a devastating presentation of the disease, where the lack of information occurs and even the professionals in the field are a few. Local disease progression, local and regional recurrence, lymph node or distant metastases are the focus of this review chapter. The characteristics of the tumors arising in the trunk and extremities are different from those in the head and neck, and they are described and discussed separately.

2. Advanced squamous cell carcinoma of the skin of the trunk and extremities

2.1 Definition

We consider as patients with advanced squamous cell carcinoma of the skin of the trunk and extremities, those with T3/T4 (tumor invading deep structures/axial esqueleton) or N1/2/3 (regional lymph node metastasis) tumors according the 7th UICC TNM classification(Sobin and Compton). Tumors arising from genital or anus are not considered.

2.2 Epidemiology, clinical presentation, diagnostic methods and defining a risk population

There are some clinical conditions associated to locally advanced disease. The patients are typically old, with risk conditions to skin carcinomas (chronic U.V. exposition and fair skin) and may have other local disease as burn scars, chronic skin ulcer and systemic pathologies related to immune system suppression (organ transplant receptors, hematopoietic disorders)(Cherpelis, Marcusen et al. 2002; Trakatelli, Ulrich et al. 2007). Low economic and educational status or difficult access to the health system may also play a role to the presentation of advanced cases, but not confirmed in studies.

The usual presentation is a patient with a long story of a "chronic ulcer" with many previous local treatments. Some present with pathological bone fractures or lymph node metastasis. (de Lima Vazquez, Sachetto et al. 2008)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor ≤ 2 cm in greatest dimension with 2 high-risk features*
T2 Tumor > 2 cm in greatest dimension with or without one additional high-risk feature,* or any size with ≥ 2 high-risk features*
T3 Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4 Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

*High-risk features include depth (> 2-mm thickness; Clark level ≥ IV); perineural invasion; location (primary site ear; primary site nonglabrous lip); and differentiation (poorly differentiated or undifferentiated).

Table 1. Definition of cutaneous squamous cell carcinoma tumor (T) staging system in 7th edition of American Joint Committee on Cancer

NX. Regional lymph nodes cannot be assessed
N0. No regional lymph node metastasis
N1. Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2. Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a. Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b. Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c. Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3. Metastasis in a lymph node more than 6 cm in greatest dimension

Table 2. Definition of cutaneous squamous cell carcinoma Nodes (N) staging system in 7th edition of American Joint Committee on Cancer

2.3 Factors related to prognosis

2.3.1 Clinical

The clinical factors classically related to prognosis are the tumor size and regional lymph node status (TNM stage). Many studies have confirmed both tumor size our local infiltration and presence and number of lymph node metastasis as the main prognosticator for advanced disease. The incidence of lymph node metastasis varys according the population studied from 4.5 to 17%(North, Spellman et al. 1997; Cherpelis, Marcusen et al. 2002; Mullen, Feng et al. 2006). Other factors have being pointed but the association is uncertain as

anatomic location and previous chronic disease locally on the skin (i.e. Marjolin ulcer). (Collins, Nickoonahand et al. 2004)

2.3.2 Pathological

A detailed histopathological descriptive classification considering all subtypes of squamous cell carcinoma of the skin was proposed by Cassarino (Cassarino, Derienzo et al. 2006), categorized tumors as low, intermediated and high risk, but it was not confirmed by well designed studies. The tumor length in millimeters (Breslow measurement) is associated with prognosis in some studies, but not confirmed(Breuninger, Black et al. 1990). The tumor grade, proposed by Broders and simplified to grade I, II and III (I well differentiated and III undifferentiated) is other controversial factor related to the prognosis, as well as the mitotic index and the Intratumoral lymphocytic infiltrate (ILI). In our retrospective study, the tumor grade was related to prognosis and the ILI was related to the lymph node metastasis.(de Lima Vazquez , Scapulatempo et al. 2011)

2.3.3 Molecular

With the advent of the molecular diagnosis, some authors looked at the relation of molecular changes and disease progression. Knowledge of the role of molecular markers in tumor progression and metastasis is limited. The tyrosine kinases Human Epidermal Receptor (HER) family (EGFR - Epidermal Growth Factor Receptor, HER-2, HER-3 and HER-4) are transmembrane glycoproteins related to cell proliferation, differentiation and apoptosis. Altered expression of the HER family is associated with several epithelial tumors such as breast carcinoma and esophageal squamous cell carcinoma. Small studies have also shown altered HER expression in localized squamous cell carcinoma when compared to normal skin. HER 2 expression in advanced CSCC of the trunk and extremities is not well studied and may be related to prognosis allowing the use of target therapies that block the HER pathway(Krahn, Leiter et al. 2001). E-cadherin is a transmembrane glycoprotein and it is a mediator of calcium-dependent cell-cell adhesion in normal cells. Reduced cell-cell adhesiveness is considered important in both early and late carcinogenis. High E-cadherin expression in cell cytoplasm and low expression in the cell membrane is associated with tumor aggressiveness in different cancers.(Koseki, Aoki et al. 1999) Podoplanin is a membrane protein found on lymphatic vessel endothelium. Its function is poorly understood although it may govern endothelial motility and its absence in animal studies is associated with lymphedema and malformation of lymphatic vessels.(Schacht, Ramirez et al. 2003)

In our study with 55 patients with advanced cutaneous squamous cell carcinoma (CSCC) of the trunk and extremities, Primary tumor positivity was 25.5% for EGFR, 87.3% for HER-3 and 48.1% for HER-4. Metastases were positive for EGFR in 41.7%, for HER-3 in 83.3% and HER-4 in 43.5%. HER-2 was negative in all samples. Membrane E-cadherin and cytoplasmic E-cadherin were positive in 47.3% and 30.2% of primary tumors and 45.5%and 27.3% of metastases respectively. Podoplanin was positive in 41.8% of primary tumors and 41.7% of metastases. The hiperexpression of Podoplanin in the primary tumor was related to lower survival rates. The HER family and the E-cadherin were not related to prognosis. The HER-4 hiperexpression in the lymph node metastasis was associated to lower survival and showed that the HER family may play a role in the disease progression.(de Lima Vazquez , Scapulatempo et al. 2011)

2.4 The treatment modalities

2.4.1 Surgery

Surgery is the classic treatment for skin cancers and for advanced tumors it is still the most effective treatment. Unfortunately, in advanced cases amputations and extensive resections and dissections (i.e. extensive lymph node dissection with skin resection) are usual and have a high morbidity and sometimes mortality rate. Complex reconstructions with surgical flaps (figure 1) and other advanced techniques may be applied but local and clinical suboptimal conditions contraindicate them frequently. Local control is the goal, and the main objectives are to obtain clear margins and in case of lymph node metastasis, to clear completely the lymphatic chain (i.e. axilla or groin). Due the tumor characteristics of local and regional dissemination, aggressive approaches are indicated if clinical conditions are satisfactory. Recurrence rate vary in the literature achieving 50% {de Lima Vazquez, 2008}.

2.4.2 Radiation therapy

When surgery is not an option for advanced tumours, i.e – patient refusal, clinical adverse conditions - radiation may be applied, but with limited results. The main role of the radiation therapy is when incomplete resection occurs, and in the adjuvant setting, when tumour margins are not sufficient or after resection of bulky lymph node metastasis. Indications are personalised since there is no standard care with this method.

3. Head and neck tumors

3.1 Introduction

Squamous cell carcinoma accounts for 20% of non-melanoma cancers of the head and neck (Alam and Ratner 2001). In most cases, these tumors are cured with surgical treatment and / or radiotherapy, but a small portion of these patients had unfavorable outcomes with high rates of metastases and regional recurrence after treatment, which is associated with 20% of deaths from skin cancer (Alam and Ratner 2001). This more aggressive presentation is found in patients referred for high risk, which the literature has discussed the factors involved in this group (Veness 2007). In head and neck surgery, it is particularly associated with the presence of regional metastasis and invasiveness of the primary tumor. The latest edition of the UICC AJCC, published in 2010 (Edge and Compton 2010), showed major changes in the staging of nonmelanoma skin cancers, remarking lymph node staging aligned with the other sites of head and neck and including new factors for classification of the primary tumor.

