European Dermatology Forum

Guideline on the diagnosis and treatment of Invasive Squamous Cell Carcinoma of the Skin

Developed by the Guideline Subcommittee of the
European Dermatology Forum

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5	Payment for writing or reviewing the manuscript	no	no	no	no
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Relevant financial activities outside the submitted work					
1	Board membership	no	no	no	no
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4	Expert testimony	no	no	no	no
5	Grants/grants pending	no	no	no	no
6	Payment for lectures including service on speakers bureaus	no	no	no	no
7	Payment for manuscript preparation	no	no	no	no
8	Patents (planned, pending or issued)	no	no	no	no
9	Royalties	no	no	no	no
10	Payment for development of educational presentations	no	no	no	no
11	Stock/stock options	no	no	no	no
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Yes	Yes	Yes	Yes
13	Other (err on the side of full disclosure)	no	no	no	no

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Other relationships					
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4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
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Relevant financial activities outside the submitted work					
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3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	BMS	GSK	Roche	
6	Payment for lectures including service on speakers bureaus	Amgen	BMS, GSK	MSD, Novartis	Roche
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	BMS	Roche		
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Other relationships					
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Conflicts of interests Jean Jacques Grob

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3	Support for travel to meetings for the study or other purposes	0			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	0			
5	Payment for writing or reviewing the manuscript	0			
6	Provision of writing assistance, medicines, equipment, or administrative support	0			
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Relevant financial activities outside the submitted work					
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3	Employment	0			
4	Expert testimony	0			
5	Grants/grants pending	0			
6	Payment for lectures including service on speakers bureaus	0			
7	Payment for manuscript preparation	0			
8	Patents (planned, pending or issued)	0			
9	Royalties	0			
10	Payment for development of educational presentations	Linked to SCC/KA Almirall	*Unrelated to SCC* GSK, Roche, BMS		
11	Stock/stock options	0			
12	Travel/accommodations/meeting expenses unrelated	0	*Unrelated to SCC* GSK, Roche,		

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13	Other (err on the side of full disclosure)	Institutional funding from approx.. 20 pharma companies (fee for service for commercial clinical trials)			

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6	Payment for lectures including service on speakers bureaus				
7	Payment for manuscript preparation				
8	Patents (planned, pending or issued)				
9	Royalties				
10	Payment for development of educational presentations				
11	Stock/stock options				
12	Travel/accommodations/meeting expenses unrelated to activities listed**			Support to go to the ASCO and ESMO meeting in 2014	
13	Other (err on the side of full				

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4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
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2	Consultancy	LEO	ALMIRALL	MEDA	
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5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	ALMIRALL	MEDA	ISDIN	
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	LEO	ALMIRALL	ISDIN	
11	Stock/stock options	no			
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5	Payment for writing or reviewing the manuscript	NO			
6	Provision of writing assistance, medicines, equipment, or administrative support	NO			
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Relevant financial activities outside the submitted work					
1	Board membership	LEO	MEDA	ROCHE	ABBVIE
2	Consultancy				
3	Employment	NO			
4	Expert testimony	NO			
5	Grants/grants pending	NO			
6	Payment for lectures including service on speakers bureaus	NO	NO	NO	ABBVIE
7	Payment for manuscript preparation	NO			
8	Patents (planned, pending or issued)	NO			
9	Royalties	NO			
10	Payment for development of educational presentations	NO			
11	Stock/stock options	NO			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	NO			
13	Other (err on the side of full disclosure)	NO			

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4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No			
5	Payment for writing or reviewing the manuscript	No			
6	Provision of writing assistance, medicines, equipment, or administrative support	No			
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Relevant financial activities outside the submitted work					
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2	Consultancy	Millenium, Amgen, Roche, Merck, GSK, AZ, BMS			
3	Employment	No			
4	Expert testimony	No			
5	Grants/grants pending	No			
6	Payment for lectures including service on speakers bureaus	No			
7	Payment for manuscript preparation	No			
8	Patents (planned, pending or issued)	No			
9	Royalties	No			
10	Payment for development of educational presentations	BMS			
11	Stock/stock options	No			
12	Travel/accommodations/meeting expenses unrelated	BMS, Merck			

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13	Other (err on the side of full disclosure)	Institutional funding from approx.. 20 pharma companies (fee for service for commercial clinical trials)			

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Conflicts of interests Hubert Pehamberger

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3	Support for travel to meetings for the study or other purposes	No			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No			
5	Payment for writing or reviewing the manuscript	No			
6	Provision of writing assistance, medicines, equipment, or administrative support	No			
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Relevant financial activities outside the submitted work					
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2	Consultancy	LEO	Almirall	Roche	BMS
3	Employment	No			
4	Expert testimony	No			
5	Grants/grants pending	No			
6	Payment for lectures including service on speakers bureaus	No			
7	Payment for manuscript preparation	No			
8	Patents (planned, pending or issued)	No			
9	Royalties	No			
10	Payment for development of educational presentations	No			
11	Stock/stock options	No			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	BMS	LEO	Roche	
13	Other (err on the side of full disclosure)	No			

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Conflicts of interests – Ketty Peris

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2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
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Relevant financial activities outside the submitted work					
1	Board membership	LEO	Meda	Roche	Novartis
2	Consultancy	LEO	Meda	Roche	
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4	Expert testimony	no			
5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	LEO	Meda	Roche	
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	LEO	Meda	Roche	Abbvie
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Conflicts of interests Philippe Saiag

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2	Consulting fee or honorarium	0			
3	Support for travel to meetings for the study or other purposes	MSD			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	0			
5	Payment for writing or reviewing the manuscript	0			
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1	Board membership	Roche-Genentec	GSK	Novartis	BMS, Merck
2	Consultancy	GSK			
3	Employment	0			
4	Expert testimony	0			
5	Grants/grants pending	Roche			
6	Payment for lectures including service on speakers bureaus	GSK	Roche		
7	Payment for manuscript preparation	GSK			
8	Patents (planned, pending or issued)	0			
9	Royalties	0			
10	Payment for development of educational presentations	0			
11	Stock/stock options	0			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Roche-Genentec	GSK	Novartis	BMS, Merck
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Conflicts of interests – Alexander J. Stratigos

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2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
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2	Consultancy	novartis	roche	LEO	MEDA
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4	Expert testimony	no			
5	Grants/grants pending	Jannsen-Cilag			
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8	Patents (planned, pending or issued)	no			
9	Royalties	MacGraw Hill (Pediatric dermatology atlas)			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	LEO	Jannsen-Cilag	Abbvie	

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Other relationships					
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Conflicts of interests Alessandro Testori

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1	Grant	NO			
2	Consulting fee or honorarium	NO			
3	Support for travel to meetings for the study or other purposes	NO			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	NO			
5	Payment for writing or reviewing the manuscript	NO			
6	Provision of writing assistance, medicines, equipment, or administrative support	NO			
7	Other				

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Relevant financial activities outside the submitted work					
1	Board membership	GSK	BMS	AMGEN	ROCHE
2	Consultancy	NO			
3	Employment	NO			
4	Expert testimony	NO			
5	Grants/grants pending	NO			
6	Payment for lectures including service on speakers bureaus	NO			
7	Payment for manuscript preparation	NO			
8	Patents (planned, pending or issued)	NO			
9	Royalties	NO			
10	Payment for development of educational presentations	NO			
11	Stock/stock options	NO			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	NO			
13	Other (err on the side of full disclosure)	NO			

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Other relationships					
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Diagnosis and Treatment of Invasive Squamous Cell Carcinoma of the Skin: European Consensus-based Interdisciplinary Guideline

On behalf of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC)

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Abstract

Cutaneous squamous cell carcinoma (cSCC) is one of the most common cancers in Caucasian populations, accounting for 20% of all cutaneous malignancies. A unique collaboration of multi-disciplinary experts from the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization of Research and Treatment of Cancer (EORTC) was formed to make recommendations on cSCC diagnosis and management, based on a critical review of the literature, existing guidelines and the expert's experience. The diagnosis of cSCC is primarily based on clinical features. A biopsy or excision and histologic confirmation should be performed in all clinically suspicious lesions in order to facilitate the prognostic classification and correct management of cSCC. The first line treatment of cutaneous SCC is complete surgical excision with histopathological control of excision margins. The EDF-EADO-EORTC consensus group recommends a standardized minimal margin of 5 mm even for low-risk tumors. For tumors, with histological thickness of $\geq$ 6 mm or in tumors with high risk pathological features, e.g., high histological grade, subcutaneous invasion, perineural invasion, recurrent tumors, and/or tumors at high risk locations an extended margin of 10 mm is recommended. As lymph node involvement by cutaneous SCC increases the risk of recurrence and mortality, a lymph node ultrasound is highly recommended, particularly in tumors with high-risk characteristics. In case of clinical suspicion or positive findings upon imaging, a histologic confirmation should be sought either by fine needle aspiration or by open lymph node biopsy. In large infiltrating tumors with signs of involvement of underlying structures, additional imaging tests, such as CT or MRI imaging may be required to accurately assess the extent of the tumor and the presence of metastatic spread. Current staging systems for cSCC (TNM/UICC 2009; AJCC 2010) are not optimal, as they have been developed for head and neck tumors and lack extensive validation or adequate prognostic discrimination in certain stages with heterogeneous outcome measures.