This part of the chapter will present some specific features of the therapy of skin cancers of the head and neck that often overlap with those found in other regions of the body, but in advanced tumors may limit surgical treatment and carry a poor prognosis for these tumors.

3.2 Advanced tumors: Characteristics of primary tumor

The following factors define a high risk of metastasis and recurrence in skin cancers (Edge and Compton 2010):

Size of the primary tumor greater than 2 cm
Breslow tumor thickness greater than 2 mm, Clark level IV or greater

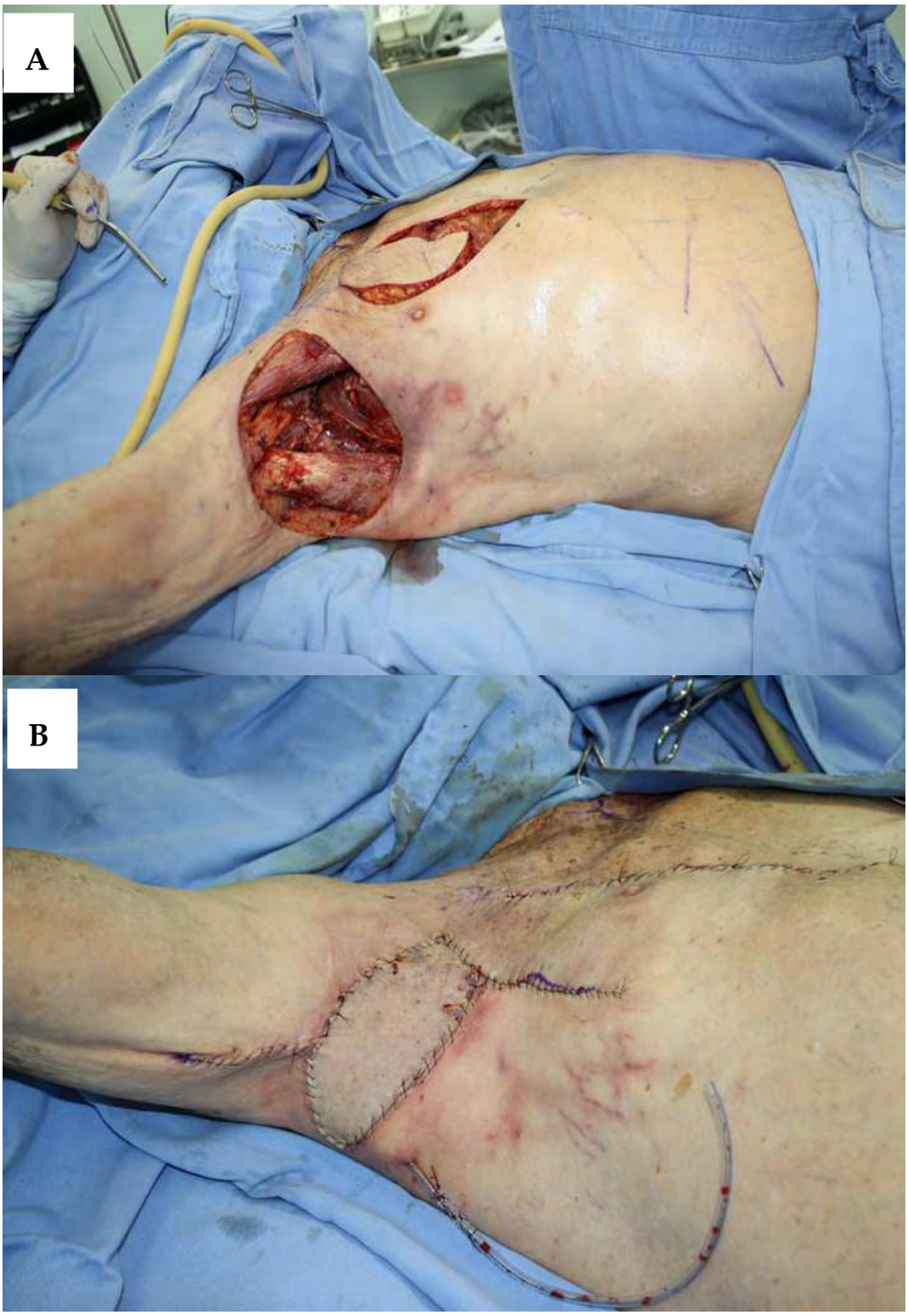


Fig. 1. A - Axilar lymphadenectomy with skin resection and miocutaneous flap prepared for the reconstruction. Fig. 1. B - Final aspect of the reconstruction

Perineural invasion (PNI)
Poor differentiation
Anatomic sites that which carry high risk for recurrence or metastasis
Immunocompromised state of the patient

These changes are based on data-derived, evidence-based medicine and some changed in the last edition of the AJCC and will be detailed below.

Tumor size: this parameter does not present a linear correlation of increased risk of metastasis and recurrence, according to tumor growth, however a limit of 2 cm is shown in several articles as a risk factor for locoregional recurrence. In the sixth edition of the AJCC edition, the limit of 5 cm separated the tumors in T2 and T3, however this limit did not have enough evidence to be sustained and was abolished in the seventh edition, being replaced by parameters more related to the invasiveness than the diameter of tumor (Farasat, Yu et al. 2011).

Tumor depth and PNI: Even the tumor thickness and depth of invasion are important risk factors to SCCHN metastasis and local recurrence (Farasat, Yu et al. 2011). So, in the last edition of AJCC, Breslow depth and Clark level were incorporated. These changes directly affected head and neck tumors that invade the facial bones or skull base, being classified as advanced tumors, with higher risk of metastases and local recurrence (Edge and Compton 2010).

Another factor was added is the perineural invasion of nerves at the base of the skull, which often restricts a craniofacial resection with clear margins and is associated with a worse prognosis. Although based on retrospective studies, PNI showed a higher association with tumors in the face, lower degree of differentiation, tumors larger than 2 cm and recurrent tumors (Leibovitch, Huilgol et al. 2005). There is evidence of an increased incidence of cervical lymphadenopathy and distant metastasis, along with significantly reduced survival in patients with tumors that showed PNI(Farasat, Yu et al. 2011).

A careful radiological preoperative assessment may reveal tumor invasion of branches of the trigeminal or facial nerve. The use of CT and MRI in invasive tumors of the skull base shows high accuracy in detecting perineural invasions, when correlated with intraoperative and pathological findings (Gandhi, Panizza et al. 2010).

Immunosuppression: Although not a specific factor that affects tumor staging, AJCC, in his last edition, highlights this as a risk factor for increased aggressiveness of skin tumors. Organ transplant recipients are 65 times greater risk of developing squamous cell carcinoma of the skin than the general population and have much more aggressive evolution.

Location of primary tumor: some anatomical sites are more associated with worse outcomes in head and neck. This can be seen in sites that drain to the parotid gland like external ear, temple, forehead and anterior scalp. The lower lip also has an increased risk of nodal metastasis.(Veness 2007)

Some series showed a poor outcome of cutaneous squamous cell carcinoma of external ear (Brantsch, Meisner et al. 2008; Turner, Morgan et al. 2009). Faustina et al found 24,3% of regional metastasis in 111 patients with squamous cell carcinoma of the eyelid and periocular region, advising close observation of parotid after the treatment of this site(Faustina, Diba et al. 2004)

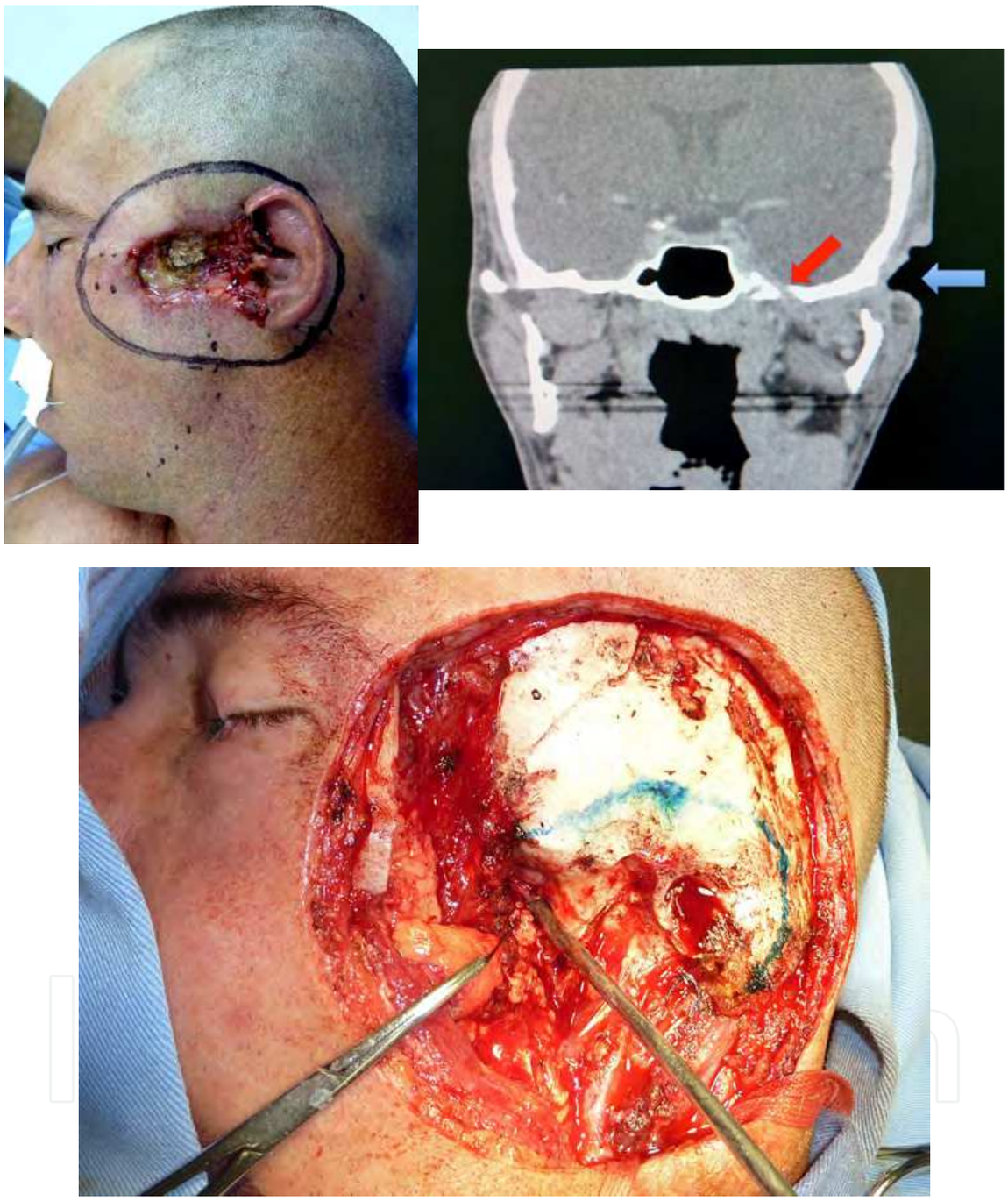


Fig. 2. A (On the left): Clinical aspect of the patient with invasive skin tumor and bone exposure of the zigomatic arc with installed facial nerve paralysis. Fig. 2. B (right): The red arrow reveals perineural invasion of V3 and the blue arrow shows the skin tumor of temporal region. Fig. 2. C: Surgical aspect after removal of skin tumor, with sacrifice of the facial nerve, zigomatic arc, ascending mandible and parotid gland. The blue line delimits the temporal bone resection by the neurosurgical team and the instruments pointing V3 at skull base, with perineural invasion

Histopathological differentiation grade: tumors less differentiated are associated with a more aggressive outcome. This item also has changed in the last edition of the AJCC, becoming one of the high risk factors, opposed to being a separate classification as in the sixth edition. (Farasat, Yu et al. 2011)

Lymph node metastases

SCCHN that develop nodal metastasis in the parotid gland or the neck is an aggressive disease and show poor outcomes. Some studies these prognosis revealing 5-years overall survival rates from 22 to 36% (Khurana, Mentis et al. 1995; Kraus, Carew et al. 1998).

Untill the sixth edition of AJCC, the nodal staging of squamous carcinoma of skin only separate the presence of nodal metastasis or no. This classification was pointed by several authors as insufficient, what have already indicated the need of a new proposal for lymph nodes staging, including a P stage for parotid metastasis and stratification of nodal disease (O'Brien, McNeil et al. 2002; Ch'ng, Maitra et al. 2006). The seventh edition of AJCC incorporated some changes in nodal classification aligning with the staging of lymph nodes from others sites of head and neck but the P staging has not been implemented, because of the benefit of having subgroups of P and N stage is uncertain, but further research may demonstrate the need of this staging system (Palme, MacKay et al. 2007; Forest, Clark et al. 2010; O'Hara, Ferlito et al. 2010)

In a survey of tertiary treatment centers, about 5% of squamous cell carcinomas present skin present metastasis, usually to regional lymph nodes of the parotid and cervical level II. (2, 5). Sites such as cheek, ear, forehead, temple and lateral scalp are the most implicated in the onset of regional disease, which usually occurs on an average of 13 months of primary treatment, but may occur until 2 to 3 years later (Hong, Kriesel et al. 2005). The rate of regional metastases in head and neck can be between 10 and 20% when clinical and pathological characteristics of high-risk primary tumor are present.

When parotid metastasis with clinical negative neck are present, the risk of occult metastases in the cervical lymph nodes reaches 35-50%, which justifies elective neck dissection in the presence of parotid involvement(O'Hara, Ferlito et al. 2010). The data by Vauterin revealed when positive pathological neck is observed, level II is involved in 79% of cases and external jugular chain lymph nodes are particularly at risk, what should have not be forgot to be included in the neck dissection. (Vauterin, Veness et al. 2006).

Levels IV and V are only involved in massive lymph node disease to the neck, except in situations where the primary is located in the posterior scalp, in which the involvement of this code chain can be isolated. Metastases to the level I is present alone when the primary occurs in the anterior region of the face (O'Hara, Ferlito et al. 2010).

The radiological search of metastases to the parotid and neck should be performed only in patients at high risk, which can use CT, MRI and USG-guided FNA (O'Hara, Ferlito et al. 2010).

The use of sentinel lymph node in squamous cell carcinoma in head and neck is not yet defined and is not routinely used in cancer not melanoma, due to the low risk of nodal metastasis, but has potential for improved survival in patients at high risk (O'Hara, Ferlito et al. 2010). The sentinel lymph node study in the parotid region should be done with caution because it adds a possible morbidity due to the risk of facial nerve injury.

3.3 Treatment

3.3.1 Treatment of primary tumor

The treatment of advanced SCCHN tumors usually involves surgical resection and adjuvant radiotherapy. The goal of surgical treatment is tumor resection with clear margins. Tumors that fail to be cleared surgically often recur despite radiation. In contrast, high-risk SCCHN with clear surgical margins has documented excellent outcomes when compared to those with unreported margin status (local recurrence 5% vs. 8%, nodal metastasis 5% vs. 14%, distant metastases 1% vs. 7%, and disease-specific death 1% vs. 7%).

Skin squamous cell carcinoma with invasion of skull base are treated with craniofacial resections and have worse survival when compared to basal cell carcinomas. (Backous, DeMonte et al. 2005). Backous used as contraindication criteria for this type of resection encasement of the carotid artery or optic chiasm, cavernous sinus invasion or distant metastasis. Factors found to reduce survival are perineural invasion, intracranial extension with invasion of brain parenchyma and impossibility of adjuvant radiotherapy because of previous radiation.