Sentinel lymph node biopsy has been used in patients with cSCC, but there is no conclusive evidence of its prognostic or therapeutic value. In case of lymph node involvement by cSCC, the preferred treatment is a regional lymph node dissection. Radiation therapy represents a fair alternative to surgery in the non-surgical treatment of small cSCC's in low risk areas. It generally should be discussed either as a primary treatment for inoperable cSCC or in the adjuvant setting. Stage IV cSCC can be responsive to various chemotherapeutic agents; however, there is no standard regimen. EGFR inhibitors such as cetuximab or erlotinib, should be discussed as second line treatments after mono- or polychemotherapy failure and disease progression or within the framework of clinical trials. There is no standardized follow-up schedule for patients with cSCC. A close follow-up schedule is recommended based on risk assessment of locoregional recurrences, metastatic spread or development of new lesions.

Keywords: cutaneous scquamous cell carcinoma, diagnosis, prognosis, management, surgical excision, pathology, metastasis, follow up.

INTRODUCTION

These guidelines have been written under the auspices of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization of Research and Treatment of Cancer (EORTC) in order to assist clinicians in treating patients with cutaneous squamous cell carcinoma (cSCC) in Europe. The paper was initiated due to advances in the histological diagnosis and the prognostic classification of cSCC with implications for treatment selection. The guidelines address in detail aspects of cSCC management, from the clinical and histological diagnosis of primary tumor to the systemic treatment of advanced or metastatic disease. We focus on invasive cSCC, excluding the early intraepi-demic SCC like AK, and Bowen's disease, and mucosal tumors, such as those located in the genital area, or those in the labio-bucco-nasal area, which are often mixed with cSCC under the label of "head and neck" tumors. Prevention issues are also briefly addressed. It is hoped that this set of guidelines will assist healthcare providers in managing their patients according to the current standards of care and evidence-based medicine. It is not intended to replace national guidelines accepted in their original country. These guidelines reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may modify the conclusions or recommendations in this report. In addition, it may be necessary to deviate from these guidelines for individual patients or under special circumstances. Just as adherence to the guidelines may not constitute defense against a claim of negligence, deviation from them should not necessarily be deemed negligent.

METHODS

To construct this EDF-EADO-EORTC guideline, an extensive search with terms “cutaneous squamous cell carcinoma” using the PubMed, EMBASE and Cochrane Library was conducted (until October 31st). Articles included systematic reviews, pooled analyses and meta-analyses. We excluded case reports and studies on specific localizations, particularly oral and anogenital SCC. The search was restricted to English-speaking language publications. We also searched for existing guidelines on cutaneous squamous cell carcinoma and precursor lesions in the databases mentioned above as well as in relevant websites (national agencies, medical societies). A subgroup among the authors produced a working draft that was extensively discussed at a consensus meeting and thereafter through email communication. In addition, the panel looked for concordances and differences among recently published guidelines[1,2,3,4]. Previous recommendations on distinct items (epidemiology, diagnosis, prognosis, treatment, follow-up) were discussed extensively in view of the available evidence-based data. Items that were agreed upon by our expert panel were adapted within our guideline proposal with appropriate reference. Items that differed from previously published guidelines or were originally recommended by our working group were clearly stated as proposed by the EADO consensus group. The guideline draft was circulated between panel members from EADO, EDF, and EORTC before reaching its final form.

DEFINITION

Cutaneous Squamous Cell Carcinoma (cSCC) is a common skin cancer characterized by the malignant proliferation of keratinizing cells of the epidermis or its appendages. cSCC usually arises from precursor lesions such as actinic keratosis, and Bowen's disease (SCC *in situ*) but can also grow *de novo* or on irradiated skin with or without manifestations of chronic radiodermatitis, or on chronically inflamed skin such as in chronic wounds or chronic inflammatory skin disorders. When only invasive forms are taken into account, it is the second most common form of non-melanoma skin cancer (NMSC) and accounts for 20% of all cutaneous malignancies[5]. Although epidemiological data are questionable due to the non-systematic record of cases in registries, the incidence of cSCC seems to have increased over the past 30 years by 50 and up to 200%, with stabilization trends or slower rates of increase in certain countries [6,7,8]. The implications of the disease in public health are widely underestimated.

In contrast to basal cell carcinoma, which rarely metastasizes, cSCC can metastasize initially to regional lymph nodes and subsequently to distant sites. Although the rate of metastasis in cSCC has been estimated to range from 2 to 5%, this estimation has been primarily based on assessments by biased subgroups, and should thus be considered with caution. Despite its low distant metastatic potential, the presence of distant metastasis is associated with a dismal prognosis and a median survival of less than 2 years. Thus, it is crucial to preserve the general high chances of cure of cSCCs by a careful evaluation and proper early management of all cases, and to never underestimate the potential aggressiveness of this tumor.

EPIDEMIOLOGY

The exact incidence of cSCC is unknown, and statistics often mix strictly cutaneous and mucosal SCC. In Australia, where the highest rate of NMSC has been recorded, the overall incidence

rate of cSCC in 2002 was estimated to be 387 cases per 100,000 people[9]. In the USA, estimates from national population-based data sources reported that 2.2 million persons were treated for NMSC in 2006 of which roughly 600,000 cases were SCCs. A recent US study estimated that 3,900 to 9,000 patients died from the cSCC in 2012.[10] In central and southern United States, deaths from cSCC may be as common as deaths from renal and oropharyngeal carcinomas, and melanoma[10].

A systematic review of 19 studies examining incidence trends of cSCC in European white populations showed a marked geographic variation with the highest incidence rates in South Wales, UK (31,7 per 100 000 person-years) and Switzerland (28,9 per 100 000 person-years) and the lowest in Croatia (8,9 per100 000 person-years). These differences suggest that comprehensiveness of case recording may account more for incidence variability rather than phenotypic variability[11]. Population-based studies from Ireland, Sweden and Denmark demonstrated that age-standardized incidence rates are rapidly increasing, with absolute increases of approximately 2,000 new SCC cases annually in populations of 4.5-9 million inhabitants[12, 13, 14]. In the cancer registry of the German federal state of Schleswig-Holstein, the age-standardized incidence of squamous cell carcinoma of the skin was 18.2 for men and 8.5 for women[15]. A recent study from the Netherlands also reported a significant increase of the European Standardized Rates (ESR) from 22.2 to 35.4 per 100,000 inhabitants for males and from 7.9 to 20.5 for females between 1989 and 2008[16]. cSCC is a rare tumor in the age groups under the age of 45, even though the incidence of cSCC seems to be significantly increasing in younger individuals[17].

As a whole, a range of twice the incidence of melanoma in a usual environment for Caucasians (Europe) up to 10 times in the most sunny environment (Australia) is probably a relevant estimation for invasive cSCC, demonstrating that this tumor is even more susceptible to UV radiation (UVR) than melanoma, in particular chronic UVR.

RISK FACTORS

The most prominent risk factors for cSCC include sun exposure, advanced age, and UVR-sensitive skin. Cumulative chronic UVR exposure is the strongest environmental risk factor for cSCC development[18], which explains why the incidence of cSCC increases dramatically with age. The incidence of cSCC is increased at lower latitudes, correlating with an increased intensity of ambient light. In 90% of cases, the tumor occurs on chronically UVR- exposed anatomic areas such as the head and neck, and the dorsal aspects of the hands and forearms. cSCC is more common in patients working outdoors[19]. Moreover, artificial sources of UVR, such as PUVA therapy and indoor tanning devices, have also been implicated in the pathogenesis of cSCC[20]. Other environmental factors are X-ray radiation (as accident or historically occupational exposure) but also chemical factors such as arsenic (as a toxic agent, poison, or therapy) and polycyclic hydrocarbons, mostly in the context of occupational exposure. More rarely, very long-lasting chronic inflammatory processes such as those observed in chronic wounds, old burn or other scars, leg ulcers, sinus tracts or certain chronic genetic diseases, such as epidermolysis bullosa, may also contribute to the development of cSCC, which are often advanced due to late diagnosis.