Immunosuppressed patients should receive more aggressive surgical treatment and adjuvant radiotherapy should be strongly considered.

A multisciplinary aproach is recommended for the treatment of SCCHN, with combination of head and neck surgeon and plastic surgery, so that the reconstrution should not carry a limiting resection.

3.3.2 Treatment of regional metastasis

The published evidence suggests that the optimum treatment for metastatic SCCHN should be surgical resection with adjuvant radiotherapy. (O'Hara, Ferlito et al. 2010)

The most common site of metastases in the head and neck is the parotid gland. Usually when performing parotidectomy is associated the dissection of cervical levels I-III in negative neck and a radical neck dissection in positive necks (14, 18). This treatment option can save adjuvant irradiation in the pathologically negative neck restricting the field of radiation only to the parotid field, but another option is the radiation of the clinically negative neck.

In patients undergoing parotidectomy, Ebrahimi recommends selective neck dissection including level I to III for facial primaries, level II and III for anterior scalp and external ear primaries, and levels II to V for posterior scalp and neck primaries(Ebrahimi, Moncrieff et al. 2010). Isolated metastases of level V and primary region of the scalp or posterior subocipital region, a posterior lateral neck dissection (II to V) is recommended. (O'Hara, Ferlito et al. 2010)

Cervical neck node disease without parotid involvement can be seen in 18 to 41% of patients.(Andruchow, Veness et al. 2006; Vauterin, Veness et al. 2006) In this situation, the recommendation is the treatment of the neck with classic or modified radical dissection associated with elective parotidectomy in primaries of anterior regions of scalp and lateral face (Barzilai, Greenberg et al. 2005; Jennings and Schmults 2010).

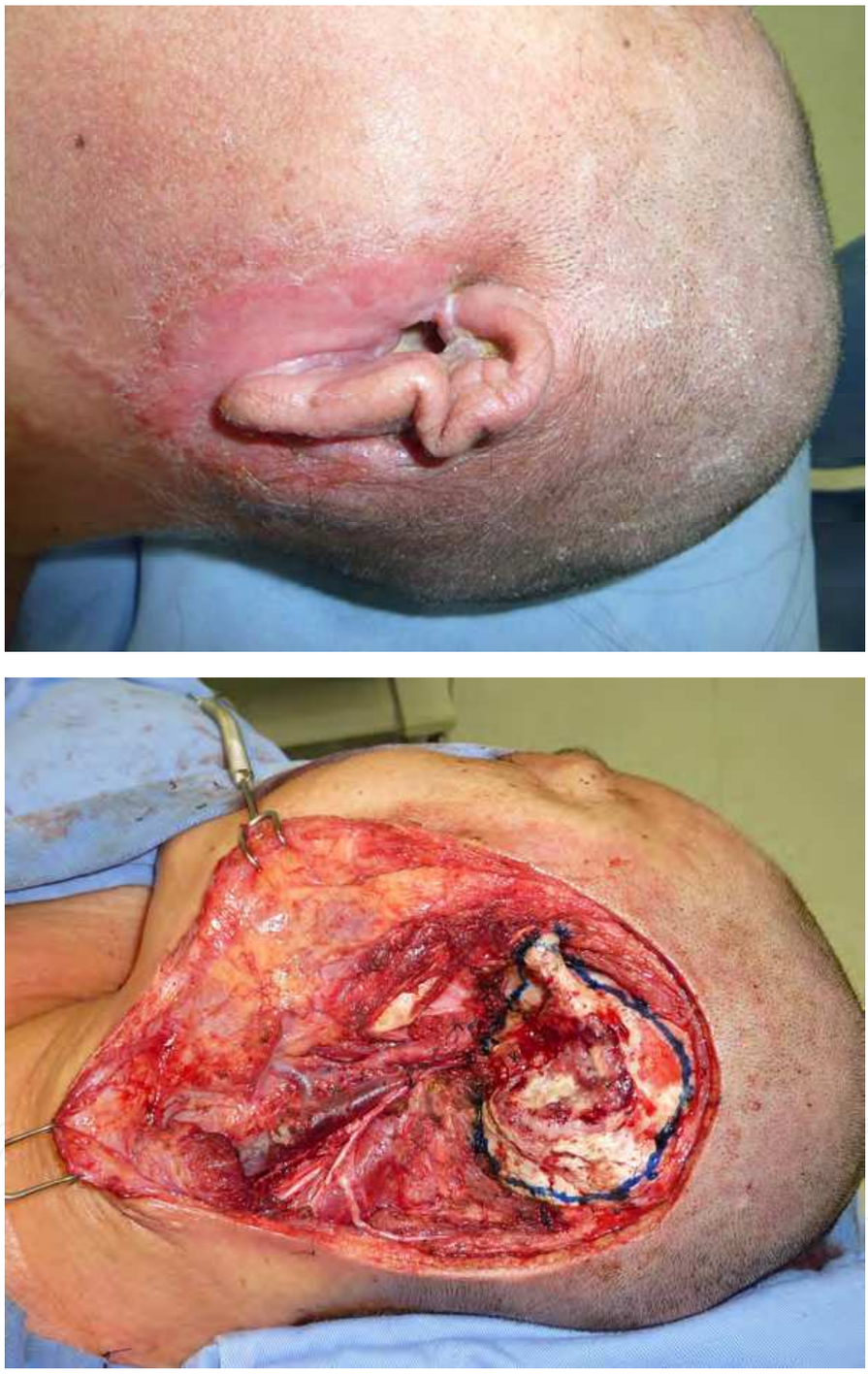


Fig. 3. A: Example of multidisciplinary aproach: recurrent squamous cell carcinoma after local excision and radiation therapy. Facial nerve paralysis and intratemporal perineural nerve spread. Fig. 3. B: Surgical field of total parotidectomy and sacrifice of the facial nerve and ascending portion of mandible and neck dissection of levels I-III with sacrifice of sternocleidomastoid muscle. The blue line delimits the temporal bone resection by the neurosurgical team, with frozen sections of the nerve stump.

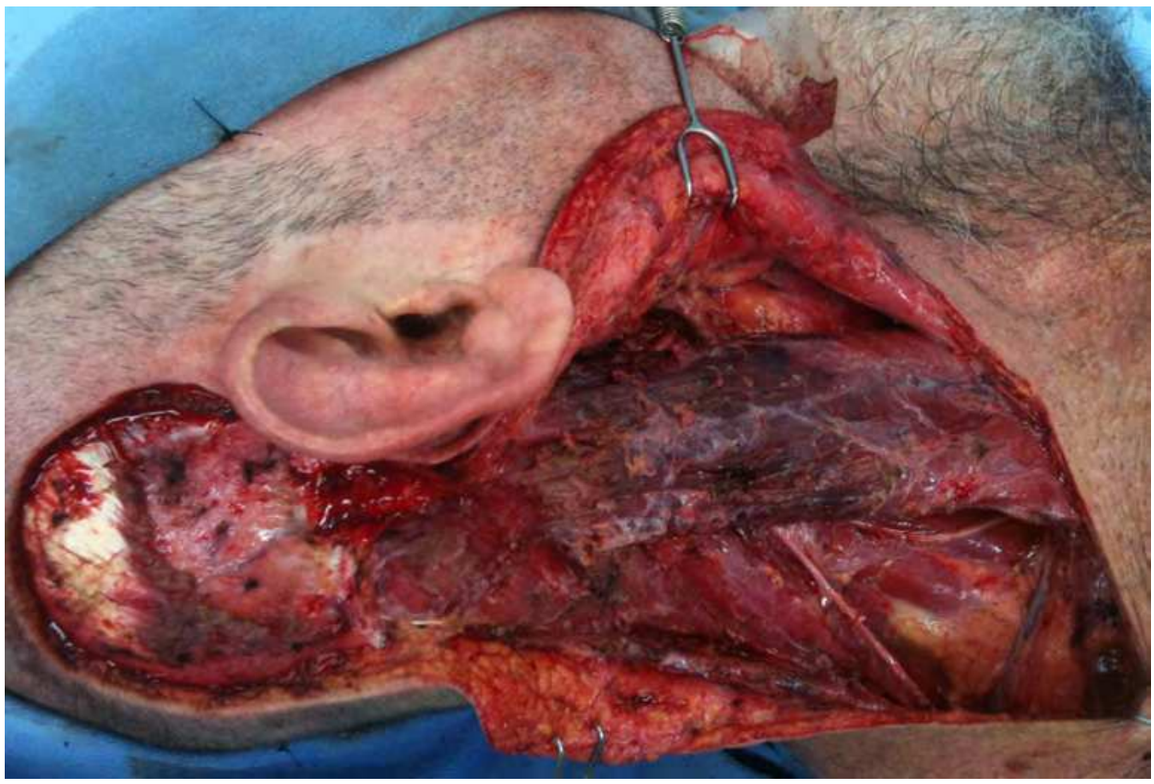


Fig. 4. Surgical treatment aspect of a posterior scalp skin tumor with posterior lateral neck dissection (cervical levels II-V), sparing the spinal acessory nerve