Genetic factors are crucial to facilitate the role of environmental factors. A fair pigmentary trait (skin phototypes I and II) predisposes to sensitivity to chronic ultraviolet radiation exposure and is thus associated with a high incidence of cSCCs[21]. As expected, genetic risk factors that underlie light skin complexion, such as variations in the MC1R gene are also associated with this high incidence[22]. In a similar way, oculo-cutaneous albinisms, which encompass a panel of disorders of melanin production, and xeroderma pigmentosum, a rare disorder which covers a spectrum of genetic defects in DNA repair, are characterized by multiple and early cSCCs. Apart from genetic syndromes with deficiencies of the protective mechanisms against UVR,

other inherited conditions such as epidermodysplasia verruciformis, a genetic disorder with a defect in the protection against HPV is also associated with a high rate of cSCC.

Therapeutic agents can also promote the development and progression of cSCCs. Immune suppression, including allogeneic organ transplantation, therapy of immune-mediated or oncologic diseases, such as lymphoma or leukaemia, are associated with an increased risk of cSCC due to lack of immunosurveillance against cancer and HPV. All immunosuppressive agents including chemotherapy, classical immunosuppressives or even biologic agents have an impact on this risk, but at a very different degree. The best illustration of iatrogenic immunosuppression is the group of organ transplant recipients which is associated with a 65- to 250- fold increased risk for developing cSCC compared with the general population[23]. cSCC in this subgroup of patients exhibit a more aggressive course of the disease, with higher rates of local recurrence, metastasis and death[24]. Other therapies, such as BRAF inhibitors, promote eruptive cSCC via other mechanisms, ie, by boosting the effect of pre-existing mutations in chronically sun-exposed areas[25,26,27].

ETIOPATHOGENESIS

The development of cSCC follows the multistage model of malignant transformation. It starts with clones of mutated cells within the epidermis, which subsequently give rise to a focal area of loss of normal architecture and cellular atypia resulting in a focal disorder of keratinization that is clinically perceived as an “actinic keratosis”. Proliferation of atypical keratinocytes through the entire epidermis forms intraepithelial or *in situ* neoplasms, usually presenting as Bowen’s disease. The accumulation of further mutational and cellular events will lead to invasive growth and, more rarely, to metastases. Mutations in the tumor suppressor gene p53 are the most common genetic abnormality found in cSCCs[28]. P53 is commonly mutated in AKs and SCCs in situ indicating that p53 loss occurs prior to tumor invasion. One possible role of early p53 muta-

tions in SCCs is resistance to apoptosis allowing for clonal expansion at the expense of neighboring keratinocytes containing a wild type p53 gene. A significant proportion of p53 mutations is localized opposite pyrimidine dimer sites (C-C) and likely derives from UVB exposure[29]. Other genetic alterations found in cSCCs include aberrant activation of EGFR and Fyn that lead to downregulation of p53 mRNA and protein levels through a c-Jun dependent mechanism, revealing another mechanism for controlling p53 function[30]. The latest data from the catalog of somatic mutations in cancer (COSMIC; Sanger Institute) indicate that 21% of cSCCs harbor activating Ras mutations (9% Hras, 7% Nras, 5% Kras)[31].

CLINICAL PRESENTATION AND DIAGNOSIS

Common form of cSCC

The most common clinical appearance of invasive cSCC is an actinic keratosis that becomes hyperkeratotic or its base becomes infiltrated, or else becomes tender or exulcerated. While most cSCCs will arise in the context of actinic keratosis, the rate of transformation of AKs into invasive cSCC is apparently low, at least in a few years period of follow-up (less than 1/1,000 per year during a 5-year follow up)[32,33]. Notably, the progression appears to be more frequent in AKs harboring persistent beta papilloma virus infections[34].

When the tumour arises *de novo* or the early keratosis phase is lacking, cSCC can present as an asymptomatic small plaque or nodule that enlarges over time. It can become crateriform ("keratoacanthoma-like"), ulcerated, necrotic, or botryomycotic. Alternatively, patients may present with a flat ulcer with a raised border.

Predilection sites of cSCC are the chronically exposed areas, face (particularly the lip, ear, nose, cheek and eyelid) and the dorsum of the hands. The head and neck region is the prefer-

ential site in males while the upper limbs followed by the head and neck are the more common locations in females.

Tumor extension or infiltration may extend beyond the visible borders of the lesion. SCCs can infiltrate locally and progress gradually through fascias, periostea, perichondria and neural sheaths.

The differential diagnosis of cSCC depends on the tumor location and appearance. Although SCC are usually easily recognized, small lesions or non-keratotic lesions may be confused with basal cell carcinoma, amelanotic melanoma or atypical fibroxanthoma , cSCC of the genital or extremities may be initially interpreted as benign skin lesions, such as warts, i.e., in cases of cSCC of the nail apparatus, HPV-induced papillomas and bowenoid papulosis of the genital area. Pseudoepitheliomatous hyperplasia can mimick SCC developed on chronic inflammation, while metastatic squamous cell carcinoma can only be suspected from the context of the patient's medical history. Malignant adnexal tumors are most often pathological discoveries. Dermoscopy can aid in the differential by revealing diagnostic features such as white circles, white structure-less areas, glomerular or hairpin vessels. A biopsy or excision of the lesion is usually required for a definite diagnosis.

A conceptual differential diagnosis of cSCC is keratoacanthoma, which has been individualized as a less aggressive lesion that simulates cSCC but usually does not metastasize[35]. It presents as a rapidly growing dome-shaped nodule with a central keratin plug and a crateriform appearance that occasionally resolves spontaneously. The tumor has a non-specific but evocative pathological aspect combining a well-defined follicular-centered proliferation with abrupt limits and inflammation. Clinical and histological differentiation of keratoacanthoma from invasive SCC is not always possible even after a complete excision. Often termed "self-healing SCC", keratoacanthoma was earlier presumed to be a pseudo-cSCC. Currently, it tends to be considered

as a true SCC although distinct by means of its less aggressive behavior, especially after being described in patients receiving BRAF inhibitors[36].

Pathological Variants of cSCC

Verrucous SCC of the skin is a particularly well-differentiated form of SCC, demonstrating locally invasive growth but low metastatic potential. It presents as a well-defined, exophytic, cauliflower-like growth that resembles large warts. A number of entities with similar histology are grouped together, according to anatomic location, and are classified as Buschke-Loewenstein tumors (verrucous carcinoma involving the penis, scrotum or perianal region) and carcinoma cuniculatum (verrucous carcinoma on the plantar foot).

Spindle cSCC is a relatively rare form of cSCC, mostly observed on sun-exposed sites in elderly patients[37]. The histologic presence of keratinocyte differentiation is not always evident, complicating the differential diagnosis from other fusiform cell neoplasms (atypical fibroxanthoma, sarcoma, melanoma). Immunostaining demonstrates positivity with cytokeratins, particularly CK5-6 and 34βE12, and epithelial membrane antigen (EMA) by tumor cells, although in some cases both cytokeratin and vimentin may be expressed[38]. The course of spindle cSCC arising on sun-exposed sites is non-aggressive although cases occurring in the setting of radiation therapy have been reported to have a more dismal prognosis.

Desmoplastic SCC is a distinct type of cSCC that is histologically characterized by a highly infiltrative growth, often with perineural or perivascular distribution, in combination with large amounts of stroma and narrow cords of cells. There are no differences of age, gender or anatomic distribution among desmoplastic SCC and the more common types of cSCC, but its rate of recurrence and metastatic potential are high (25% and 10% respectively)[39].

The acantholytic and adenosquamous variants also seem to carry a greater metastatic risk compared to the more common form of cSCC. Acantholytic SCC accounts for 2-4% of all SCC cases and is characterized by the formation of intratumoral pseudoglandular structures resulting from extensive acantholysis. In a series of 49 patients, metastatic disease was recorded in 19% of cases[40]. Adenosquamous SCC is distinguished by the co-existence of malignant keratinocytes, expressing keratin 7, and mucosecretory tubular structures with content positive for mucicarmine and alcian blue. These tubular structures are bordered by atypical cuboid cells, which express the carcinoembryonic antigen (CEA).

HISTOLOGICAL DIAGNOSIS

The diagnosis of cSCC is established histologically. A biopsy or excision and histologic confirmation should be performed in all clinically suspicious lesions. Depending on the size of the tumor and treatment approach, an incisional biopsy, ie, incision, punch or shave biopsy or an excisional biopsy of the entire lesion can be performed initially. Preoperatively, the maximum diameter of the lesion should be recorded. Histologic examination using routine H&E stains are used to confirm the diagnosis. In rare cases of uncertain diagnosis, especially in non-keratinizing tumors, immunohistochemical markers of differentiation, such as cytokeratins, or molecular biological markers can be applied.