Although some anatomical regions have an increased risk of developing regional metastases, it is difficult to recommend elective neck dissection as a routine base, because of the low rate of nodal spread and high prevalence of these skin cancers. Others risk factors should be added to consider elective regional treatment like immunnocompromised host, poorly diferentiated grade (Veness 2007). Elective parotidectomy for patients without clinical or radiological evidence of metastasis of the neck or parotid is not recommended by most authors (Osborne, Shaw et al. 2008).

Intraparotid metastasis to lymph nodes may be attached to the facial nerve, which is at risk of sacrifice in some situations. All facial nerve not functioning in the preoperative evaluation or completely surrounded by tumor should be sacrificed but it should rarely be done when it has normal function before surgery. According to Iyer, surgical approaches to the parotid metastatic cancers shall, as far as possible, spare the facial nerve with normal function, even if that causes resection with microscopic involved margins and the need for adjuvant radiotherapy. Such strategie do not generate differences in the rates of recurrence and overall survival compared with patients undergoing resection with microscopically free margins. However, this study shows no statistical difference between groups, but shows a tendency to a worse local control and survival, which could have significance with a larger number of cases. In fact, free surgical margins greater than 5 mm are rarely obtained due to the proximity of parotidectomy metastasis with the facial nerve (Iyer, Clark et al. 2009).

Parotidectomy may be associated with resection of skin tumors of the parotid region and the series of Lai reveals perineural invasion of the facial nerve in 6 of the 23. Lai recommends

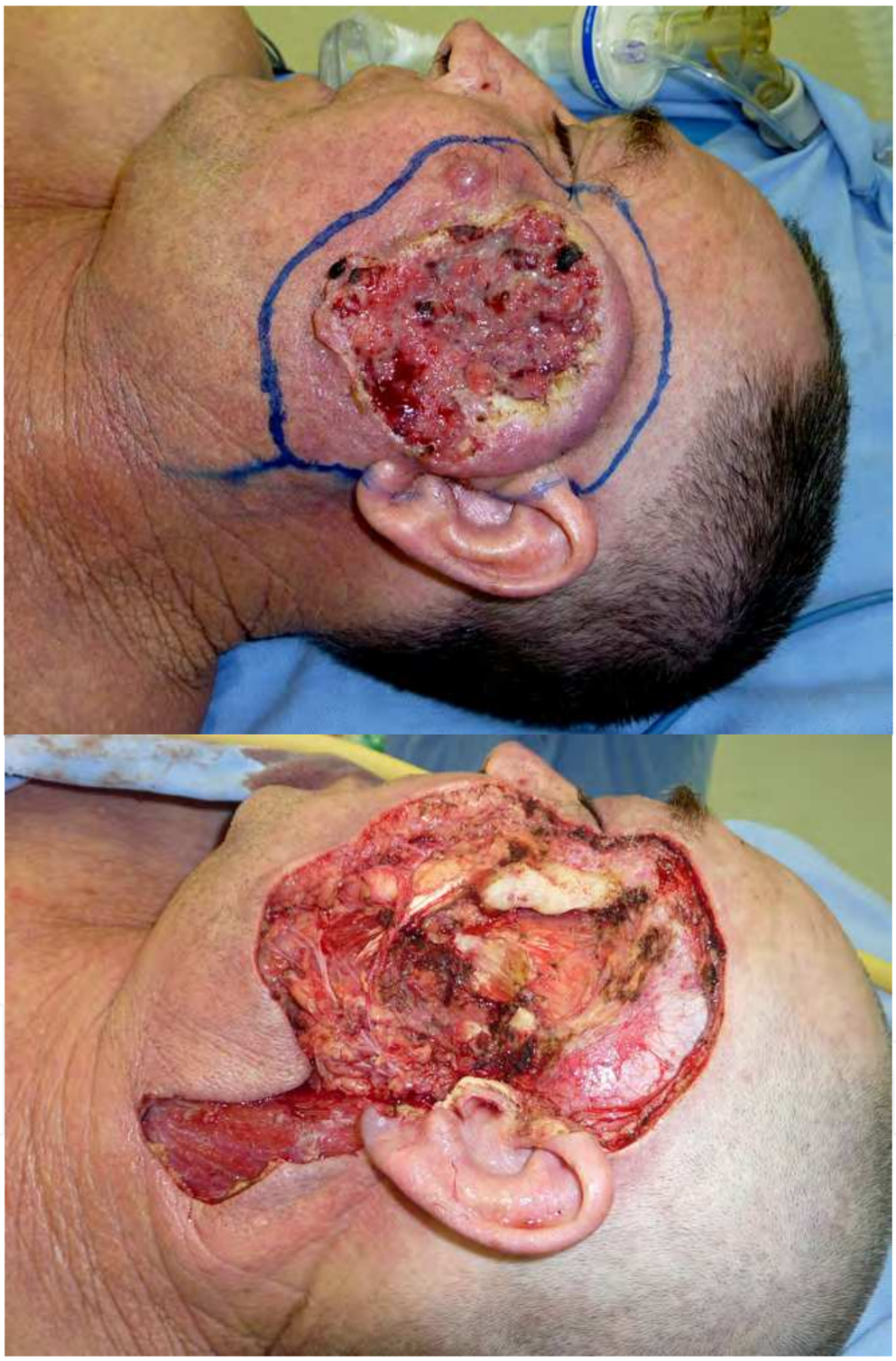


Fig. 5. A: Squamous cell carcinoma of skin of parotid region, with in transit metastasis. Fig. 5. B: Surgical field after ressection including superficial parotidectomy and the zigomatic arc with sacrifice of the superior branch of facial nerve that was involved by the tumor.

parotidectomy depending on the depth of the primary lesion, especially in the preauricular region. Similarly, facial nerve dissection is necessary in superficial parotidectomy for nodal involvement or deep invasion from preauricular primary lesions. As the facial nerve is identified, areas of gross tumor involvement may necessitate partial or total facial nerve resection. When there is sacrifice of the facial nerve, some authors recommend frozen sections of the facial nerve stumps, to ensure free margins before a microsurgical nerve reconstruction (Lai, Weinstein et al. 2002).

3.3.3 Radiotherapy

Primary radiation for SCCHN can be an alternative treatment when the surgucal defect causes challenging reconstructions and should be used in lesions with little invasiveness. Local tumor control in small lesions rivals that of surgical resection, even in recurrent disease. However, as T stage increases, local control decreases when compared to surgical excision.(Mendenhall, Amdur et al. 2009)

The treatment of neck or parotid metastasis, surgery and adjuvant radiotherapy should be done rather than radiation alone(Palme, O'Brien et al. 2003). Multiple studies have noted decreased disease-specific survival in patients treated with RT alone (delCharco, Mendenhall et al. 1998; Veness, Palme et al. 2003)

The use of adjuvant radiation should be strongly considered in incomplete excision or positive margins, perineural invasion, multiple nodal involvement and recurrent tumors. (Veness 2007)

4. Systemic therapy (for all tumors)

4.1 Adjuvant therapy for high risk SCCS

The risk of locoregional recurrence and regional or distant metastasis is the most important factor in determining the treatment for cutaneous SCC. In a large review of studies of SCC of the skin, lip and ear, between 1940 and 1992 it was observed that recurrence rates double from 7.4% to 15.2% for tumors greater than 2 cm in diameter, and that tumors less than 4 mm in depth are at low risk for metastasis compared with tumors deeper than 4 mm (6.7% and 45.7%, respectively). (Rowe, Carroll et al. 1992) Also, 30% of locally recurrent SCCS develop metastases. Long-term prognosis for metastatic disease is extremely poor. Ten-year survival rates are less than 20% for patients with regional lymph node involvement and less than 10% for patients with distant metastases. (Cherpelis, Marcusen et al. 2002).

Histopathologic features associated with an increased risk of local failure or metastasis include large lesion size, perineural invasion, and involvement beyond the subcutaneous tissue. (Clayman, Lee et al. 2005)]

Chemotherapy in the management of high-risk SCCS remains relatively unexplored. (Jennings and Schmults 2010) The role of retinoids, which are known to decrease new cancer formation, but do not alter the course of an existing tumor, as prophylactic agents in patients with diffuse actinic damage or recurrent CSCCs is well established, especially in organ transplant recipients (OTRs). (Harwood, Leedham-Green et al. 2005) Unfortunately, randomized trials of retinoids, either used alone for the adjuvant-treatment of established mucosal SCC of the head and neck (Toma, Bonelli et al. 2004) or in combination with interferon (Brewster, Lee et al. 2007) for established SCCS, have shown no benefit.

Many of the available agents with activity demonstrated in advanced SCCS, including EGRF inhibitors and oral capecitabine, are well tolerated with relatively low risks, and are potential candidates for adjuvant therapy in highest-risk cases. Further work remains to identify patient subsets likely to benefit from adjuvant chemotherapy and to define optimal regimens. Collaborative clinical trials are needed to establish standardized prognostic or treatment models to assist clinicians in most effectively identifying and managing patients at risk for poor outcomes. (LeBoeuf and Schmults 2011)

4.2 Systemic therapy for advanced SCCS

The use of systemic therapy is limited to patients with distant metastases or locally advanced disease that cannot be adequately managed with surgery or radiotherapy. Because of the rarity of metastatic squamous cell cancers of the skin, the approach to systemic treatment is based primarily upon isolated case reports, with only a few small case series.

Treatment of metastatic SCC may include systemic chemotherapy or treatment with biologic response modifiers. The efficacy of these methods has not been established.

Wollina and colleagues (Wollina, Hansel et al. 2005) reported 4 patients with advanced SCC of the skin who were treated with oral capecitabine and IFN subcutaneously, resulting in complete remission in 2 patients and partial response in the other 2. IFN may act synergistically to capecitabine by causing a forced accumulation of 5-FU in tumor cells as a result of stimulation of dThdPase. In another report the use of oral capecitabine alone for the treatment of 14 patients with advanced cutaneous SCC resulted in 2 partial remissions and 3 minimal remissions. (Cartei, Cartei et al. 2000)

Cisplatin-based combinations appear to be the most active regimens in the published experience. Most regimens that have been studied for the treatment of advanced SCCS were adapted from those used for squamous cell cancers arising in other sites. Sadek et al. reported on the treatment of 14 patients with advanced squamous cell carcinoma of the skin or lip with a combination of bolus cisplatin, plus a five-day infusion of bleomycin and 5-fluorouracil. (Sadek, Azli et al. 1990) Four complete and seven partial responses were observed and in seven patients, tumor regression permitted subsequent definitive local treatment with either surgery or radiation therapy.

Using a combination of cisplatin daily times four plus a four day continuous infusion of bleomycin to treat five patients with locally advanced disease of the head and neck (three squamous cell and two basal cell), Denic observed one complete response and 3 partial responses. (Denic 1999) One patient had disease progression.

Multiple targeted therapies are being developed for many malignancies, including those with squamous cell histologies. These may ultimately have utility in patients with advanced or metastatic non melanoma skin cancers. The primary targets of molecular inhibition in squamous cell carcinoma include the epidermal growth factor receptor (EGFR), the vascular endothelial growth factor (VEGF) and its receptor, and tyrosine kinase (TK). (O'Bryan and Ratner 2011) Molecular studies have demonstrated that these molecules are overexpressed in a subset of SCCS and may be associated with more aggressive clinical behavior. (Detmar, Velasco et al. 2000; Maubec, Duvillard et al. 2005; Ch'ng, Low et al. 2008)

Intracellular signal transduction mediated by the epidermal growth factor receptor (EGFR) has been one of the most studied pathways in carcinogenesis. The phosphorylation of EGFR activates multiple biological processes, including apoptosis, differentiation, cellular proliferation, motility, invasion, adhesion, DNA repair, and survival. EGFR is a transmembrane tyrosine kinase receptor involved in the proliferation and survival of many cancer cells and is one of the first molecular target against which monoclonal antibodies have been developed for cancer therapy. EGFR plays an important role in tumorigenesis of non melanoma skin cancer, especially metastatic squamous cell carcinoma, via mechanisms similar to those of other visceral tumors. (Khan, Alam et al. 2011)

Several case reports suggest that Cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor (EGFR), has antitumor activity in patients with advanced squamous cell carcinoma of the skin. (Bauman, Eaton et al. 2007; Suen, Bressler et al. 2007; Arnold, Bruckner-Tuderman et al. 2009)

Maubec and colleagues reported the results of a phase II study that included 36 patients with advanced squamous cell carcinoma of the skin treated with cetuximab in the first line setting. (Maubec, Duvillard et al. 2010) In this study, cetuximab was administered on a weekly schedule (400 mg/m2 on week 1 and then 250 mg/m2 weekly). Eight partial and two complete responses were observed, and 21 had stable disease for an overall disease control rate of 69 percent. Furthermore, three patients were able to undergo complete resection of their tumor following systemic treatment with cetuximab. Similarly to what is reported in other malignancies, patients developing acneiform rash apparently had a better outcome.

The combination of cetuximab with chemotherapy is a promising approach. Association with platinum-based chemotherapy and 5-FU in patients with recurrent or metastatic SCC of the head and neck (SCCHN) has shown benefit in a large prospective randomized trial. (Vermorken, Mesia et al. 2008) In this study, 442 eligible patients with untreated recurrent or metastatic SCCHN were randomized to receive 5-FU with cisplatin or carboplatin, with or without cetuximab. The ORR was 36% versus 20% with and without cetuximab ($P = 0.001$). Survival increased from 7.4 to 10.1 months with the addition of cetuximab ($P = 0.04$), and progression-free survival increased from 3.3 to 5.6 months ($P \leq 0.0001$).

Other targeted EGFR inhibitors are also currently under investigation in clinical trials mainly for the treatment of SCCHN, including Panitumumab (Vectibix, Amgen, Thousand Oaks, CA) which is a fully human monoclonal antibody to EGFR. (Lacouture and Melosky 2007; AMGEN 2011; AMGEN 2011)

Additionally, many targeted molecular therapies to VEGF and VEGF TKs have proven efficacy in other malignancies. Research into their use for SCCHN is growing and these agents may also be useful for the treatment of SCCS. (Wang and Agulnik 2008) Bevacicumab (Avastin, Genentech, South San Francisco, CA) is a fully human monoclonal antibody against VEGF, and is being tested for recurrent and metastatic SCCHN in a phase 3 trial comparing chemotherapy alone versus chemotherapy plus bevacizumab. (Wang and Agulnik 2008) There is hope that the combination of EGFR and VEGF pathway inhibitors will provide an increased clinical benefit in such patients. This alternative is

being studied in an ongoing phase 2 trial, cituximab, radiotherapy, and pemetrexed with or without bevacizumab is being tested in patients with locally advanced SCCHN. (Gold, Lee et al. 2009)

As mentioned earlier, the vast majority of studies focus on the use of molecular inhibitors in SCCHN. More research is needed, for the development of new treatment modalities and to establish their role in treating patients with advanced or aggressive CSCC.