The histopathological picture of SCCs reveals strands of atypical keratinocytes originating in the epidermis and infiltrating into the dermis. Morphologic features of differentiation are variably present and include horn pearl formation, parakeratosis and individual cell dyskeratosis. SCCs range from well-differentiated SCCs which show minimal pleiomorphism and prominent keratinization with extracellular horn pearls to poorly differentiated SCCs showing, pleomorphic nuclei with high degree of atypia, frequent mitoses and very few - if any- keratin horn pearls.

In order to facilitate the prognostic classification and correct management of cSCC, the pathology report should also include several well-established prognostic features including histologic subtype ("acantholytic", "spindle", "verrucous", or "desmoplastic" type), grade of differentiation (well-differentiated, moderately differentiated, poorly differentiated or undifferentiated grade), tumor depth (maximum vertical tumor diameter, in mm), level of dermal invasion (Clark's level), presence or not of perineural, lymphatic or vascular invasion, and whether margins are free or involved by tumor cells (along with the minimum distance between the tumor and the resection margin in cases of both complete and incomplete resection) – Table 1.

STAGING WORK UP- CLASSIFICATION –

The suspicion of cSCC should prompt a complete examination of the entire skin and palpation and/or ultrasound examination of the regional lymph nodes for nodal involvement.

Up to date, no satisfactory prognostic classification for primary cSCC has been proposed. The classification and staging of cutaneous SCC is based on the most recent TNM system of the UICC [International Union Against Cancer, 2009] and the AJCC [American Joint Committee on Cancer, 2010] (Table 2-4). These staging systems are not optimal since they have been developed for all head and neck SCCs, which encompass tumors with very different aggressiveness. They also lack extensive validation, as they have been only validated in series of organ transplant recipients with cSCC[41]. In addition, they are short of an accurate prognostic discrimination in certain stages where outcome measures vary significantly. The T1 category is used to define the "low risk" tumors based on a horizontal tumor size of $\leq$2 cm. T2 is used for "high risk" tumors based on a diameter of > 2 cm. Due to the heterogeneity of clinical outcome in T2 tumors of the TNM/AJCC staging systems, an alternate staging system has been proposed that stratifies more accurately this stage in low and high risk tumors based on clinical outcome and prognosis[42]. Four factors are being considered in this system which was validated in a single academic

institution, e.g., 1) poorly differentiated histological characteristics, 2) diameter of 2 cm or more, 3) perineural invasion, and 4) invasion beyond subcutaneous tissue. T2 tumors (with thickness of >2 mm) are stratified into a low risk T2a stage (with one of the above risk factors) with 16% of these patients accounting for all SCC-related events (recurrence, nodal metastasis and/or death) and a high risk T2b with tumors combining 2-3 risk factors and accounting for 64% of all SCC-related events. T3 stage includes tumors that combine all risk factors as well as those with bone invasion (no T4 stage exists in the alternate staging system). Further validation by larger multicenter prospective studies are needed in order to better stratify cSCCs prognostically and delineate those patients that are more in need of adjuvant treatment.

As lymph node involvement by cutaneous SCC increases the risk of recurrence and mortality (survival rate of 30% at 5 years), a lymph node ultrasound is highly recommended (EDF-EADO-EORTC expert consensus), particularly in tumors with high-risk characteristics[43]. In case of clinical suspicion or positive findings upon imaging, a histologic confirmation should be sought either by fine needle aspiration or by open lymph node biopsy. In large infiltrating tumors with signs of involvement of underlying structures (soft tissue, bone), additional imaging tests, such as CT or MRI imaging may be required to accurately assess the extent of the tumor and the presence of metastatic spread. In the TNM/UICC classification scheme, nodal disease was classified in three groups (N1, N2, N3) taking in account only size and number of affected nodes. The AJCC staging systems categorized nodal disease in 5 categories (N1, N2a, N2b, N2c, N3) based on the number (single versus multiple), location (ipsilateral/ contralateral) and size of lymph nodes ($\leq$3cm, 3 - 6 cm, >6 cm). Other factors that may improve prognostic discrimination between patient subgroups include the presence or absence of extracapsular invasion and immunosuppression. The role of micrometastatic disease, evaluated by sentinel lymph node biopsy, is not taken into account in the proposed classification systems so far[44,45].

PROGNOSIS - PROGNOSTIC RISK FACTORS FOR cSCC

The overall prognosis for the majority of patients with cSCC is excellent, with an overall five-year cure rate of greater than 90%, which is much better than other SCCs of the head and neck area. A large single center study of more than 900 patients with cSCC followed for approximately 10 years demonstrated a 4.6% rate of recurrence, 3.7% for nodal disease and 2.1% of disease-specific death[46]. When initial removal is incomplete, cSCC is more likely to recur, mostly locally or less frequently in regional lymph nodes. Approximately 75% of recurrences present within two years and 95% within five years after initial diagnosis[47]. The metastatic risk for cSCCs is low in most patients, not exceeding 3-5% over a 5-year follow up period or even longer[48]. Approximately 85% of metastases involve regional lymph nodes, followed by distant metastases in the lungs, liver, brain, skin and bones.

The risk for locoregional recurrence and distant metastasis are impacted by pathological tumor characteristics (Table 5). Several clinical and histological parameters have been well established as high-risk prognostic factors bearing an increased metastatic potential. These include tumor location (ear, lip, and areas of long lasting chronic ulcers or inflammation), clinical size (> 2 cm), histological depth extension (beyond the subcutaneous tissue), histologic type (acantholytic, spindle, and desmoplastic subtypes), degree of differentiation (poorly differentiated or undifferentiated), recurrence, and immunosuppression. Rate of growth (rapidly versus slowly growing tumors) has been also included in several risk stratification schemes. In addition, margin-positive re-excision (positive re-excision) of incompletely removed cSCC upon primary excision has been identified as an independent risk factor for loco-regional recurrence and should be considered as a high-risk tumor[49]. The recent addition of the maximum vertical tumor thickness measured by histology is supported by evidence showing that tumors with $\leq$ 2mm have 0% metastatic rate compared to tumors of > 2mm thickness which carry a metastatic rate of > 4%,

depending on the actual tumor depth. The presence of perineural invasion is an adverse prognostic factor for cSCC and should also be included in histology reports[40]**.** The estimated prevalence of perineural invasion is 2.4-14%. In a study of 520 patients bearing 967 cutaneous SCCs, the rates of both lymph node metastasis and distant metastasis among patients with perineural invasion were significantly higher than among "perineural-negative" patients (35% and 15% vs 15% and 3%, $p<0.0005$)[50]. However, the caliber of affected nerves may be important, based on recent evidence by which, in the absence of other risk factors, involvement of unnamed small nerves (<0.1 mm in caliber) have a lower risk of poor outcome compared to larger caliber nerves[51].

Among the host factors influencing prognosis, any kind of immunosuppression has the strongest impact. Tumors in immunosuppressed patients demonstrate more rapid growth, an increased likelihood for local recurrence and a 5- to 10-fold risk for metastasis[52,53]. Duration and intensity of immunosuppression play an important role: For example, heart transplant patients carrying an almost 3-fold higher risk than renal transplant patients[54,55].

TREATMENT

Treatment of primary site

The goals of primary treatment of cSCC are the cure of the tumor and the preservation of function and cosmesis.

In patients in which cSCC grows among multiple actinic keratoses and multiple in situ tumors~~,~~ a number of destructive but blind modalities (cryotherapy, curettage & electrodessication, photodynamic therapy with ALA or methyl ALA) or topical agents (imiquimod 5 and 3.75%; 5-fluorouracil 0.5%, 1% and 5%; diclofenac 2.75%, ingenol mebutate 0.05% and 0.015%; chemi-

cal peels) can be employed to “sterilize” the field of cancerization (see EDF guidelines of actinic keratosis)[56].

In cases of clinical uncertainly about invasiveness, i.e., a doubt between in situ tumors and early invasive cSSC, a surgical resection or at least a biopsy followed by histology should always confirm the diagnosis of precancerous lesions before using any therapeutical modality different than surgery.

Surgical excision (at times in combination with plastic reconstruction) is the treatment of choice and by far the most convenient and effective means of achieving cure of any invasive cSCC, as it allows to confirm the tumor type and assess the tumor-free status of the resection margins. Surgery is rarely contra-indicated even in old debilitated patients, or in difficult tumor size and locations with potential functional and cosmetic consequences, if these patients are carefully managed in a daycare hospital setting.

Surgery is also preferable to a panel of other destructive or topical options since failure of these techniques usually leads anyway to surgery a few months or years later in even poorer conditions. However, in a limited number of cases, in which patients cannot or refuse to undergo surgery, destructive (radiotherapy, cryotherapy, curettage & electrodessication, photodynamic therapy with ALA or methyl ALA) or topical modalities (imiquimod 5 and 3.75%; 5-fluorouracil 0.5%, 1% and 5%; diclofenac 2.75%, ingenol mebutate 0.05% and 0.015%; chemical peels) can be used, provided that risks and benefits have been thoroughly explained. In this regard, radiotherapy represents the best alternative to surgery, but cannot be advised as a rule given its side effects and limitations[57,58]. Although neoadjuvant use of oral retinoids (acitretin) may decrease the size of the tumor and reduce the overall tumor load in cases with multiple SCCs, there is currently a lack of supporting evidence from randomized studies[59].

In cases of typical keratoacanthomas, mainly on the face, intralesional chemotherapy (methotrexate, 5-FU, bleomycin) may be considered, although a benefit with respect to side effects, patients' burden and outcome over surgery has never been demonstrated[60,61]. If the resolution is not straightforward, these tumors should be rapidly treated surgically like any other cSCC.

Surgery

The first line treatment of cutaneous SCC is complete surgical excision with histopathological control of excision margins. Surgical removal provides excisional tissue that enables histologic confirmation of the diagnosis and assessment of surgical margins. It also provides very high rates of local control with cure rates of 95%[1].

Although it is important to maintain normal tissue function and satisfactory cosmetic results in sensitive areas (periorificial areas, lips, nose, ears), it is important to be reminded that the main aim of surgical treatment is to obtain complete, histologically confirmed tumor resection in order to achieve local control and ultimately preserve patient survival. Tumors requiring extensive tumor resection and reconstruction should be managed by surgeons with the appropriate surgical expertise.

There are two forms of surgical excision that can be performed in the case of primary cSCCs: standard surgical excision followed by post-operative pathologic assessment of margins (conventional histology that can be obtained both at an intraoperative frozen sections evaluation and at a paraffin-embedded definitive evaluation) and micrographic surgery and its variants (Mohs micrographic surgery, "slow Mohs" technique)[62].

Standard excision with post-operative margin assessment

Excision margins should be adapted to the clinical size and degree of aggressiveness of cSCC, as defined by a number of clinical and histological factors.

It is important to note that both the actinic keratotic and the *in-situ* components of the tumor may not be necessarily taken into account for the assessment of the margins, which must be determined primarily based on the invasive part of the SCC. When using an intraoperative frozen session evaluation, it is often difficult to distinguish the presence of the precancerous versus the in situ of these epithelial tumors. If extensive tissue surgical reconstruction is needed, the precancerous or *in-situ* parts can be managed on a later stage with minimal destructive or topical modalities.

Prospective studies have shown that a 4 mm margin is sufficient to remove 95% of clinically well-defined low risk tumors measuring less than 2 cm in diameter[63]. Larger tumors require larger excision margins since they are more likely to have a greater clinically undetectable microscopic tumor extension. For cSCCs of more than 2 cm in clinical diameter, or for tumors with more than 6 mm thickness, or tumors with other high risk prognostic characteristics (moderate or poor differentiation, recurrent tumor, perineural invasion, extension deep into the subcutaneous layer, and/or location on scalp, ear, lip, scalp and eyelids), a margin of at least 6 mm is considered necessary to obtain the same result[1]. However an extended margin of 10 mm margin seems a safer margin to be obtained according to our expert consensus.

Given the fact that tumor size is only an approximate reflection of the actual degree of tumor aggressiveness, the EDF-EADO-EORTC consensus group recommends a standardized minimal margin of 5 mm even for low-risk tumors, i.e., tumors with a vertical thickness of < 6mm and no high risk factors (Table 6). For small aggressive tumors, ie, $\leq$ 6 mm deep with high risk features, e.g., high histological grade, subcutaneous invasion, perineural invasion, recurrent tumors, and/or tumors at high risk locations (as defined above), an extended margin of 10 mm is recommended[1]. The same applies for tumors with histologic vertical thickness of $\geq$ 6 mm. Wider

excision should be considered when margins appear more limited than described in the pathology report. If a tumor free resection cannot be achieved, postoperative or intra-operative radiation therapy should be considered.

The depth of excision should involve the hypodermis, while sparing the aponeuroses, perichondrium and periosteum, provided that these structures have not been invaded by the tumor[2].

In patients with multiple tumors on the dorsal hands and forearms, *en bloc* excision is the effective treatment. Split thickness skin grafting albeit with the cost of prolonged healing and increased morbidity may be necessary in some patients.

Microscopically controlled surgery

Microscopically controlled surgery (MCS) is a technique that permits the complete assessment of all deep and peripheral margins using intraoperative frozen sections, and whose target is to spare as much tissue as possible while still controlling disease. The excised tissue, which is topographically marked, undergoes a histological analysis using horizontal sections of the tumor in the first description of the technique. If the margins are positive for tumor cells, precisely localized re-excisions are made until the margins are tumor-free. Examination by histopathology is performed either intra-operatively using frozen sections (Mohs surgery) or on paraffin sections ("slow Mohs" surgery). The disadvantages of micrographic surgery include a longer duration of the operations, higher costs and the need for trained and specialized staff. There has been no randomized prospective study comparing micrographic surgery with standard excision in cSCCs. Moreover, comparative studies focusing on long-term recurrent rates did not demonstrate a significant advantage of micrographic surgery[64]. Therefore, MCS can be only considered in selected cases of cSCCs at sites where broad excision margins can cause significant

functional impairment (central areas of the face, lips, ears) and should be performed by a trained staff.

A rationale modern and faster alternative is the intraoperative histological frozen sections evaluation of margins which can be conducted always following a topographical marking of the specimen either through horizontal random sections of the specimen at 2-3 mm thickness each or by analyzing parallel sections of the margins to evaluate the radicality of the procedure [65].

Radiotherapy

Radiotherapy represents a fair alternative to surgery in the non-surgical treatment of small cSCC's in low risk areas, and it generally should be considered either as a primary treatment for inoperable cSCC or in the adjuvant setting[66, 67].

In case of large tumors on problematic locations such as the face or the hands cosmetic and functional concerns about the surgical outcome, as well as the patient's medical background (comorbidities, concomitant medication) may gear the treatment selection in favor of RT. Moreover RT should be discussed as primary treatment option if a R0-resection is technically hardly feasible or for patients who refuse surgery[1,4,66].

RT should be carefully considered in immunosuppressed patients. It is not advised in multiple tumors on severely photodamaged skin, unless the life expectancy is very short, since it will deteriorate the preexisting field cancerization (defined as the presence of multiple clinical and sub-clinical cancerous lesions in chronically UV-exposed sites). RT is not recommended in verrucous SCC as an increased risk of metastasis after RT has been observed in these patients [68].

RT is also contraindicated in patients with genodermatoses predisposing to skin cancer (xeroderma pigmentosum, basal cell nevus syndrome) and with connective tissue disease (scleroderma)[69].

The age of patients and life expectancy should be taken into account in the selection of radiotherapy with regard to rare but possible radiation-induced malignancies[70]. Tumors in poorly vascularized or easily traumatized areas, advanced lesions invading bones, joints or tendons, and lesions in previously irradiated areas are contraindications for RT [67].

Prior to RT, appropriate confirmation of the diagnosis by histology is mandatory. RT can be carried out by means of low-energy photons (contact X-ray therapy), gamma rays (telecobalt), high energy X photons, or electron beams (linear accelerators). The choice of radiotherapy, the dose administered and other technical aspects of the treatment should be considered by an experienced radiation oncologist. The proposed algorithm by the NCCN includes doses of 45–50 Gy in fractions of 2.5–3 Gy for tumors of <2 cm and doses of 60–66 Gy in fractions of 2 Gy or 50–60 Gy in fractions of 2.5 Gy for tumors of >2 cm[4]. Acute side effects (acute radiodermatitis) and late side effects (atrophy, hair loss, pigmentary changes, fibrosis, lymphoedema and telangiectasia) are common and their incidence depends on the type of RT, the area treated, the extent of tumor destruction, the dose delivered and the fractionation, with only few late side effects if the dose delivered in multiple small daily fractions.

Elective nodal surgery and sentinel node biopsy

Elective lymph node dissection is not recommended in cSCC, because of the low probability of metastases in most cases. Although the use of sentinel lymph node biopsy (SLNB) has been investigated in several studies, there are no conclusive data on its prognostic information or the possible therapeutic value[71,72]. A meta-analysis of 19 reports on SLNB in 130 patients with non-anogenital cSCC identified a positive SLN in 12.3% of patients with tumors > 2 cm in diameter[73]. If stratified by AJCC stage, a positive SLNB was found in none of T1 tumors, 11% of T2 tumors and 60% of T4 tumors; for some reason no data were reported for T3 stage. Future prospective studies are needed to assess the prognostic and therapeutic role of SLNB in patients with cSCC

and its potential incorporation in an optimal staging system. Like in patients with melanoma, the current trend favors the use of SLN for complete patient staging for patients in high risk of cSCC (grade 2 and 3).

Treatment of regional (nodal) disease

Surgery

Our comprehensive literature research did not retrieve any reports, which are strictly limited to cSCC; indeed, most reports were on in studies performed in head and neck and mucosal SCC (HNSCC). It is however likely, that despite a lower probability of nodal involvement, nodal metastases, once they occur, should be managed as those of any solid skin tumor (melanoma, merkel cell carcinoma, adnexal carcinomas).

In case of lymph node involvement by cSCC, the preferred treatment is a regional lymph node dissection[2,3,4]. If the nodes within parotid gland are involved, our consensus group supports performing a superficial parotidectomy concominatly with the nodal dissection, as studies have shown an inferior disease-specific survival with radiation therapy alone[74].The typical nodal basins in which the majority of therapeutical lymphadenectomies (TLNDs) are performed are the neck, axilla and groin basins. Few patients experience the possibility of unusual metastatic deposits in the popliteal fossa or in the epitroclear region or in the dorsal posterior triangle on the back. A scientific discussion is ongoing on the definition of what can be considered the standard of care for these patients.

The classic surgical procedure indicates to perform a lymph node dissection of the 5 levels of nodes of the neck, of the 3 levels of Berg of the axilla and of the superficial, deep inguino-femoral and ilio-obturatory nodes after a positive node or SN has been identified in these basins (see addendum 1 on detailed surgical aspects of lymph node dissection).

For all tumors not amendable by surgery, the readers are asked to see the section below on ‘Treatment of locally advanced and metastatic SCC“. In such cases, however, a re-evaluation of the possibility of a complete surgical resection subsequent to radiation is recommended[4].

Adjuvant treatment

Adjuvant radiation therapy

Adjuvant or post-operative RT should be considered in the following situations: (i) cSCC with substantial perineural involvement, and (ii) when tissue margins are not tumor free after surgical excision and further surgery is not possible or unlikely to completely eradicate the tumor[2,3,4]. Studies in patients with parotid lymph node involvement experience an improved relapse-free survival by a combination of surgery and RT compared to each modality alone[75,76,77].

The recommended dose of RT is 45-55 Gy in daily fractions of 2.0 to 2.5 Gy.

Adjuvant RT should be also considered in all patients with regional disease of the head and neck, trunk or extremities who have undergone lymph node dissection, particularly if multiple nodes are affected or if extracapsular involvement is observed. In cases with nodal disease of the head and neck that involves only a small node and no extra-capsular involvement observation is a reasonable alternative to RT[4].

Adjuvant systemic treatment

There are no solid data to support the use of adjuvant systemic treatment in cSCC. In a phase III randomized trial of adjuvant 13-cis-retinoic acid (13cRA; dose of 1 mg/kg/d orally) plus interferon alpha (IFN-alpha; 3 x 10(6) U subcutaneously three times per week) for 6 months following surgery and/or radiation therapy in patients with aggressive cSCC, there was no improve-

ment of time to recurrence or time to second primary tumors in the treatment versus the control group[78].

Treatment of locally advanced and metastatic SCC

Our comprehensive literature research only retrieved a few reports, which are strictly limited to cSCC, particular for stage IV disease; indeed, most reports were on in studies performed in head and neck SCC (HNSCC). It is however likely, that despite a lower probability of distant metastases, once they occur they should be managed as for those of any SCC of the head and neck.

Surgery/ radiation therapy/electrochemotherapy

Satellite or in-transit metastases around the primary site should be removed surgically if the number, size and location allow a complete removal of the metastatic sites. RT alone or in combination with chemotherapy may be used as an alternative option when surgery is not feasible. RT is particular helpful as a palliative treatment, in order to relieve pain and to stop hemorrhage as well to limit the extension of the tumor to adjacent critical areas such as the orbita or oral cavity.

Electrochemotherapy is a treatment modality that can find indication in locally advanced lesions. It helps to control the progression of inoperable loco-regional SCC recurrences with the benefit of controlling bleeding lesions and of reducing painful symptoms when present. The two most commonly used drugs in electrochemotherapy are bleomycin and cisplatin. Its application requires a day-hospital planning or a short admittance for a short procedure in the surgical room. Various reports indicate its efficacy in controlling the disease in terms of local response in a range of 20-70% of cases[79].

Systemic treatment of locally advanced and metastatic cutaneous SCC

In many respects, the data situation is still patchy. Most published reports represent small case series or isolated observational studies. A pooled analysis of 28 observational studies involving 119 patients with advanced, non-metastatic cSCC using diverse treatment modalities, ie, chemotherapy, biologic response modifiers, targeted agents, demonstrated an overall response rate of 72%[80]. However, such retrospective analyses are intrinsically hampered by a strong publication bias towards responding patients.

Chemotherapy

Stage IV cSCC can be responsive to various chemotherapeutics, however, there is no established standard regimen. The following chemotherapeutic agents that have been used in cSCC: platin derivates (ie, cisplatin or carboplatin), 5-fluorouracil, bleomycin, methotrexate, adriamycin, taxanes, gemcitabine or ifosfomide alone or in combination. Notably, remission rates of up to 80% have been reported for combined treatments and monochemotherapy still may achieve remissions in up to 60% (e.g. with 5- fluorouracil)[81,82,83,84,85]. However, it is important to note that these responses rates were neither observed within controlled trials nor confirmed by subsequent studies. Thus, as already mentioned above, a possible publication bias should be kept in mind. Moreover, the responses are mostly short lived and are followed by rapid recurrence and do not lead to a curative effect. Table 7 summarizes the results of the reported prospective studies.

Palliative systemic chemotherapy is indicated in patients with distant metastases, but especially given the toxicity of most chemotherapy agents should be adjusted for elderly patients (limited liver and renal function as well as hematopoiesis). It is essential to take into account the princi-

ples of geriatric oncology[86]. To avoid chemotherapy-induced toxicity besides dose adjustments prophylactic supportive measures should be considered, including, the use of hematopoetic growth factors, as well as analgesic and antiemetic support. In general, polychemotherapy should be reserved for cases requiring more aggressive management while otherwise mono-chemotherapy, e.g. with 5-fluorouracil (or its oral analogue capecitabine), should be considered as a first-line treatment[87].

Biologic response modifiers

Currently there is no supporting evidence for the use of biologic response modifiers in advanced cSCC outside the framework of clinical trials as first line treatment. Two phase II studies using a combination of interferon alpha-2a at a dose of 3-5 10^6 U three times per week, and 13-cis-retinoid 1 mg/kg body weight daily, with or without cisplatin showed some clinical activity in extensive locally advanced disease[88,89]. Mild to moderate fatigue, mucocutaneous dryness, moderate to severe neutropenia were the most common side effects.

Targeted therapies - EGFR inhibitors

EGFR inhibitors such as cetuximab, currently approved for the treatment of metastasized head and neck SCC, should be discussed as second line treatments after mono- or polychemotherapy failure and disease progress. Participation of patients with metastasized cSCC in clinical trials should be encouraged as treatment of choice if possible, taking into consideration the limitations of chemotherapeutic regiments due to associated toxicity and advanced age of the patients.

The relevant role of epidermal growth factor receptor (EGFR) signalling in tumorigenesis has been demonstrated in a variety of human cancers. Activation of EGFR has been observed in

cSCC, while its overexpression has been associated with a worse prognostic outcome[27,90]. Consequently, inhibition of EGFR signaling has been tested as treatment for metastatic SCCs. EGFR inhibitors, either as monocloncal antibodies (cetuximab, panitumumab) or small molecule kinase inhibitors (erlotinib, gefitinib, dasatinib), have been approved for the treatment of HN SCCs. Initially, the chimeric mAb Cetuximab demonstrated encouraging results in the treatment of cSCC in anecdotal case reports. Supporting evidence from a phase II study of 36 patients with unresectable cSCC treated with cetuximab at an initial dose of 400 mg/m^2 body surface followed by weekly doses of 250 mg/m^2 for at least 6 weeks, showed an objective response rate of 25% (3% complete and 22% partial responses) and a disease stabilization in 42%[91]. On the other hand, a randomized phase III study of 117 patients with metastatic HNSCC revealed that the addition of weekly cetuximab to a standard regimen of cisplatin every 4 weeks improved response rates but did not have any significant effect on progression-free and overall survival [92]. In a phase II study, gefitinib (250 mg/day) was used for 2 cycles as a neo-adjuvant treatment followed by surgery and/or radiotherapy (plus maintenance gefitinib for 12 months) in 23 patients with locally aggressive cSCC showing an overall response rate of 45.5% (CR= 18%, PR= 27.3%), a 2-year disease-specific survival rate of 72% and a progression free survival rate of 63%[93]. However, neo-adjuvanant treatment strategies are currently not advised outside the framework of clinical trials as a standard of treatment. In the metastatic setting the available data on gefitinib efficacy are even less conclusive.

FOLLOW-UP

It is estimated that about 30-50% of patients with cSCC are at risk to develop another one within 5 years. In addition, the majority of all cSCC recurrences will develop within 2 years of the initial intervention. For these reasons, patients with cSCC should be followed closely, particularly during the first years after diagnosis (Table 8). In addition, a regular self-skin and lymph node ex-

amination should be performed by patients in order to detect early any local recurrences, nodal disease or new cSCCs.

There is no standardized follow-up schedule for patients with cSCC. Follow-up examination is largely based on risk ascertainment of second cSCCs, local recurrences or metastatic spread. Thus, the entire integument of patients should be examined once annually. In high risk cSCCs, (> 2 cm diameter, deep infiltrating tumors, high histological grade, perineural involvement, recurrent tumors, location on the lip or ear) the skin examination should be supplemented by palpation of the primary excision site and of the regional lymph nodes every 3 months for the first 2 years, every 6 months for an additional 3 years and annually thereafter. In case of uncertain findings, a lymph node ultrasound should be performed[1]. In patients with locally advanced tumors and loco-regional metastases, ultrasound examination of the draining lymph node region every 3 months is advised.

A close follow-up schedule, such as every 6 months, should be applied in patients at high risk for new tumors (immunosuppression, genetic predisposition, prior multiple cSCC), depending on the total number of tumors, the frequency of development of new tumors and the aggressiveness of these tumors, based on clinical and histological criteria.

PREVENTION

In patients with precancerous lesions, early detection and intervention is critical in order to prevent the development of invasive cSCCs. Education on sun avoidance and sun protection measures (protective clothing, sunscreens) is essential. The protective effect of high SPF, broad UV-A/B coverage sunscreens in the prevention of new cSCCs has been well established in prospective studies[94], while the role of diet, vitamin D supplementation, statins and non-steroidal anti-inflammatory agents as chemopreventive agents are currently under investigation.

Treating field cancerization in photo-damaged skin is an attractive objective that aims at preventing the development of cSCC. Photodynamic therapy, ingenol mebutate, topical 5-fluorouracil, or imiquimod are increasingly used for this purpose. However, there is still very limited evidence that this indeed results in prevention of cSCC[95,96].

In patients at high risk of developing precancerous and malignant lesions, e.g., organ transplant recipients or PUVA-treated patients, the use of oral retinoids (acitretin or isotretinoin) has been shown to be effective in reducing tumor load and in slowing the formation of new lesions, in the cost of significant side effects, mainly affecting quality of life, but also including teratogenesis in female patients of child-bearing age[97,98]. An indication of retinoids as a chemopreventive agent may include patients on BRAF inhibitors developing multiple cSCCs[99]. Therapeutic effects disappear shortly after cessation of the drug. If a patient is an immunosuppressed transplant recipient with a life-threatening SCC or multiple, rapidly developing tumors, then a dose reduction of the immunosuppressive agent and/or a change from calcineurin inhibitors or antimetabolites to mTOR inhibitors is recommended[100].

TABLES

Table 1. Basic features included in the histopathologic report of a cutaneous squamous cell carcinoma (cSCC) diagnosis (modified from Bonerandi et al, 2012[2]).

HISTOPATHOLOGIC REPORT		
Histologic subtype:	☐ Common ☐ Verrucous ☐ Desmoplastic ☐ Acantholytic	☐ Adenosquamous ☐ Basosquamous ☐ Other:
Histological grade	☐ Well differentiated ☐ Moderately differentiated ☐ Poorly differentiated ☐ Undifferentaited	
Maximum tumor thickness	.....mm	
Clark level	☐ <IV (above subcutaneous fat) ☐ >IV(below subcutaneous fat)	
Perineural invasion	☐ No ☐ Yes	
Lymphatic/vascular invasion	☐ No ☐ Yes	
Complete excision:	☐ Yes ☐ No	
Minimum lateral margin: Minimum deep margin:	.....mm .....mm	

Table 2. TNM classification of invasive cutaneous squamous cell carcinoma based on the UICC [2009/2010] (without including tumors on the eyelids, penis, or vulva).

UICC TNM classification	
T classification	
T1	Tumor ≤2 cm at largest horizontal width
T2	Tumor >2 cm a largest horizontal width
T3	Deep infiltration (skeletal muscle, cartilage, bone)
T4	Infiltration of the skull base or vertebral column
N classification	
Nx	Regional lymph nodes cannot be evaluated
N0	No regional lymph node metastases
N1	Solitary lymph node metastasis, maximum diameter <3 cm
N2	Solitary lymph node metastasis, maximum diameter ≥3 cm to max. 6 cm Multiple lymph node metastases, all with a max. diameter ≤6 cm
N3	Lymph node metastasis, diameter >6 cm
M classification	
M0	No distant metastases
M1	Distant metastases

Table 3. TNM classification of invasive cutaneous squamous cell carcinoma based on the AJCC [2010] (without including tumors on the eyelids, penis, or vulva).

AJCC TNM classification	
T classification	
T1	Tumor ≤2 cm at largest horizontal width +0–1 high-risk feature
T2	Tumor ≤2 cm at largest horizontal width +2–5 high-risk features **or** tumor >2 cm a largest horizontal width
T3	Infiltration of facial and cranial bones
T4	Infiltration of skeletal bone or skull base
N classification	
N0	No regional lymph node metastases
N1	Solitary, ipsilateral lymph node metastasis, maximum diameter ≤3 cm
N2a	Solitary, ipsilateral lymph node metastasis, maximum diameter >3 cm to max. 6 cm
N2b	Multiple, ipsilateral lymph node metastases, all with a maximum diameter ≤6 cm
N2c	Multiple, ipsilateral or contralateral lymph node metastases, all with a maximum diameter <=6 cm

N3	Lymph node metastasis, diameter >6 cm
M classification	
M0	No distant metastases
M1	Distant metastases

Table 4. Clinical stage based on AJCC-TNM classification

Clinical Stage			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Every T	N3	M0
	T4	Every N	M0
	Every T	Every N	M1

Table 5. Prognostic risk factors in primary cutaneous squamous cell carcinoma

	Tumor Diameter	**Location**	**Depth/level of invasion**	**Histologic features**	**Surgical margins**	**Immune status**
Low risk	Less than 2 cm	Sun exposed sites (except ear/lip)	Less than 6 mm / invasion above subcutaneous fat	Well-differentiated Common variant or verrucous	Clear	Immunocompetent
High risk	More than 2 cm	Ear/lip Non-sunexposed sites (sole of foot) SCC arising in radiation sites, scars, burns or chronic inflammatory conditions Recurrent SCCs	More than 6 mm/ invasion beyond subcutaneous fat	Moderately, or poorly differentiated grade Anantholytic, spindle, or desmoplastic subtype Perineural invasion	Incomplete excision	Immunosuppressed (organ transplant recipients, chronic ummunosuppressive disease or treatment)

Table 6. Recommended excisional margins on the basis of vertical tumor thickness of cSCC.

Level of risk	**Tumor characteristics**	**Metastatic rates**	**Excisional Margins, EDF-EADO-EORTC recommendations**
Minimal risk	Vertical tumor thickness ≤ 2 mm	0 %	5 mm
Low Risk*	Vertical tumor thickness 2.01–6 mm	4 %	5 -10 mm (depending on additional risk factors)
High risk	Vertical tumor thickness >6 mm	16 %	10 mm

* Should be managed as high risk tumors when combined with additional unfavorable prognostic factors, such as > 2.0 cm in clinical diameter, high histological grade, localization on ear, lip, perineural invasion, recurrence, immunosuppression.

Table 7. Synopsis of prospective studies of systemic therapies in advanced or metastatic cSCC (adapted from Breuninger et al, JDDC 2012[1])

Reference	Trial Design	Patients	Chemotherapy	RR	Comments
Chemotherapy					
Cartei et al, 2000	Prospective Observational	14	Oral 5-FU 175mg/m2 for 3 weeks every 5 weeks	2 PR (14.3%) 7 SD (50%)	Aggressive, multiple, recurrent SCCs in aged patients
Sadek et al, 1990	Prospective observational	14/13 evaluable	Cisplatin bolus injection 5-FU and Bleomycin continuous 5-day infusion	4 CR (30%) 7 PR (54%) 2 SD (16%)	Advanced SCC of the skin or lip
Guthrie et al, 1990	Prospective Observational	12	Cisplatin and doxorubicin (n=7) Neoadjuvant to surgery or radiation (n=5)	4 CR (33%) 3 (PR) (25%)	
Khansur et al, 1991	Prospective observatonal	7	Cisplatin and 5-FU every 21 days	3 CR (43%) 3 PR (43%) 1 SD (14%)	
1976	Phase III randomized control trial	70 advanced SCC – 6 cutaneous SCCs	Bleomycin twice weekly vs other cytotoxicdrugs	39% RR	Only 3 patients with cSCC in the treatment arm
Targeted therapies/ EGFR Inhibitors					
Maubec E, et al 2011	Phase II uncontrolled trial	36	Cetuximab administered weekly	2 CR 8 PR	Unresectable or metastatic cSCC. Chemotherapy-naive patients.

				25 DCR (disease control rate)	
Glisson B, et al 2006	Phase II uncontrolled trial	18/17 evaluable	Gefitinib orally for 4 wks	4 SD	
Lewis CM, 2012	Prospective phase II clinical trial	23/22 evaluable	Gefitinib for 2 cycles prior to surgery and/or radiotherapy (plus maintenance gefitinib for 12 months)	4 CR 6 PR 5 SD 7 PD	Aggressive cSCC of the head and neck
Heath CH et al, 2013	Non randomized single-arm phase I clinical trial	15	Erlotinib combined with postoperative adjuvant therapy	2 year OS 65% 2 year DFS 60%	
Kalapurakal SJ, et al 2012	Retrospective study	4	Cetuximab administered weekly	3 CR 1 PR	Recurrent cSCC with a history of multiple recurrences in the past
Read W, 2007	Case report	3	Erlotinib for 1-3 months	1 CR 1 PR 1 PD	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

Table 8. Follow – up time schedule for patients with cSCC proposed by EDF-EADO-EORTC

	Clinical examination	**Imaging examination**	**Main risk to be covered**
Low risk primary	1st -5th year: every 12 months		Low risk of new skin cancers
High risk *primary	1st- 2nd year: every 3 to 4 months 3rd-5th year: every 6 months After 5th year: annually	Lymph node U/S recommended at time of clinical examination during 2 years.	Low risk of new skin cancers Low risk of regional metastases
Advanced or regional disease	Every 3 months for 5 years Like high-risk primary thereafter	Lymph node U/S every 3 to 4 months and imaging every 6 months during 5 years	Mainly high risk of regional and distant metastases
High risk (immunosuupression) **	Every 6 months life long + according to the different primary tumors		Mainly very high risk of new skin cancers

* > 6 mm histological depth or ≤ 6 mm depth with at least 2 high risk features, such as: > 2cm clinical diameter, perineural involvement, invasion at level beyond subcutaneous fat, moderately to poorly differentiated tumors, recurrent tumors, tumors located on the ear, lip, immunosuppression.

** transplanted patients or with xeroderma pigmentosum

Addendum 1: Surgical aspects of lymph node dissection in nodal disease

The neck dissection consists in the ablation of the nodes of the 5 levels. The parotid gland is included into the specimen when a primary SCC originates on the face or on the scalp between the eye and the mastoid regions. But not all investigators proceed with the dissection of the five levels of nodes if the metastatic nodes are not directly in the parotid gland. Similarly the indication of performing the dissection of the submental mandibular (level I-II) nodes can be avoided when the metastases lie in the posterior triangle (V level) nodes.

There are 3 levels of dissection in the groin. Superficial groin dissection captures node-bearing tissue between the superficial fascia and the fascia lata, in a triangular area bound by the adductor longus medially, the Sartorius laterally, and the inguinal ligament superiorly, also called the Scarpa triangle. The fascia lata is continuous with the fascia overlying the Sartorius and adductors, an easily identifiable plane defining the deep border of dissection and the roof of the femoral canal. The tissue superficial to the fascia lata has the greatest number of inguinal nodes, draining most of the cutaneous portion of the lower extremity. A deep groin dissection includes the same areas, but also encompasses the tissue within the femoral sheath, deep to the fascia lata, containing few more deep inguinal nodes, as well as several lymphatic channels. This requires skeletonization of the femoral vessels and increased associated morbidity. Both areas of dissection include excision of Cloquet's node at the superior end of the dissection along the femoral canal, usually located between the femoral vein and the Cooper's ligament. The saphenous vein is usually sacrified in both cases, but surgeons may also decide to preserve it as usually it does not compromise the oncological radicality of the procedure. The iliac and obturatory dissection accompanies the groin dissection, it involves the dissection of both the obturatory and the nodes along the external iliac vessels from the inguinal ligament to the

origin of the internal iliac artery. This tecnique requires skeletonization of the external iliac vessels until the biforcation of the common iliac vessels.

The dissection in this area is associated with significant morbidity. Overall morbidity rates have been reported between 17% and 90%, with incidence of wound infection of 13–33%, seroma formation, skin flap necrosis, and long lasting limb lymphedema. It is important to mention that this wide range for morbidity can be also due to lack of uniform evaluation criteria.

The axillary dissection is characterized by the dissection of the nodes lying between the media aspect of the dorsal muscle, to the lateral aspect of the minor pectoralis muscle representing the first level of Berg nodes, followed by the dissection of the nodes lying below the minor pectoralis muscle representing the second level of Berg nodes and concluding the dissection of the nodes lying between the medial aspect of the minor pectoralis muscle and the subclavear tendon which is just in correspondence of the axillary vein entering in the chest wall and representing the limit of the third level of Berg nodes. The minor pectoralis muscle can be easily preserved without compromising the quality of the surgical radicality. The procedure should be completed by excising the Rotter nodes located in the space in between the two pectoralis muscles and the nodes between the axillary vein and the subclavear fossa.

Disclosure of Potential Conflicts of Interests

Dr. Bastholt reports personal fees from Astra-Zeneca, personal fees from Bristol Myers Squibb, personal fees from Roche, personal fees from Merck, outside the submitted work; Dr. Becker reports personal fees from Amgen, personal fees from LEO, personal fees from MSD, personal fees from Merck Serono, personal fees from Roche, personal fees from Glaxo Smith Kline, outside the submitted work; Dr. Garbe reports personal fees from Amgen, grants and personal fees from Bristol Myers Squibb, grants and personal fees from Glaxo Smith Kline, personal fees from Merck, personal fees from Novartis, grants and personal fees from Roche, outside the submitted work; Dr. Grob reports personal fees from Meda, personal fees from LEO, personal fees from Galderma, personal fees from Almirall, personal fees from Roche,outside the submitted work; .Dr. Lebbé reports personal fees from Bristol Myers Squibb, personal fees from Merck, personal fees from Roche, personal fees from Novartis, personal fees from Glaxo Smith Kline, personal fees from Amgen, outside the submitted work; .Dr. Malvehy reports personal fees from LEO, personal fees from Almirall, personal fees from MEDA, personal fees from ISDIN, outside the submitted work; Dr. del Marmol reports personal fees from LEO, personal fees from Roche, personal fees from MEDA, personal fees from AbbVie, outside the submitted work; Dr. Middleton reports personal fees from Millenium, personal fees from Amgen, personal fees from Roche, personal fees from Merck, personal fees from Glaxo Smith Kline, personal fees from Bristol Myers Squibb, outside the submitted work; Dr. Pehamberger reports personal fees from LEO, personal fees from Almirall, personal fees from Roche, personal fees from Bristol Myers Squibb, outside the submitted work; Dr. Peris reports personal fees from LEO, personal fees from MEDA, personal fees from Roche, personal fees from Novartis, personal fees from AbbVie, outside the submitted work; .Dr. Saiag reports personal fees from Merck, during the conduct of the study; personal fees from Bristol Myers Squibb, personal fees from Glaxo Smith Kline, personal fees from Merck, personal fees from Novartis, grants and personal fees from Roche, outside the submitted work; Dr. Stratigos reports personal fees from LEO, personal fees from Novartis, personal fees from Roche, personal fees from MEDA, grants from Jannsen-Cilag, personal fees from Pfizer, personal fees from AbbVie, outside the submitted work; Dr.Tesstori declared that he has no conflict of interests. Dr. Zalaudek reports personal fees from Bristol Myers Squibb and LEO, during the conduct of the study; personal fees from LEO, personal fees from Almirall, personal fees from Roche, personal fees from Bristol Myers Squibb, outside the submitted work

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