5. References

(2008). "Cancer incidence in five continents." *IARC Sci Publ* IX(160): 1-837.

Alam, M. and D. Ratner (2001). "Cutaneous squamous-cell carcinoma." *N Engl J Med* 344(13): 975-83.

AMGEN. (2011, April 7, 2011). "PARTNER: Panitumumab Added to Regimen for Treatment of Head aNd Neck Cancer Evaluation of Response." Retrieved July 14, 2011, from http://clinicaltrials.gov/ct2/show/record/NCT00454779.

AMGEN. (2011, January 20, 2011). "PRISM (Panitumumab Regimen In Second-line Monotherapy of Head and Neck Cancer)." Retrieved July 14, 2011, from http://clinicaltrials.gov/ct2/show/record/NCT00446446.

Andruchow, J. L., M. J. Veness, et al. (2006). "Implications for clinical staging of metastatic cutaneous squamous carcinoma of the head and neck based on a multicenter study of treatment outcomes." *Cancer* 106(5): 1078-83.

Arnold, A. W., L. Bruckner-Tuderman, et al. (2009). "Cetuximab therapy of metastasizing cutaneous squamous cell carcinoma in a patient with severe recessive dystrophic epidermolysis bullosa." *Dermatology* 219(1): 80-3.

Backous, D. D., F. DeMonte, et al. (2005). "Craniofacial resection for nonmelanoma skin cancer of the head and neck." *Laryngoscope* 115(6): 931-7.

Barzilai, G., E. Greenberg, et al. (2005). "Pattern of regional metastases from cutaneous squamous cell carcinoma of the head and neck." *Otolaryngol Head Neck Surg* 132(6): 852-6.

Bauman, J. E., K. D. Eaton, et al. (2007). "Treatment of recurrent squamous cell carcinoma of the skin with cetuximab." *Arch Dermatol* 143(7): 889-92.

Brantsch, K. D., C. Meisner, et al. (2008). "Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study." *Lancet Oncol* 9(8): 713-20.

Breuninger, H., B. Black, et al. (1990). "Microstaging of squamous cell carcinomas." *Am J Clin Pathol* 94(5): 624-7.

Brewster, A. M., J. J. Lee, et al. (2007). "Randomized trial of adjuvant 13-cis-retinoic acid and interferon alfa for patients with aggressive skin squamous cell carcinoma." *J Clin Oncol* 25(15): 1974-8.

Cartei, G., F. Cartei, et al. (2000). "Oral 5-fluorouracil in squamous cell carcinoma of the skin in the aged." *Am J Clin Oncol* 23(2): 181-4.

Cassarino, D. S., D. P. Derienzo, et al. (2006). "Cutaneous squamous cell carcinoma: a comprehensive clinicopathologic classification. Part one." *J Cutan Pathol* 33(3): 191-206.

Ch'ng, S., I. Low, et al. (2008). "Epidermal growth factor receptor: a novel biomarker for aggressive head and neck cutaneous squamous cell carcinoma." *Hum Pathol* 39(3): 344-9.

Ch'ng, S., A. Maitra, et al. (2006). "Parotid metastasis--an independent prognostic factor for head and neck cutaneous squamous cell carcinoma." *J Plast Reconstr Aesthet Surg* 59(12): 1288-93.

Cherpelis, B. S., C. Marcusen, et al. (2002). "Prognostic factors for metastasis in squamous cell carcinoma of the skin." *Dermatol Surg* 28(3): 268-73.

Clayman, G. L., J. J. Lee, et al. (2005). "Mortality risk from squamous cell skin cancer." *J Clin Oncol* 23(4): 759-65.

Collins, G. L., N. Nickoonahand, et al. (2004). "Changing demographics and pathology of nonmelanoma skin cancer in the last 30 years." *Semin Cutan Med Surg* 23(1): 80-3.

de Lima Vazquez, V., T. Sachetto, et al. (2008). "Prognostic factors for lymph node metastasis from advanced squamous cell carcinoma of the skin of the trunk and extremities." *World J Surg Oncol* 6: 73.

de Lima Vazquez , V., C. Scapulatempo, et al. (2011). "Prognostic and Risk Factors in Patients with Locally Advanced Cutaneous Squamous Cell Carcinoma of the Trunk and Extremities " *Journal of Skin Cancer* 2011: 9

delCharco, J. O., W. M. Mendenhall, et al. (1998). "Carcinoma of the skin metastatic to the parotid area lymph nodes." *Head Neck* 20(5): 369-73.

Denic, S. (1999). "Preoperative treatment of advanced skin carcinoma with cisplatin and bleomycin." *Am J Clin Oncol* 22(1): 32-4.

Detmar, M., P. Velasco, et al. (2000). "Expression of vascular endothelial growth factor induces an invasive phenotype in human squamous cell carcinomas." *Am J Pathol* 156(1): 159-67.

Ebrahimi, A., M. D. Moncrieff, et al. (2010). "Predicting the pattern of regional metastases from cutaneous squamous cell carcinoma of the head and neck based on location of the primary." *Head Neck* 32(10): 1288-94.

Edge, S. B. and C. C. Compton (2010). "The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM." *Ann Surg Oncol* 17(6): 1471-4.

Farasat, S., S. S. Yu, et al. (2011). "A new American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: Creation and rationale for inclusion of tumor (T) characteristics." *J Am Acad Dermatol* 64(6): 1051-9.

Faustina, M., R. Diba, et al. (2004). "Patterns of regional and distant metastasis in patients with eyelid and periocular squamous cell carcinoma." *Ophthalmology* 111(10): 1930-2.

Forest, V. I., J. J. Clark, et al. (2010). "N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases: results of 2 Australian Cancer Centers." *Cancer* 116(5): 1298-304.

Gandhi, M. R., B. Panizza, et al. (2010). "Detecting and defining the anatomic extent of large nerve perineural spread of malignancy: comparing "targeted" MRI with the histologic findings following surgery." *Head Neck* 33(4): 469-75.

Gold, K. A., H. Y. Lee, et al. (2009). "Targeted therapies in squamous cell carcinoma of the head and neck." *Cancer* 115(5): 922-35.

Harwood, C. A., M. Leedham-Green, et al. (2005). "Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study." *Arch Dermatol* 141(4): 456-64.

Hong, T. S., K. J. Kriesel, et al. (2005). "Parotid area lymph node metastases from cutaneous squamous cell carcinoma: implications for diagnosis, treatment, and prognosis." *Head Neck* 27(10): 851-6.

Iyer, N. G., J. R. Clark, et al. (2009). "Outcomes following parotidectomy for metastatic squamous cell carcinoma with microscopic residual disease: implications for facial nerve preservation." *Head Neck* 31(1): 21-7.

Jennings, L. and C. D. Schmults (2010). "Management of high-risk cutaneous squamous cell carcinoma." *J Clin Aesthet Dermatol* 3(4): 39-48.

Khan, M. H., M. Alam, et al. (2011). "Epidermal Growth Factor Receptor Inhibitors in the Treatment of Nonmelanoma Skin Cancers." *Dermatol Surg*.

Khurana, V. G., D. H. Mentis, et al. (1995). "Parotid and neck metastases from cutaneous squamous cell carcinoma of the head and neck." *Am J Surg* 170(5): 446-50.

Koseki, S., T. Aoki, et al. (1999). "An immunohistochemical study of E-cadherin expression in human squamous cell carcinoma of the skin: relationship between decreased expression of E-cadherin in the primary lesion and regional lymph node metastasis." *J Dermatol* 26(7): 416-22.

Krahn, G., U. Leiter, et al. (2001). "Coexpression patterns of EGFR, HER2, HER3 and HER4 in non-melanoma skin cancer." *Eur J Cancer* 37(2): 251-9.

Kraus, D. H., J. F. Carew, et al. (1998). "Regional lymph node metastasis from cutaneous squamous cell carcinoma." *Arch Otolaryngol Head Neck Surg* 124(5): 582-7.

Lacouture, M. E. and B. L. Melosky (2007). "Cutaneous reactions to anticancer agents targeting the epidermal growth factor receptor: a dermatology-oncology perspective." *Skin Therapy Lett* 12(6): 1-5.

Lai, S. Y., G. S. Weinstein, et al. (2002). "Parotidectomy in the treatment of aggressive cutaneous malignancies." *Arch Otolaryngol Head Neck Surg* 128(5): 521-6.

LeBoeuf, N. R. and C. D. Schmults (2011). "Update on the management of high-risk squamous cell carcinoma." *Semin Cutan Med Surg* 30(1): 26-34.

Leibovitch, I., S. C. Huilgol, et al. (2005). "Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia II. Perineural invasion." *J Am Acad Dermatol* 53(2): 261-6.

Maubec, E., P. Duvillard, et al. (2010). Cetuximab as first-line monotherapy in patients with skin unresectable squamous cell carcinoma: Final results of a phase II multicenter study (abstract #8510). *ASCO*. Chicago. 28: 613s.

Maubec, E., P. Duvillard, et al. (2005). "Immunohistochemical analysis of EGFR and HER-2 in patients with metastatic squamous cell carcinoma of the skin." *Anticancer Res* 25(2B): 1205-10.

Mendenhall, W. M., R. J. Amdur, et al. (2009). "Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck." *Laryngoscope* 119(10): 1994-9.

Mullen, J. T., L. Feng, et al. (2006). "Invasive squamous cell carcinoma of the skin: defining a high-risk group." *Ann Surg Oncol* 13(7): 902-9.

North, J. H., Jr., J. E. Spellman, et al. (1997). "Advanced cutaneous squamous cell carcinoma of the trunk and extremity: analysis of prognostic factors." *J Surg Oncol* 64(3): 212-7.

O'Brien, C. J., E. B. McNeil, et al. (2002). "Significance of clinical stage, extent of surgery, and pathologic findings in metastatic cutaneous squamous carcinoma of the parotid gland." *Head Neck* 24(5): 417-22.

O'Bryan, K. W. and D. Ratner (2011). "The role of targeted molecular inhibitors in the management of advanced nonmelanoma skin cancer." *Semin Cutan Med Surg* 30(1): 57-61.

O'Hara, J., A. Ferlito, et al. (2010). "Cutaneous squamous cell carcinoma of the head and neck metastasizing to the parotid gland-A review of current recommendations." *Head Neck*.

Osborne, R. F., T. Shaw, et al. (2008). "Elective parotidectomy in the management of advanced auricular malignancies." *Laryngoscope* 118(12): 2139-45.

Palme, C. E., S. G. MacKay, et al. (2007). "The need for a better prognostic staging system in patients with metastatic cutaneous squamous cell carcinoma of the head and neck." *Curr Opin Otolaryngol Head Neck Surg* 15(2): 103-6.

Palme, C. E., C. J. O'Brien, et al. (2003). "Extent of parotid disease influences outcome in patients with metastatic cutaneous squamous cell carcinoma." *Arch Otolaryngol Head Neck Surg* 129(7): 750-3.

Ries, L. A. G., D. Melbert, et al. (2007). "SEER Cancer Statistics Review, 1975-2005." Retrieved November, 2007, 2007, from http://seer.cancer.gov/csr/1975_2005/.

Rowe, D. E., R. J. Carroll, et al. (1992). "Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection." *J Am Acad Dermatol* 26(6): 976-90.

Sadek, H., N. Azli, et al. (1990). "Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin." *Cancer* 66(8): 1692-6.

Schacht, V., M. I. Ramirez, et al. (2003). "T1alpha/podoplanin deficiency disrupts normal lymphatic vasculature formation and causes lymphedema." *EMBO J* 22(14): 3546-56.

Sobin, L. H. and C. C. Compton "TNM seventh edition: what's new, what's changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer." *Cancer* 116(22): 5336-9.

Staples, M. P., M. Elwood, et al. (2006). "Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985." *Med J Aust* 184(1): 6-10.

Suen, J. K., L. Bressler, et al. (2007). "Cutaneous squamous cell carcinoma responding serially to single-agent cetuximab." *Anticancer Drugs* 18(7): 827-9.

Toma, S., L. Bonelli, et al. (2004). "13-cis retinoic acid in head and neck cancer chemoprevention: results of a randomized trial from the Italian Head and Neck Chemoprevention Study Group." *Oncol Rep* 11(6): 1297-305.

Trakatelli, M., C. Ulrich, et al. (2007). "Epidemiology of nonmelanoma skin cancer (NMSC) in Europe: accurate and comparable data are needed for effective public health monitoring and interventions." *Br J Dermatol* 156 Suppl 3: 1-7.

Turner, S. J., G. J. Morgan, et al. (2009). "Metastatic cutaneous squamous cell carcinoma of the external ear: a high-risk cutaneous subsite." *J Laryngol Otol* 124(1): 26-31.

Vauterin, T. J., M. J. Veness, et al. (2006). "Patterns of lymph node spread of cutaneous squamous cell carcinoma of the head and neck." *Head Neck* 28(9): 785-91.

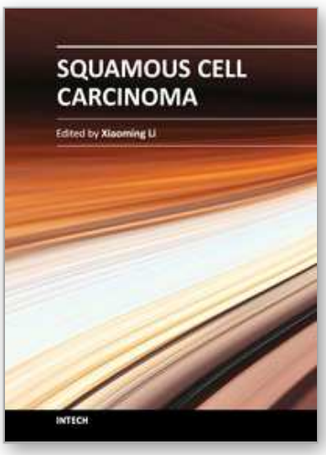
Veness, M. J. (2007). "High-risk cutaneous squamous cell carcinoma of the head and neck." *J Biomed Biotechnol* 2007(3): 80572.

Veness, M. J., C. E. Palme, et al. (2003). "Cutaneous head and neck squamous cell carcinoma metastatic to cervical lymph nodes (nonparotid): a better outcome with surgery and adjuvant radiotherapy." *Laryngoscope* 113(10): 1827-33.

Vermorken, J. B., R. Mesia, et al. (2008). "Platinum-based chemotherapy plus cetuximab in head and neck cancer." *N Engl J Med* 359(11): 1116-27.

Wang, L. X. and M. Agulnik (2008). "Promising newer molecular-targeted therapies in head and neck cancer." *Drugs* 68(12): 1609-19.

Wollina, U., G. Hansel, et al. (2005). "Oral capecitabine plus subcutaneous interferon alpha in advanced squamous cell carcinoma of the skin." *J Cancer Res Clin Oncol* 131(5): 300-4.



Squamous Cell Carcinoma
Edited by Prof. Xiaoming Li

ISBN 978-953-51-0024-9
Hard cover, 302 pages
Publisher InTech
Published online 03, February, 2012
Published in print edition February, 2012

This book points to some new areas for investigation on squamous cell carcinoma (SCC). Firstly, the features and management of some specific SCC is discussed to give the readers the general principles in dealing with these uncommon and sophisticated conditions. Some new concepts in adjuvant therapy including neoadjuvant therapy and gold nanoparticle-based photo dynamic therapy are introduced. Secondly, a detailed discussion of molecular aspects of tumor invasion and progression in SCC is provided with the emphasis on the roles of some important factors. The role of tumor microenvironment in head and neck SCC is specifically discussed. Thirdly, the roles of cancer stem cells (CSC) in cancer therapy of SCC are described. Molecular mechanisms involving therapeutic resistance and new therapeutic strategies targeting CSC are discussed in detail. Finally, other aspects concerning SCC are included, which involve the assessment, genetic manipulation and its possible clinical implications for the treatment of SCC.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen