THESIS

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Evaluation of epidemiologic and morphologic data of facial lesions in a cohort of patients from South Italy

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Glossar and abbreviation

NMSC – Non melanoma skin cancer

SL – Solar lentigo

LPLK – Liken planus like keratosis

SK – Seborrheic keratosis

AK – Actinic Keratosis

BD – Bowen's desease

BCC – Basal cell carcinoma

SCC – Squamous cell carcinoma

LM – Lentigo maligna

LMM - Lentigo maligna melanoma

NM – Nodular melanoma

TE - Trichoepitelioma

Abstract

Rational:

Syracuse is a city located in the South of Sicily, a region with high solar radiation during most of the year. The chronic sun exposure mostly leads to facial photoaging, which is associated with different forms of skin tumors (both benign and malignant). The aim of this study is to evaluate the frequency, localization and subtype of these facial lesions.

Materials and methods:

All patients, who visited the private medical office "Studio Medico Farina" with the recent onset facial skin lesion between June 2012 and March 2015, were included. The following parameters were recorded for each patient: age, sex, skin phototype, history of melanoma or non-melanoma skin cancer, co-morbidities, previous medical treatments, location of the new lesion on the face, clinical and dermoscopic diagnosis and, if available, histopathological diagnosis were recorded. The physician made a diagnosis based on the clinical and dermoscopic examination and proposed a treatment strategy (surgery, no intervention, follow-up). Each lesion has been evaluated by two physicians with more than 10 year of training in dermoscopy and dermato-oncology. Data were collected from the first and second observer and compared to determine diagnostic agreement. The agreement assessed by Cohen's Kappa calculation.

Results:

A total of 246 patients with 296 lesions (125 male; 50.81% and 121 female; 49.19%) and with a mean age of 68 years were evaluated. Most of the patients (35.37%) felt into the age group ranging from 71 to 80 years old. Comparing the age groups, the incidence of precancerous and cancerous lesions (in particular AK and BCC and to lesser extend cSCC) doubled in the age group 71 to 80 years. The prevailing phototype of the patients was skin type III (141 patients; 57,32%), followed by phototype II (80 patients; 32,53%) and finally phototype IV (25 patients; 10,16%). For 81 lesions (33%) a histopathological examination was performed. The following lesions were found according to frequency: basal cell carcinoma (n=87/296; 29.4%) actinic keratosis (n=67/296; 22.6%), liken planus like keratosis (n=17/296; 5,7%), lentigo maligna: n=12; 4,1%), squamous cell carcinoma (n=11/296; 3,7%), Bowen's disease (n=1; 0,3%), and trichoepithelioma (n=1 ;0,3%).

Conclusion:

This study confirms that chronically photodamaged areas are at higher risk of developing a non-melanoma skin cancer (NMSC) and the risk is higher in in the population between 71 and 80 years old.

Introduction

The entire human organism ages over time, while changes in internal organs are mostly due to biological processes, facial ageing is accelerated by environmental factors such as chronic UV-exposure. This can lead to an increase of various benign and malignant skin tumors, as UV radiation alters the anti-tumour immune response, which plays an important role in the removal of tumour cells, contributing to cancer progression and development. (1-2)

It is well known that the incidence of several skin cancers increases in regions exposed to cumulative UV exposure (e.g., face, décolleté).
The skin of the head and face is usually often exposed to sunlight, leading to damages as UV-radiation causes the expression of apoptosis-related molecules resulting in genomic alterations. Typical skin changes observed in these regions are the solar elastosis, deep wrinkles and pigment shifts (i.e., freckles and lentigo solaris).

These alterations can progress into (pre) malignant changes like actinic keratoses, Bowen's disease, squamous cell carcinoma, basal cell carcinoma and melanoma. (3)
The aim of the thesis presented herein was to evaluate the most common facial skin diseases in a group of adults attached to a medical practice in Syracuse.

Benign Facial Lesions

Solar Lentigo

Clinical aspect

Solar Lentigo is a benign, acquired, pigmented macule and is a cluster of pigments on the skin. It may appear as single lesion, bur mostly multiple lesions are observed. It is mostly present on skin exposed to natural or artificial UVR such as the face or the back of the hand, but can also appear in areas protected from the sun. (5) The prevalence is in increasing with age; for example, 90% of the Caucasian population over 60 years have at least one solar lentigo. with a smooth or irregular edge and appears on sun-exposed skin. (4) The prevailing color is light brown; dark brown or black color is seldom seen and mostly linked to darker skin types. The lesions are typically flat, oval to

round, well circumscribed and partially bizarrely configured. Their presence is a risk factor for melanoma and non-melanoma skin cancer. (5)

Dermoscopy

The main dermoscopic aspect of solar lentigo are in order, homogeneous pigmentation ranging from light brown to dark brown in the absence of dermoscopic structures;
Moth-eaten border, characterized by sharply demarcated border that often present curvilinear recesses. Fingerprint-like areas, like dermatoglyphics, consist of light or dark brown color parallel lines.

Histopathology

It is observed in club-shaped network ridges with small nub-like extension, increased pigmentation in basal keratinocytes and increased numbers of melanocytes.

Treatment

Solar lentigo is treated for aesthetic purposes by procedures such as q-switch lasers, cryotherapy or chemical peels. However, it should be noted that a solar lentigo may be clinically mistaken for malignant Lentigo or vice versa, especially when it presents with a solitary spot. (6)

Seborrheic Keratosis

Clinical aspect

The morphological spectrum of seborrheic keratosis is highly variable. They can be single or multiple, light brown or black plaques, early lesion are usually flat light brown, in the time forms a keratotic surface and sharp edges.

Are found in people over 30 years subjects but they can also be seen in young adults (from the age of 20), tend to increase in number and size over the years.
Although they may be found in any region of the body (with except of the palms and soles), they are common on the face, chest and the back. (11)

They are usually numerous and appear as sharply demarcated, round or oval, flesh-colored or brown-black warty plaques with a rather greasy texture.
Sometimes they are dome-shaped with a smooth surface and they can have features like an inflammatory halo or eczematous changes (Meyerson's phenomenon). (7-10)

Occasionally, deeply pigmented or traumatized lesions are mistaken clinically for melanoma. Irritated seborrheic keratoses (inverted follicular keratosis) are challenging lesions and present as a warty papulo-nodule. This commonly affects elderly males and affects face. (12)
The clinical diagnosis is easy in most cases. However, the differentiation to other tumors like pigmented BCC, lentigo maligna or pigmented actinic keratosis may be challenging. In such cases dermoscopy can facilitate the diagnosis.

Dermoscopy

Early-flat SK show an appearance of curved brown lines/fingerprint pattern.
The most frequent dermoscopic aspect of a non initial SK is: milia-like cysts, white or yellow round structures with a bright appearance and more evident under non polarized light. Milia-like cysts, however, can also be seen in congenital nevi, basal cell carcinomas and melanoma.
Comedo like openings are round or oval brown openings. Histologically correspond to a keratin-filled invagination on the skin surface and can also be found in melanoma and inflammatory skin deseases (lichen sclerosus).
If there are fissures, ridges, brown or black straight comedo-like openings within the lesion in large number they give a cerebriform appearance.
Fingerprint like network structures, seen in early SK, are tiny ridges running in parallel arrangement.
Hairpin blood vessels, surrounded by a whitish halo of keratin, aspect typically observable in case of non pigmented SK. (13)

Histopathology

Characterized by exophytic proliferation of basaloid keratinocytes with hyperkeratosis, acanthosis and papillomatosis, keratin plugs and keratin islands are common features.

Treatment

The treatment of SK is also just for aesthetic purposes; cryotherapy, curettage, CO2-laser or in rare cases an excision can be applied.

Ink spot lentigo

Clinical aspect

Ink-spot lentigines typically appear in fair-skinned individuals on sun-exposed regions and clinically present as single, dark-brown to black pigmented, sharply demarcated macule with peripheral extensions.

Dermoscopy

It is characterized by a black reticulated pattern, with thin o thick lines in the same lesion, which stop abruptly at the edge of the lesion ("broken-up lines") a very important dermoscopic feature.

Histology

Lentiginous hyperplasia with marked basal cell hyperpigmentation and characteristic achromic skip area. (14)
This is a benign type of lesion and surgical intervention is rarely applied for diagnosis.

Lichen planus like keratosis

The lichen planus like keratosis, also called lichenoid keratosis, it is considered as an early acutely inflamed and later regressive form of solar lentigo or seborrheic keratosis.

Clinical aspect

Subject most affected by LPLK are caucasian female between the ages of forty and seventy. (15)
The most common locations are face, neck and the upper trunk.
Lichen planus-like keratosis usually presents a solitary brown to red or gray macule of flat plaque, there may be multiple lesion in some cases. The diameter ranges from some mm to one centimeter and more and the outline is frequently irregular.

The surface is often scaly and lesions are generally asymptomatic but sometimes could give a mild pruritus. (12)
The differential diagnosis mainly includes pigmented actinic keratosis, lentigo maligna, bowen's desease or superficial basal cell carcinoma. (16)

Dermoscopy

The dermoscopic aspect varies depending on the stage; in early stages dermoscopy features included light brown pseudonetworks due to residual solar lentigo and overlapping pinkish areas attributed to lichenoid inflammation.
Over the time dermoscopic findings are found: light brown pseudonetwork, pinkish area, gray pseudonetwork, annular granular structures, and blue-gray fine dots sometimes arranged in a reticular way (granular dust), we can find also a pattern similar to a gray pseudo pigment network (especially on the face) annular granular structures and gray pseudonetwork appeared to be the main features of the regressing stage; these features seemed to progress to "blue-gray fine dots" in the late regressing stage. (17)
The gray granules correspond to melanophages in the upper dermis. They can be arranged regularly or irregularly.
Although dermoscopy is greatly effective to diagnose, histopathological evaluation is often required in order to determine the type of lesión.

Histology

The features are similar to lichen planus, is observed hyperkeratosis, hypergranulosis, variable acanthosis, basal cell liquefactive degeneration, typically present chronic inflammatory cell infiltrate in the superficial dermis. (18-19)

Treatment

The treatment of LPLK varies according to the clinical and dermoscopic context. Lesions showing a clear clinical and dermatoscopic aspect need a close long term observation supported by dermatoscopic images taken at the time of the first evaluation.
In case of lesions uncertain under dermatoscopyc observation, is needed a deeper histological diagnosis after biopsy.

The problem with lesions that show complete regression is that histology will not give clear indications, in which case careful clinical monitoring of the affected area over time is appropriate.

MALIGNANT FACIAL LESIONS

Actinic keratosis and field of cancerization

Actinic keratosis is an intraepithelial neoplasm, usually presenting as multiple, scaly lesions in sun-exposed regions in middle-aged or elderly patients.
The incidence is rising worldwide mostly due to increasing levels of UVR exposure, lifestyle and demographic changes.
Epidemiological studies indicate that the prevalence of AK increases constantly with increasing age, with rates ranging from 10% between the age of 20–29 years to 80% in those of 60–69 years old.
They are more common in man than in women and especially in those with fairy skin type. (26).
AK were considered as premalignant lesions for a long time; however, these lesions were recently redefined as malignant neoplasm and a nowadays considered as as squamous cell carcinomas in situ and may be precursors of invasive squamous cell carcinoma. (20)
The knowledge and the treatment of actinic keratosis is important, because it is a sensitive indicator of exposure to UV light and strongly predicts the likelihood of developing cutaneous squamous cell carcinoma. (21)
Based on scientific studies only an estimated 0.1-10% of actinic keratosis is thought to become an invasive squamous cell carcinoma. (21) On the other hand, the chance of developing an invasive squamous cell carcinoma in patients with 10 or more actinic keratosis has been estimated to be 14% over a period of 5 years. (22-25)
The main risk factor for developing AK is the cumulative UV-exposure. It was recently discovered that sun exposure is particularly important during childhood. (26).
Other risk-factors include phototypes from I to III, life in a rural residence after the age of 30, outdoor sports practice, sunburns especially during childhood, immunosuppression, certain genetic syndromes such as albinism and xeroderma pigmentosum. (27)
The development of actinic keratosis is strongly influenced by latitude, a prevalence ranging from approximately 10% of the adult population in Galway, Ireland, to 40% in Queensland, and in excess of 60% in Victoria, Australia. (28)

Clinical aspect

AK can be divided into three different grades clinically, dermoscopically as well as in histology and with reflectance confocal microscopy.
According to the classification, we can recognize grade 1, describes slightly palpable AK (better felt than seen); grade 2, shows moderately thick AK (easily felt and
seen) and grade 3 is very thick, hyperkeratotic.
Additionally, there are several variants, these include classical non-pigmented variants, lichenoid, atrophic, hyperkeratotic or pigmented AK.
The surrounding skin frequently shows additional features caused by sun damage including atrophy, pigment changes and telangiectasias.
An important point to mention is the so-called “field cancerization”. This term describes the subclinical presence of changes of chronically UV-exposed skin, which are not visible to the eye. These genetic alterations are responsible for the presence of multifocal clinical and sub-clinical cancerous lesions. Due to this phenomenon, the treatment/follow-up of actinic keratosis can be exhausting and has to be continuous.
The diagnosis of AK is usually easy; however, in ambiguous lesions and in high-risk patients (e.g., immune-compromised patients) a biopsy is recommended.

Dermoscopy

The appearance varies depends on whether the keratosis is non pigmented or pigmented. In nonpigmented keratosis we found the so-called strawberry pattern characterized by marked erythema of yellow keratin plugs in follicular openings and fine linear vessels.
Grade 1 AKs are dermoscopically typified by red pseudonetwork patterns and discrete
white scales, grade 2 corresponds to an erythematous background intermingled by white-to-yellow, keratotic and enlarged follicular openings (these features are reminiscent of the surface of a strawberry; therefore, this pattern has been termed strawberry pattern).
Grade 3 AK exhibits either enlarged follicular openings filled with keratotic plugs over a scaly and white-yellow appearing background or, marked hyperkeratosis seen as white-yellow structureless areas.
It’s possible to see the so-called rosette sign by polarized light and it consists in a white four closely aggregated small dots in correspondence to the follicular opening and resembling a four-leafed clover connecting the four dots with a line, a geometrical figure of a rhombus can be formed. (29)

In pigmented actinic keratosis an irregular pseudo pigmented network, hair follicle opening of different sizes, grey rhomboidal structures, white circles and pigmented scales are observable. (30-31)
PAK enters in differential diagnosis with benign lesions (SK-SL) and malignant lesions such as pigmented BCC or LM.
In the dermoscopic evaluation of PAK, compared to LM, white and evident follicles, scales and red colour represent significant diagnostic clues for PAK. Conversely, intense pigmentation and grey rhomboidal lines appear highly suggestive of LM.

Histopathology

Are characterized by a slightly thickened epidermis, orthokeratosis alternating with parakeratosis ('pink and blue') with loss of the underlying granular layer and a disarrangement of the epidermis with atypical keratinocytes at the basal layer ('crowding of nuclei'). Atypical keratinocytes lose polarization and have pleomorphic nuclei, increased size and hyperchromatic, with pale or vacuolated, eosinophilic cytoplasm. Solar elastosis is constantly present in the dermis and is often accompanied by a lymphocytic infiltrate with plasma cells in the upper dermis.
There are several histopathological variants of AKs. In some cases, the epidermis may be thin, and focal parakeratosis and atypia may be limited to the basal layer (atrophic AK); contrarily, the epidermis may show an irregular psoriasiform hyperplasia with prominent orthokeratosis alternating with parakeratosis (hypertrophic AK). In advanced stages, atypical keratinocytes may extend to almost the full thickness of the epidermis; this variant is named Bowenoid keratosis. (32)
Similar to cervical intraepithelial neoplasia and vaginal intraepithelial neoplasia in the cervix and vulva, AK was proposed a classification schema, by Yantsos et al., that was divided into three levels of keratinocyte intraepithelial neoplasia: level I (mild), with atypia restricted to the basal and suprabasal layers; level II (moderate), with atypia extending to the lower two-thirds of the epidermis; and level III (severe), with atypia throughout the epidermal thickness. (33)

Treatment

The therapeutic strategy differs depending on several factors

- local factors: number of lesions, the depth of the lesion (degree of infiltration), localization, high risk lesions, recurrence
- general factors: age, comorbidity, use of drugs, pain sensitivity, adherence to therapies, therapy costs

According to the guidelines for the care of patients with actinic keratosis of 2017, many options are available and management can be directed at individual lesions or over a wider area (field treatment).
The advantage of field treatments is the possibility to treat those lesions on a sub-clinical level, not visible to the naked eye or by dermoscopy.
The use of dermoscopy is particularly advantageous in the follow-up of treated lesions, both in detecting any signs of persistence of the disease and in ascertaining healing, the finding of clinical and dermoscopic healing corresponding to histological healing.

Therapeutic options

5-Fluorouracil
A cream, which active substance works by the inhibition of thymidylate synthetase, which is needed for DNA synthesis.
Topical therapy with 5-fluorouracil is a mainstay in the treatment of multiple or single grade 1 and 2 (non-hyperkeratotic) AK.
The cream formulation must be applied in the morning and in the evening for 4 weeks. It is also available a formulation of 0,5% in association with 10% salicylic acid, which should be applied only once a day, preferably in the evening and removed the following morning with moistened gauze, for up 12 weeks; healing it's about 70%. (34)
A meta-analysis of seven studies with topical 5-FU (all 2–4 weeks in duration) yielded an average AK lesion response rate of 87.8%±2.2% and an average complete patient response rate of 62.5%±12.0%.26 The analysis included concentrations of 5-FU cream 0.5%, 1%, and 5%. (34a)
Side effects include redness, soreness and crusting.
Sometimes more than a single course of therapy is required to achieve a lasting remission of the lesions.

Imiquimod 5% cream
The active substance is a topical immune-response modifier. Non hypertrophic or hyperkeratotic actinic keratosis are included in the indications for treatment with imiquimod. The cream must be applied three nights a week, and washed the following morning, in a period of 4 to 8 weeks. The complete response it's around 55%. (35)
Side effects, sometimes difficult to make the patient accept, include the worsening of erythema (with the continuation of therapy), edema, exudaution, erosions, scabbing and crusting. The extend of side effects vary from patient to patient, is directly linked to the amount of sun damage, from

minimal side effects to effects that require to stop the treatment. The therapeutic response is in direct proportion to the side effects.

Diclofenac 3%

This gel formulation must be applied in the morning and in the evening for 60-90 days. The mechanism of action seems to be related to the inhibition of cyclooxygenase pathway leading to reduce prostaglandin E2 synthesis. Its use is limited in multiple mild AKs (stage 1 and 2). Four weeks after 60 days of treatment, 100% of actinic keratoses were cleared in 33% of patients and, after 90 days of treatment, the 100% clearance rate was 50%. (36)
Side effects are minimal with high degree of satisfaction. (35)

Topical retinoids

some older trials demonstrate a modest benefit with the use of this class of drugs. Adapalene 0,3%, tretinoin 0,1-0,5% and isotretinoin 0,1% are used. (38)
Topical retinoids are partially effective in the treatment of multiple AKs even after one year of daily treatment, so their use is not justified given the availability of effective topical treatment options.

Cryosurgery

particularly suitable for single lesions or thickened lesions. Response varies from 70 to 85%, but its effectiveness is strictly operator dependent. (39)
My personal experience with cryosurgery is very good, generally a single treatment is sufficient to obtain the desired result, in the management of these patients (at risk of recurrence) I recommend daily application of sunscreen and one or two annual check-ups. Side effects include pain during and after the application of cryogen, blistering, pigmentary change (especially in dark skin type) and scarring.

Photodynamic Therapy (PDT)

a photosensitizer (delta-5-aminolaevulinc acid or its methyl ester) it is used applied under a black light-tight foil for a few ours, followed by irradiation with a visible light which initiate a tissue toxic photochemical reaction to produce apoptosis and necrosis of the target tissue, the limitation of this method is the discomfort due to the painful sensation, which is particularly intense. (40)
Recently, a simplified variant of PDT has been introduced called “day light PDT” which uses natural sunlight as a light source instead of an artificial light source, and is associated with artificial light source, and is associated with reduced pain and reduced time compared to conventional PDT.

Daylight PDT is an effective, safe effective, safe and cost-effective alternative to conventional PDT for patients with multiple actinic keratoses (defined as grade I and II), especially in large areas of large cancerization fields that can easily be exposed to daylight.

Laser therapy

the light acts through controlled damage of the skin. The systems used are ablative lasers (CO_2 and Erbium Yttrium Aluminium Garnet) in isolated AK (grade 2) the use of this method is useful in the context of general rejuvenation treatment, while cryosurgery is preferable for the treatment of individual lesions.

Side effects: persistent erythema, scarring, hyper or hypopigmentation.

Surgery

limited to high-risk lesion, in case of failure of destructive therapy or in case to rule out an invasive growth.

As general rule, in a patient with a grade 2 or 3 single lesion a targeted treatment with destructive procedures like cryotherapy or laser therapy or photodynamic therapy is preferred.

The use of topical medication (Imiquimod) acts directly on the lesion and surrounding areas that are not clinically visible, but whose DNA cell damage is ongoing and will eventually be clinically visible (cancerization field). (41)

In case of multiple, superficial (gr ½) lesions occurring in a context of chronic photodamage, so-called direct field therapies are preferred.

In case of grade 3 lesions with marked hyperkeratosis and undefined vascular appearance, a biopsy examination is required in order to rule out SCC.

Bowen's disease

Bowen's disease is considered as a specific form of squamous cell carcinoma in situ.

Clinical aspect

It predominantly affects people with white skin, most commonly found in patients over 60 years of age and occurs predominantly in women (70-85% of cases).

It can affect any part of the integument, mucous membrane or nail bed and therefore involves both sun-exposed and non-sun-exposed skin. (42-45). However, in most patients it is located on the in

sun-exposed areas and in 60-85% of these cases on the lower leg. (46). While in women there seems to be a preference for the cheeks and lower limbs, in men it is the scalp and the ears. (50) It typically presents as an asymptomatic, gradually enlarging, well demarcated, erythematous plaque with an irregular border as well as surface crusting or scaling (48). It clinically can resemble a psoriasis or eczema, predominantly affects white skinned races.
The lesion often has a yellowish surface scale in a pink-red background. Pigmented variants are very rare and can be confused with melanoma. (49-52) Etiological factors include UVR, previous ionizing radiation, previous therapy with psoralen and UVA (PUVA), immunosuppression, HPV infection. If left untreated, in a few years the lesions can progress to invasive SCC, called Bowen's carcinoma (BC), in 3-5% of cases. The presence of BD marks an individual at high risk for developing non-melanoma skin cancers (NMSC). (53)

Dermoscopy

Non-pigmented BD shows a squamous surface, visible as scales, in a significant vascular pattern with punctate or glomerular vessels (slightly larger in size) distributed in a small cluster, and/or globular vessels (small red clods) are characteristic. They may be associated with a whitish-yellow scaly surface, small brown globules, linear greyish dots and/or homogeneous pigmentation. Pigmented structures may be seen arranged in lines. White circles may be present, often in irregular clusters. There may be superficial erosion and crusting. Two new dermoscopic signs, recently described, in BD: the double-edge sign and the clusters of brown structureless areas. (54-55)

Histopathology

BD represents full-thickness dysplasia involving the entire epidermis.
There are marked acanthosis and parakeratosis with complete disorganization of the epidermal structure.
Keratinocytes show morphological atypia and loss of maturation. Apoptotic or dyskeratotic cells, multinucleated keratinocytes and mitoses may be present in the epidermis. Extension of keratinocyte atypia to the follicular epithelium is common. Moderate hyperkeratosis, lymphocytic infiltration of the upper dermis may be observed. (56)

Prognosis

If left untreated, BD may progress into an invasive SCC, the so-called bowenoid carcinoma, in 3–20% of cases. (57)

Treatment

The best treatment is surgical removal for single small lesions. For all other cases (e.g., extensive or multiple lesions, lesions with ill-defined margins or in lesions located in aesthetically relevant areas), cryotherapy, electrodessication or a laser CO2 ablative may be chosen.
Non-surgical options: Imiquimod, photodynamic therapy or topical 5 fluorouracil. (58)
5% 5-FU preparation has shown its efficacy in short- and long-term studies and can be used for the treatment of BD in good or even bad healing sites and for special sites like fingers or penis.
Topical imiquimod 5% cream is an effective alternative treatment option for patients and body sites that are unsuitable for other treatments like surgery.
PDT in the treatment of BD is a therapy option with high efficacy and good cosmetic outcome. It is non-invasive and especially suited for poor-healing sites, patients with large and multiple lesions and patients with comorbidities (eg, diabetes, immunosuppression).
Non-invasive treatment options may also be indicated for the treatment of lesions that cannot receive a complete result from surgery due to the size of the lesion or its difficult location, in which case they are added to surgery as a complementary therapy.

Squamous cell carcinoma

Cutaneous SCC is a malignant neoplasm deriving from suprabasal epidermal keratinocytes. It is the second most common type of NMSC and has an incidence of approximately 10% in the general population. (59)
Different growth types are described, most severe form is infiltrative and destructive growth type, it causes metastases of lymphatic and haematogenous spread. (60)
A distinction can be made between low-risk with a good prognosis with 5-year cure rates of greater than 90%, and a low rate of metastases (<4%), and high-risk SCC. High-risk features are depth of invasion (>2 mm), poor histological differentiation, high-risk anatomic location (face, ear, genitalia, hands, and feet), perineural involvement, recurrence, multiple SCC tumors, and immunosuppression. Some SCC tend to metastasize more than others, i.e. tumors of the lip, tongue and anogenital region.
Another frequent type of SCC it's Keratoacanthoma, is a rapidly growing nodular tumor with a low degree of malignancy.

Epidemiology and risk factors

SCC is strongly associated with advanced age, with a significant increase of incidence noted after the age of 40.
Increased exposure to ultraviolet radiation, increased time spent outdoors, changes in clothing style and ozone depletion through increased use of tanning showers have been implicated in the increased lifetime risk for SCC among Caucasians, which has doubled over the past two decades to about 15%. (61)
In italy, the 'Cancer Regisry' estimates of SCC incidence in the Trentino region were 29 cases per 100000 inhabitants in the period 1993-1998. (62)
Data from Italian cancer registries estimate that 19000 new cases of SCC were diagnosed in 2018, with higher incidence mainly in males over 65 years old. (63).
In Australia (the country with the highest frequency of NMSC), the overall incidence rate of SCC in 2002 was estimated to be 387 cases per 100 000 population. (64)

Cutaneous squamous cell carcinoma is often preceded by premalignant actinic keratosis (an American study concluded that 10% of actinic keratosis progressed to SCC) (65) or by Bowen disease. While the relative prevalence of SCC was previously considered to be 20% of all NMSC (75% BCC), a recent study indicated that the true ratio to BCC is 2.5:1. (66)
SCC is twice as common in men as in women, probably due to their higher lifetime UV exposure due to occupations, clothing and shorter hairstyles.

Chronic UVR exposure is the main environmental risk factor associated with the development of SCC. There is a linear correlation between the incidence of SCC and UVR-exposure. (67)
Other risk factors include light skin phototype and blue eyes, UV radiation and chronic viral carriage may represent unique risk factors for SCC development, and the immune system plays a key role in modulating the response to both. Advanced age, outdoor work activities, family history of skin cancer, increasing number of melanocytic nevi, freckles and/or sunburns in childhood.

Other predisposing factors include exposure to ionizing radiation, exposure to environmental and occupational carcinogens such as arsenic and aromatic hydrocarbons, exposure to chemical carcinogens, thermal radiation, the presence of scars, chronic inflammation and ulcers.
Human papillomavirus has recently been reported in the pathogenesis of cutaneous SCC and has been shown to prolong the keratinocyte cell cycle, with increased degradation of p53. HPV-16 and

HPV-18 infection has been associated with an increased risk of developing SCC of the mouth, head and neck. (68-69)

Clinical aspect

Most SCC are mainly found on uncovered areas of the body such as the lower lip, temporal and back of the hands and occur in the context of chronic photodamage where actinic keratosis is also found.
Most SCC present as an indurated slow-growing tumor, may be nodular, ulcerated, plaque-like or verrucous. When the lesion may present as a small plaques or nodules, tends to evolve rapidly towards the formation of a tumor detected as a hard, raised indolent margin ulceration.

Dermoscopy

SCC, particularly the initial form, is characterized by targetoid appearing follicular openings (white circles) on a white background.

A general non-specific pattern is observed in association with a central keratinous mass. Characteristics are the peripheral vessels, hairpin vessels, with a keratotic halo.
SCC is characterized by the presence of keratin/scales, blood spots, white circles, white structureless areas, hairpin vessels, linear-irregular vessels perivascular white halos, and ulceration. (70). Blood spots are the multiple red to black dots in the keratin mass, corresponding to small crusts or hemangiomas. (71)
In advanced lesions, an amorphous mass of yellow-white keratin is seen in the center, surrounded by polymorphic vessels consisting of peripheral hairpin, dotted/ glomerular/ or linear-irregular vessels.
There is typically a little distinction between forms where red color prevails due to intense vascularization and well-differentiated forms where white color prevails due to keratin.
The presence of vessels in more than half of the tumor's surface with a diffuse distribution of vessels and bleeding significantly increased the possibility of poorly differentiated SCC which are very hard to distinguish from melanoma/merkel cell carcinoma. Conversely, keratin/scales are a potent predictor of well- and moderately differentiated SCC. (72)

Follow-up

Since 95% of local recurrences and 95% of metastases are detected within 5 years, long-term follow-up is suggested together with ultrasound of regional lymph nodes every 4-6 months. (73) It would therefore seem reasonable for the patient who has had a high-risk SCC to be kept under observation for recurrent disease for this period of time. (Strength of recommendation A, quality of evidence II-ii.).

Treatment

The primary treatment for most SCCs is the surgical excision as it allows immediate histological and post-operative assessment of excision margins. (74)
An excision margin of 4 mm is recommended for lesions below 2 cm in clinical diameter with well-defined margins; a margin of 6 mm is proposed for high-risk SCC areas. Mohs micrographic surgery should be considered for the management of high-risk SCC particularly in difficult areas, where wide surgical margins may be technically difficult to achieve. (75)

Radiation: This can be performed, if surgical excision is contraindicated (e.g., age, general condition/comorbidities, large tumors) or in the case of lesions located on delicate sites such as the lip, ear and nose. This therapy has been reported to achieve comparable results. (75)

Basal cell carcinoma

General characteristics

BCC is a local malignant tumor that only rarely progresses into metastatic disease. It arises from malignant transformed cells of the basal cell layer of the epithelium. (76)
Basal cell carcinoma is the second most common malignant skin neoplasm in humans and is the predominant skin cancer in Caucasian populations (77) with approximately 2 million new cases per year and its treatment imposes a significant economic burden. (78)
The annual incidence of BCC varies in different countries, from over 800 cases per 100 000 inhabitants per year in Australia to 80 cases in Germany, Switzerland and Italy (79), but these figures are probably underestimated as these tumors are not routinely listed in cancer registries (80). In addition, a significant proportion of BCC are treated with destructive methods or local therapy, a percentage that eludes the statistics. Due to the ageing population and the changing sun exposure habits, its incidence has increased in recent decades and is estimated doing so in

the next years. Among others, this fact is important as people with cutaneous basal cell carcinoma are at increased risk of developing cutaneous squamous cell carcinoma and cutaneous melanoma. (81)

Race

BCC is 19 times more common in white individuals than in black individuals. This is due to the greater protection of black. (81)
There is a positive association between BCC and light skin color and Northern European ethnic origin. (82)

Age and sex

The incidence of BCC increases rapidly with age, with the incidence rate doubling between the ages of 40 and 70 (83-84). However, in the past years an increasing frequency of this tumor was also observable in the age group under 50 years (85). Concerning the gender, BCC are more commonly found in men (86), According to the current literature, BCCs are more common in males as reported in most studies, presumably due to greater occupational and recreational exposure to UV radiation (87)

Anatomic localization
BCC can appear on any part of the body, but UV-exposed areas are frequently affected (e.g., head and neck in 80%).
Depending on the affected area specific histological subtypes are predominantly observed; superficial BCC are mostly found on the trunk, whereas nodular BCC are more frequently observed in the face and nasal area (88).

Extrinsic factors

UV radiation: The main environmental risk factor for the development of BCC is exposure to UVR. Both, acute and intermittent exposure as well as the long-term continuous exposure to UV radiation are high risk factors. Consequently, areas of the body chronically exposed to the sun develop a higher proportion of BCC than those with less or no exposure. (89)
Geographical areas: It is common knowledge, that the incidence of BCC has a strong inverse relationship with latitude. (90) Following that, BCC typically occurs in the elderly population (>60

years of age) in less sunny regions. In Italy appear to have the highest incidence rates of Europe, around 70/100 000 person-years in 1995; (91). The incidence of BCC in Australia was higher than anywhere else in the world, the rate was of 884/100000 person-years (both sexes combined) in 2002. (92-93)
Ionizing radiation: Exposure to ionizing radiation is implicated in the pathogenesis of BCC. (89)

Clinical aspect

Based on their biological behavior and the growth pattern, five subtypes of BCC are distinguished. These subtypes also differ concerning their treatment (94):

- Nodular – ulcerative (45-50%)
- Diffuse (infiltrating and morpheaform) (4-17%)
- Superficial type (15-35%)
- Pigmented (1-7%)
- Fibroepithelioma of Pinkus (0.2-1.4%)

Nodular – ulcerative BCC

Nodular-ulcerative BCC, initially presents as a small translucent, whitish-red, As the tumor progresses, a pearly or red nodule, with a smooth surface and hard texture, with fine telangiectasias is seen. In late stages also ulceration, spontaneous bleeding and crusts develop. This subtype is commonly localized on the face. (95)

Diffuse type BCC

The diffuse type of BCC is not a very frequent type of BCC and is mainly localized on the face. Morpheaform BCC accounts for a low proportion of cases, estimated at 5 to 10%. (96)
It presents as an undermarketed pearly spot or indurated plaque with a smooth surface and short telangiectasias. This appearance is related to intense peritumoral fibrosis.
Notably, the clinical margins of this tumor do usually not match with the histological margins, thus requiring a radical surgical approach.

Superficial BCC

This subtype presents as a round to oval, well demarcated, scaly, red patch located on the trunk. Additionally, several micro-erosions arise over the entire lesion. Areas of spontaneous regression can occur, leaving behind atrophic, hypopigmented areas. It has slow dynamics in growth and enlarges over years.(97)

Fibroepithelioma of Pinkus

An uncommon variety of BCC looks like a pink - red plaque, without translucency. Usually located on the trunk. It manifests clinically as a solitary, and sometimes multiple, flesh-colored or slightly brown-gray, well-demarcated plaque. Infrequently, FeP may be pedunculated, polypoid, or ulcerated or may invade underlying tissues. (98)

Pigmented BCC

Pigmented basal cell carcinoma is a clinical and histological variant of basal cell carcinoma that exhibits increased pigmentation. It is a very rare variant, characterized by variable amounts of melanin may be present within these tumors.
The most important differential diagnosis clinically is with nodular melanoma, followed by blue nevus. In these cases dermoscopy is a valuable diagnostic tool to guide the diagnosis. (99)

Multifocal BCC

Multifocal BCC clinically shows two or more tumor localizations. It may arise as new one or, more often, within a pre-existing ineffectively treated or non-radically treated BCC that over time has infiltrated adjacent tissues. (100)
In order to make a correct assessment of the extent of the disease and to adopt an appropriate and radical approach, dermoscopy is an essential tool to detect portions of lesions not visible to the naked eye. In particular, careful observation of the vascular pattern allows identification of the border between the typical vessels of BCC and the vascular pattern of healthy skin.

Locally advanced BCC

These are usually ulcerated tumors, mostly found on the head, nose and cheek.

They are particularly found in elderly people living alone, without family, who often have comorbidities and poor general condition.
These lesions show a progressive growth behavior and can progress into the subcutis and the bone. progressively widen and deepen into sub-cutis to the bone.
Easy bleeding, nerve involvement and superinfections are factors that worsen the prognosis.
Patients with aggressive skin tumors, defined as tumors greater than or equal 2 cm, invading bone, muscle and nerves, or metastasis to regional lymph nodes, are characterized by multiple recurrences and secondary or primary tumors often requiring multidisciplinary care.

Metaplastic BCC
Very rarely, basal cell carcinoma may show metaplastic malignant stromal features. Histologically, typical tumor nodules are detected dispersed in a dense stroma of fusiform cells; fusiform cells show high mitotic activity and eosinophilic cytoplasm, they also express desmin indicating smooth muscle differentiation.

Dermoscopy of BCC

Dermoscopic appearance varies according to the BCC subtype; in the following, the dermoscopic patterns of BCC mainly occurring on the face are shown.

Nodular-ulcerative BCC
- Arborizing vessels: multiple branching vessels in a tree-like pattern, which are bright red and sharply focused. This vascular pattern is strongly associated with the nodular subtype. The tumor-vessels are much more focused and thicker in comparison to those of the surrounding skin.
- Background-color can be bluish-pink color or pigmented (brown-black) in case of pigmented BCC
- Large blue-grey ovoid nests (typically found in pigmented BCC): confluent or nearly confluent, well-circumscribed, pigmented ovoid areas, as opposed to blue-grey globules which are smaller in size. The histopathological correlation of the ovoid nests corresponds to the basal tumor island in the dermis and confirms that the tumor has a deep component.
- Dots and multiple blue-grey globules: Blue grey punctiform structures, typically present in early nodular or superficial-type BCC. Blue-grey globules are a well-defined round or oval structure with intermediate dimensions between ovoid nests and dots. The histopathological correlation of these structures corresponds to small basal cell tumor islands in the dermis.
- Ulceration: these are superficial erosions that may be covered by frozen blood or a serous crust.

- Shiny white spots and wisps: white spots or wisps and linear white areas called wisps visible under polarized light. (101)

Superficial BCC:

- Leaf-like structures: these areas are defined as discrete, linear to bulbous extensions connected to an off-center base area. These form a leaf-like pattern, usually brown or blue grey in color.
- Spoked wheel-like structures are radial projections surrounding a darker central point. The projections are light brown, blue or grey in color and the central point or hub is usually dark brown, blue or black.
- Small erosions over the entire lesion
- Clothing-fiber sign (adherent fabric fibers) due to the multiple micro-erosions can be seen
- Background color pink areas expecially visible on tanned skin, atrophic, hypopigmented areas. Variable amounts of melanin pigment may be present. (102)

Diffuse BCC

- Fine arborizing vessels: scattered, fine, focused, elongated telangiectasias with few branches (89)
- Short arborizing vessels: short, focused telangiectasias with few branches.
- Whitish background and structureless hypopigmentation
- Milky-red background

Histology of BCC

BCC is characterized by an island of cell proliferation (basaloid cells) resembling those of the basal layer of the epidermis and hair follicle, surrounded by a fibrous stroma.
Basaloid cells have a low cytoplasm and large hyperchromatic nuclei, peripheral palisading and peritumoral clefting (a useful element for differential histopathological diagnosis).
Mitotic figures and apoptotic bodies have already been found.

Treatment of BCC

The primary treatment for BCC is the surgical excision allowing a complete removal and histopathological report.
However, in some cases, taking into account factors such as tumor size, location, histology, general health conditions of the patient, destructive modalities such as drug treatments (Imiquimod), cryotherapy, currettage, electrodessication and radiotherapy may be used.
The latter therapies are preferred in cases of superficial or multiple BCC, in elderly patients or patients with comorbidities, whose general health conditions discourage surgery, superficial BCC located in aesthetically important areas. In all these cases, treatment must be preceded by a biopsy to assess the biology/subtype of the lesion, while careful follow-up will allow timely intervention in case of recurrence.
For infiltrative forms such as nodular or scleroderma BBC or Ulcus Rodes there is no alternative to surgery.
The Mohs technique is a serial technique of progressive removal of tumor tissue using immediate histological checks under the microscope to verify extension.
For the treatment of metastatic and locally advanced BCC vismodegib, a small molecule inhibitor of the Smoothened receptor in the hedgehog pathway. The effectiveness of vismodegib in the treatment of advanced BCC has been evaluated in a study, in which 46.4 percent of patients with locally advanced BCC and 30.8 percent of patients with metastatic BCC showed objective responses. (88B)

As far as the treatment of this disease is concerned, 95% of basal cell carcinomas are treated by local techniques (surgery) without significant cosmetic deformities.

Basosquamous carcinoma

Basal cell carcinoma plus admixed foci indistinguishable from squamous cell carcinoma it's nature is more aggressive than classic basal cell carcinoma and may metastasize. (100)
Clinically, BSC has a nonspecific clinical presentation and diagnosis is made only after biopsy. (104)
Most BSCs are located in the head and neck, mainly on the nose and in the auricular and periocular regions. (105)
Dermoscopy: BSC appears to have overlapping features of BCC and invasive SCC, most frequently detected criteria: unfocused (peripheral) arborizing vessels (73%), keratin masses (73%), white structureless areas (73%), superficial scale (68%), ulceration or blood crusts (68%), white structures (64%), blue-grey blotches (59%) and blood spots in keratin masses (55%). (106)

Treatment: The treatment options for patients with BSC are excision, radiotherapy, and MMS.15 Most authors agree that surgical excision is probably the treatment of choice. (107)

Melanoma

Lentigo maligna

Epidemiology and risk factors

Lentigo maligna (LM) is an in-situ melanoma located on the face and is the most common subtype of facial melanoma. LM and its invasive form, the lentigo maligna melanoma, account for 4-15% of all melanomas (108). This tumor typically occurs in elderly patients (>60 years of age) and is strongly associated with chronic UV-exposure during lifetime. This tumor is stated as “very-slow growing melanoma”, thus remaining in its in-situ form for years or decades.
Delayed diagnosis is common. (109) The presentation of LM can be quite subtle, particularly in the early stages.

Clinical aspect

Lentigo maligna is a poorly defined flat brown macule that gradually enlarges.
Lentigo maligna presents as a brownish to black, flat macule with ill-defined irregular borders. In larger lesions there are also greyish-white areas observable, which correspond to spontaneous regression.

The most common locations are the cheeks and nose, then neck, scalp and ears. (110)
Early stages of LM are hard to distinguish from a solar lentigo, seborrheic keratosis, lichen planus-like keratosis, actinic pigmented keratosis and a melanocytic nevus clinically. (111)
Besides dermoscopy, some clinical information can help in this differentiation: facial localization, age of the patient, slow growth in a context of chronic photodamage.
In later stages it is not uncommon that LM diagnosis is delayed, with 48.8% of lesions being >10mm in diameter at the time of biopsy, LM may evolve from a large pigmented macule into papules, nodules or thick plaques which correspond to invasive foci thus becoming LMM. (112)

Dermoscopy

The dermoscopic appearance of early LM can be very subtle; however, several features are described in literature (113)
At the beginning, LM shows asymmetric pigmented follicular openings with the following possible arrangements:

- Fine circle
- Semicircle
- Signet ring-like circle
- Irregular circle
- Double circle

Annular and granular structures can be subdivided into aggregate points around adjacent openings (often clustered) and short, polygonal lines around and between nearby openings.
Rhomboidal structures are the result of the evolution of polygonal lines, by extension and thickening of the same. They appear as a polyhedral structure around the follicle.
Dark spots and erased hair follicle. The dark spots initially spare the follicular openings, but as the disease progress they invade the follicular openings. (114)
Gray colour: in LM it is very common to find a diffuse or localised grey colour. Grey color can be detected even before the formation of the characteristic LM structures, such as circles or rhomboids. This is the single most sensitive feature for the dermoscopic recognition of early facial melanoma and its presence should always prompt the clinician to perform a biopsy. (115)

Dermoscopic criteria associated with the vertical growth phase are: ulceration, blue papular areas and black structureless areas (116).
This is because each of they may also be present in SL/early SK and PAK, and only the simultaneous presence of four or more criteria has been shown to predict accurately the diagnosis of melanoma.
Classic LM criteria, Annular-granular and grey structures in a pseudo-network also appear to be observed in regressive areas of initial SK, SL, PAK, LPLK. (117)
Differentiation from benign pigmented lesions remains troublesome even with dermoscopy.
In these cases the presence of grey color criterion becomes a very important marker for the suspicion of LM even before the formation of the characteristic LM structures. (118)
A major evaluation problem is represented by lesions that show complete regression such LPLK that show diffuse granular pattern, characterized by brownish-gray, reddish-brown, bluish-gray, or whitish-gray coarse granules with areas of tan pigmentation. In such cases, it is essential to proceed with a biopsy to reach a final diagnosis.

Histology

It originates from an epithelial field of atypical melanocytes that slowly expands centrifugally. When these atypical epithelial melanocytes breach the basement membrane and invade the connective tissue, the lesion is referred to as lentigo maligna melanoma. (119)

LM is characterized by an increase in the number of atypical melanocytes in the basal layer of the epidermis, either solitary or arranged in nests, which do not invade into the dermis.
The atypical melanocytes often extend along adjacent structures and tend to have an orientation perpendicular to the surface.
A marked solar elastosis, which is an important element in the diagnosis, is found in the dermis.

Treatment

If clinical observation suggests LM, a biopsy evaluation should be performed, preferably from more than one site and at an appropriate depth.
Surgical excision remains the preferred treatment for LM, with an unaffected neoplasm margin of 5mm from the margin of the clinically visible lesion. (120) However, lesion´s margins are not always clinically or dermoscopically well definable; in these cases, Moh´s micrographic surgery is the treatment of choice in order to achieve with a low recurrence rates. (121)
Second-line therapies include radiotherapy, topical imiquimod or cryotherapy. These regimes can either be primarily chosen (very extensive lesions not suitable for surgical removal, patients not suitable for surgery) or secondary to surgery after incomplete surgery.

Lentigo maligna melanoma (LMM)

After a period of 5 to 15 years, LM may move from the horizontal to the vertical growth phase with development of the dermis. The first clinical sign of this vertical growth is a brownish-black firm papule developing within the LM. This can evolve to a nodule showing ulceration and bleeding.

Due to its onset from the evolution of a pre-existing LM, it occurs in elderly subjects between 60 and 70 years of age. The most common location is on the chronically sun-exposed face.

Dermoscopy

Lentigo maligna melanoma shows the features of Lentigo maligna as well as the typical features of invasive extra facial melanoma (122):

- Asymmetry in two axes
- Atypical dots
- Radial streaming
- Pseudopods
- Blue-white veil
- Mixed vascular pattern
- Scar-like depigmentation
- Rhomboidal Structures
- Atypical pigment network
- Pseudonetwork
- Asymmetric pigmented follicular openings
- Annular-granular pattern
- Colors (3 or more)
- Blotches
- Increased density of vascular network
- Red rhomboidal structures
- Abrupt demarcation

Histology of LMM

Atypical melanocytes are first found on the basal layer of the epidermis, then progressively invade the dermis.

The vertical growth phase is faster than the horizontal one.

In the nodular phase of Lentigo maligna melanoma, fusiform cells characterized by cells with elongated, narrow and thinned cytoplasmic processes are frequently found.

Prognosis

Prognosis depends on factors such as tumor thickness as measured by Breslow, the presence or absence of ulceration and lymphatic invasion. (123)

Nodular melanoma (NM)

Nodular melanoma is the most aggressive subtype of melanoma.
NM account for most thick melanomas and because of fast growth and high mitotic rate, substantially contribute to melanoma-related mortality. (124)
This tumor shows very early a vertical growth without a considerable horizontal growth.
Nodular melanoma (NM) constitutes 9% to 15% of invasive melanoma and represents a potentially lethal skin tumor. It is the most frequent subtype of thick, rapidly growing melanomas and is often diagnosed at a locally advanced stage, conferring a worse prognosis. (125).
NM have been associated with a smaller total number of nevi than superficial spreading melanomas. (126)

Clinical aspect

NM may occur in sun-exposed skin without or with low cumulative sun-induced damage (low-CSD) or develop on skin with cumulative sun-induced damage. Nodular melanoma tend to occur on the heads and necks of elderly (>50) sun damaged men. (127)
NM lesions may clinically present as symmetrical, firm papules or nodules with light color (a-hypomelanotic) and with regular border.
A/hypo melanotic NM may not be clinically suspected to be melanoma but is often diagnosed as a benign lesion. (128)
NM had a subtle clinical appearance and often lacked the ABCD criteria. (129)
For the clinical diagnosis of NM the “EGF” rule has been devised, where E stand for elevation, F for firm consistency, and G for progressive growth. (130)

Dermoscopy

Dermoscopy is a very important tool especially for lesions such as NM where the clinic is often unclear due to the extreme heterogeneity of presentation. (131-132)

- blue-white veil
- multiple (5–6) colors
- crystalline structures (seen only with polarized light)

- atypical vascular patterns: the vascular morphology is dependent on the tumor volume and thickness in melanoma (133). In a study of amelanotic/hypomelanotic melanoma, thicker tumors had an increased prevalence of all kind of vessels, prevalence of pink color, and more hairpin and large-diameter–type vessels /pinpoint vessels are less frequently found as the predominant vessel type in thicker tumors. (134)
- asymmetric pigmentation
- blue–black pigmented areas
- homogeneous disorganized pattern
- combination of polymorphous vessels and milky-red globules/areas
- combination of polymorphous vessels and red homogeneous areas

Desmoplastic melanoma (DM)

It is a rare variant of melanoma with a poor prognosis and a high incidence of metastatic recurrence. It occurs mainly in males around 60 years of age. (135-140)

Clinical aspect

Most DM arise on a LM (141), however theses tumors can also occur on the trunk and the upper or lower limbs (142-147). Very rarely, a primary involvement of the mucosa (genital or oral), the conjunctiva or the anal region is described (148). A development within a congenital nevus or a burn scar has also been reported in isolated cases (149-150). At the time of diagnosis, this neoplasm is usually advanced due to its aggressive and infiltrative behavior. This subtype metastasizes early with the lungs being the most affected area. Recurrence after initial surgical excision (22%-77%) is frequently observed (151-153).
It clinically presents as a flesh-colored, erythematous amelanotic nodule or ill-defined scar-like lesions.

Dermoscopy

For hypopigmented or amelanotic lesions, the presence of white scar-like structureless areas and abnormal vascular patterns, such as linear-irregular vessels (also known as serpentine vessels) and milky-red areas. (154)
When melanocytic structures are present, they include atypical globules, atypical pigment network and features associated with LMM such as polygonal lines and asymmetric annular granular pattern regression structures such as peppering, negative network. (155)

Histology

This tumor can also be challenging to diagnose in histology. (156-157)
When the biopsy is too superficial, DM diagnosis is difficult as it may be misdiagnosed as a reactive process such as nodular fasciitis, a scarring process or fibromatosis.
DM is characterized by diffuse infiltration of the spindle tumor with marked interstitial fibrosis and collagenization. The cells are typically elongated and have basophilic cytoplasm, similar to fibroblast, smooth muscle cells or Schwann cells.
DM represents an extreme degree of fibroblastic or myofibroblastic metaplasia accompanied by collagen synthesis.
At the moment of diagnosis, the neoplasm is located deep in the subcutaneous fat.

Treatment

Surgery is the first-line treatment present recommendations are margins from 1 to 2 cm for lesions 1.0 to 2.0 mm in thickness and 2 cm margins for melanomas greater than 2.0 mm. (158)
Sentinel lymph node (LN) status is the most important survival predictor for patients with primary localized cutaneous melanoma (159), regional LN involvement in DM occurs less frequently than in other cutaneous melanomas, with a reported range of 0 to 18.8%. (160)
Radiotherapy: based on the actual literature adjuvant radiotherapy may be improve local control valuable for patients with locally recurrent of DM, DM with perineural involvement, residual gross tumor, or narrow/positive excision margins. (161)

4 AIM OF THIS STUDY

The aim of this study was to assess the incidence of various skin diseases (benign and malignant) located on the face in a cohort of patients attending a private dermatological clinic (@Farina Dermatology Private Clinic) to evaluate the most frequent tumors and their frequency of localization on the face.

5 MATERIAL AND METHODS

In this study, recent-onset facial lesions were evaluated in a group of adults who requested an evaluation in a private medical practice in a city in southern Sicily.
This was a prospective monocentric study between June 2012 and March 2015. All patients gave verbal and written consent and were treated according to general guidelines.
The study did not influence the routine treatment of the patients in any way.

Data Search

In this study, adults patients (over 18) with facial skin lesions were included. Notably, more than one lesion per patient could be included.
Exclusion criteria were age under 18 patients with inflammatory dermatoses of the face, patients with benign lesions (seborrheic keratosis etc).

Data gathering

All included lesions were documented with a camera (Digital Canon Eos 450 D) connected to a dermatoscope (Heine Delta 20 Plus with polarised or non-polarised filter plus immersion liquids), clinically and dermoscopically and saved on pc. The patients´ sex, age, history of co-morbidities or skin diseases and previous medical treatment as well as the results of skin examination were saved on pc.

Lesions´ evaluation procedure

Physician 1 (MF) carried out an objective examination: assessment of skin type according Fitzpatrick classification (or phototype) - assessment of sun damage, assessing the presence or absence of signs of photodamage, spots, deep wrinkles, skin thickening, actinic keratoses etc. - classification of facial skin lesions.
The examining physician (MF) made a diagnosis for all patients based on clinical and dermoscopic examination and proposed a treatment strategy (surgery, no intervention, follow-up). Afterwards,

the included lesions were sent electronically to a second physician (IZ), a remote evaluator, expert and consultant specialized in dermoscopy and skin cancer for evaluation and treatment suggestion. Of course, the second physician did not know about the evaluation made by the examining physician.

Criteria of evaluation

Lesion´s location was classified as follows: frontal, temporal, cheek, cheekbone, chin, eyebrow, eyelid, nose, upper lip and glabella.
We defined nine age groups to evaluate the age distribution of our patients. The first age group was under 20 years, followed by the age group 21 to 30 years, and then in 10 years-steps to the age group 91 to 100 years.
Evaluation of:
- Clinical images
- Dermoscopic images
- No information regarding patient's medical data (for physician 2)
- No information regarding remote or upcoming medical history (for physician 2)
- No information regarding the history of the observed lesion (for physician 2)
- Treatment proposal (Surgery, no intervention, follow-up)

Statistics

The agreement between the two observers was assessed by Cohen's Kappa calculation. (133)
The k-index is a tool to assess the true agreement beyond chance between two observers (or between two observations).
The k-index of agreement beyond chance can take values between -1 (maximum disagreement) and +1 (maximum agreement). If the observed agreement is equal to the expected agreement due to chance, k takes on a value of 0 (no agreement).
In concrete terms, to interpret the k index, one can use the following scheme, called the Landis and Koch scale:

k ≤0 very poor agreement
k =0.01-0.20 poor agreement
k =0.21-0.40 Fair agreement
k =0.41-0.60 moderate agreement
k =0.61-0.80 good agreement

k =0.81-1.00 excellent agreement

(Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159-74) (162)

The Kappa value was calculated for the clinical assessment of the lesions, the dermoscopic evaluation and the decision on the treatment to be performed.

6 RESULTS

Patients´ Demographics

A total of 246 patients with 296 lesions including 125 men (50.81%) and 121 women (49.19%). The average age was 68 years. Most of the patients (35.37%) felt into the age group ranging from 71 to 80 years old. The detailed distribution of number of patients by age is shown in Figure 1.

The prevailing phototype of the patients was skin type III (141 patients; 57,32%), followed by phototype II (80 patients; 32,53%) and finally phototype IV (25 patients; 10,16%).

The following lesions were found according to frequency (Table 1): basal cell carcinoma (n=87/296; 29.4%) actinic keratosis (n=67/296; 22.6%), Liken planus like keratosis (n=17/296; 5,7%), Bowen's disease (n=1; 0,3%), Squamous cell carcinoma (n=11/296; 3,7%), Lentigo maligna (n=12; 4,1%), Trichoepithelioma (n=1 ;0,3%). Table 1 summarizes the diagnosis according clinical and histopathological diagnosis.

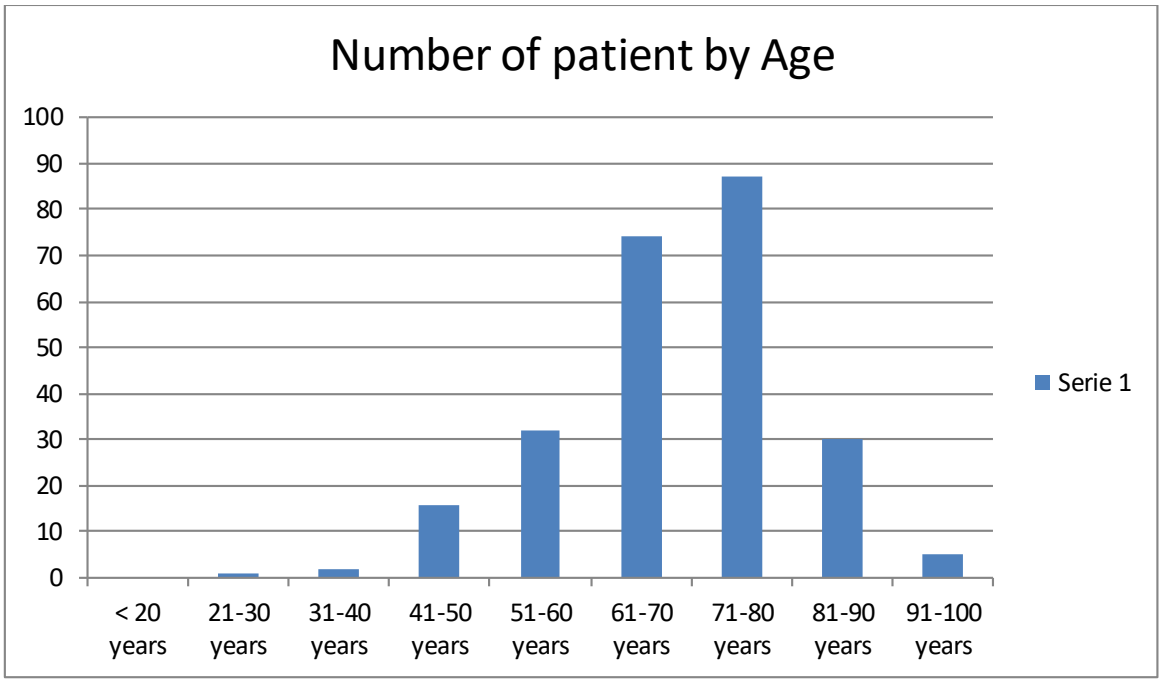

Figure 1 Distribution of the age groups

One hundred-sixty-five lesions (67%) have been diagnosed clinically while 81 lesions (33%) required an histopatological evaluation. In the following tables [Table1], the clinical and histopatological diagnosis are shown:

Diagnosis	Clinical	Histopathology	Total (n=296)
AK	159 (95,21%)	8 (4,79%)	167
LPLK	17 (100%)	0 (0%)	17
BOW	1 (100%)	0 (0%)	1
BCC	87 (100%)	57 (65,52%)	87
SCC	10 (9,91%)	6 (54,55%)	11
LM	12 (100%)	2 (16,67%)	12
TE	0 (0%)	1 (100%)	1

Table 1: clinical and histopatological diagnosis of the study

Distribution of the lesions

With regard to the special subsites of the face, SCC (36.36%), BCC (16.09%) and AK (14.97%), SCC (45.45%), LM (41.67%) and LPLK (35.29%) were mostly affecting the frontal area, while BCC (37.93%) and AK (32.34%) prevailed on the nose.

Table 2 summarized the frequency of skin tumors regarding specific subsites of the face.

	LPLK (17)	**AK (167)**	**BOWEN'S (1)**	**BCC (87)**	**SCC (11)**	**LM (12)**	**TRICHOEP (1)**
FRONTAL	2 (11,76%)	25 (14,97%)	1 (100%)	14 (16,09%)	4 (36,36%)	3 (25%)	0
TEMPORAL	0	12 (7,19%)	0	7 (8,05%)	1 (9,09%)	0	0
CHEEK	6 (35,29%)	32 (19,16%)	0	15 (17,24%)	5 (45,45%)	5 (41,67%)	1 (100%)
CHEEKBONE	7 (41,18%)	26 (15,57%)	0	3 (3,45%)	0	1 (8,33%)	0
CHIN	0	1 (0,60%)	0	2 (2,30%)	0	0	0
EYEBROWN	0	12 (7,19%)	0	1 (1,15%)	0	0	0
EYELID	0	1 (0,60%)	0	5 (5,75%)	0	0	0
NOSE	2 (11,76%)	54 (32,34%)	0	33 (37,93%)	1 (9,09%)	3 (25%)	0
UPPER LIPS	0	3 (1,80%)	0	4 (4,60%)	0	0	0
GLABELLA	0	1 (0,60%)	0	2 (2,30%)	0	0	0
NECK	0	0	0	1 (1,15%)	0	0	0

From the obtained data, AK was more frequently located on the nose (n:54; 32,34%) or in the frontal (n:25; 14.97%) and temporal area (n:12; 7,19%) followed by cheek (n:32, 19,16%) or cheekbone (n:26; 15,57%) and less frequently on eyebrows (n:12; 7,19%), and upper lip (n:3; 1,80%). Differently, BCC was the most frequent tumor located on the nose (n: 33; 37,93%), on the glabella area (n:2; 2,30%), on the neck (n:1; 1,15%) and chin (n:2; 2,30%),. [Fig.1-11]

The percentage distribution per single area of the face for the different lesions found is shown in the following diagrams:

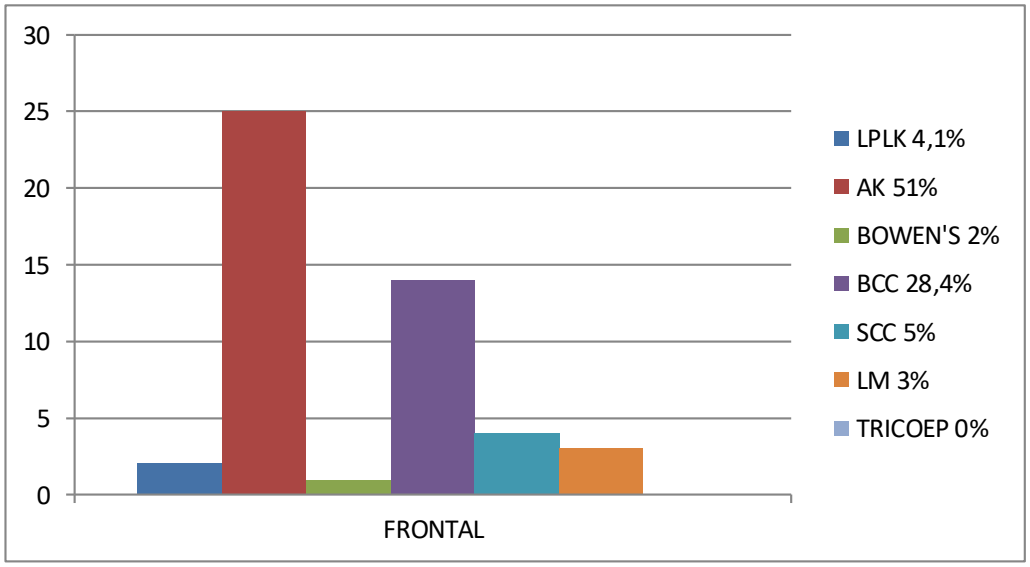

Figure 2 lesions in frontal region

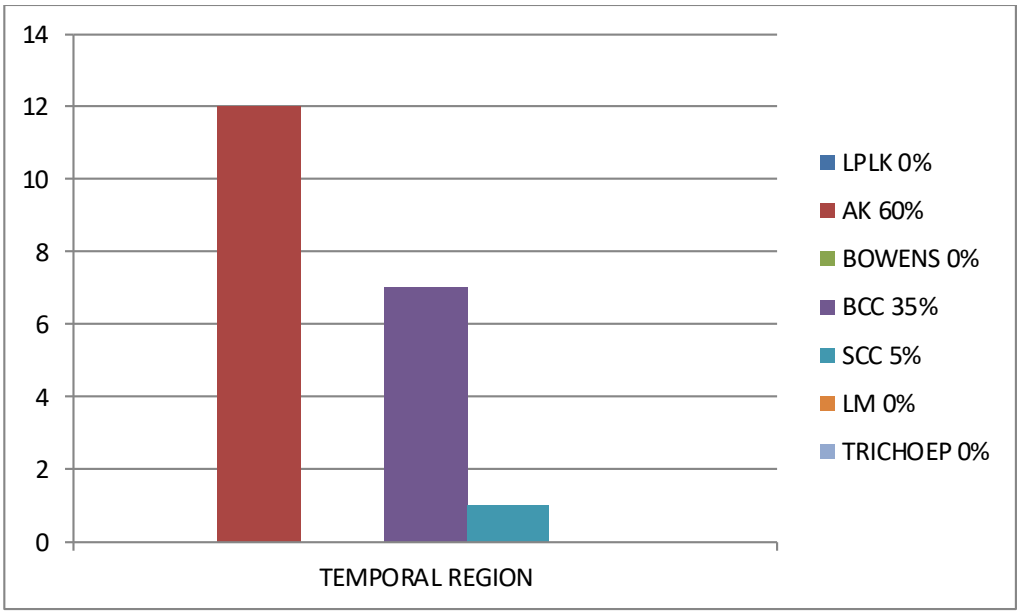

Figure 3 lesions in temporal region

CHEEK

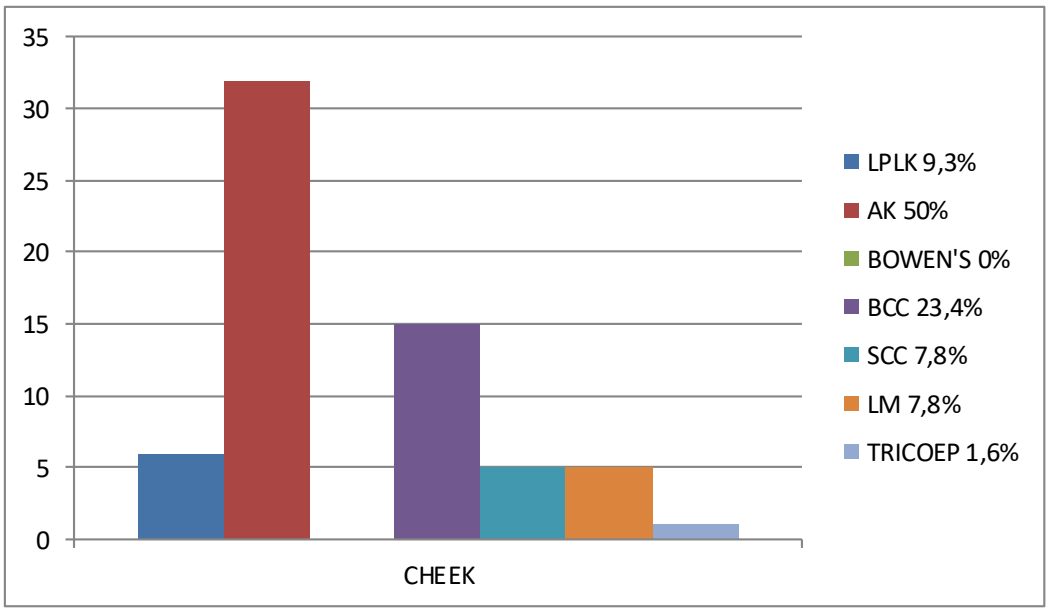

Figure 4 lesions in cheek region

CHEEKBONE

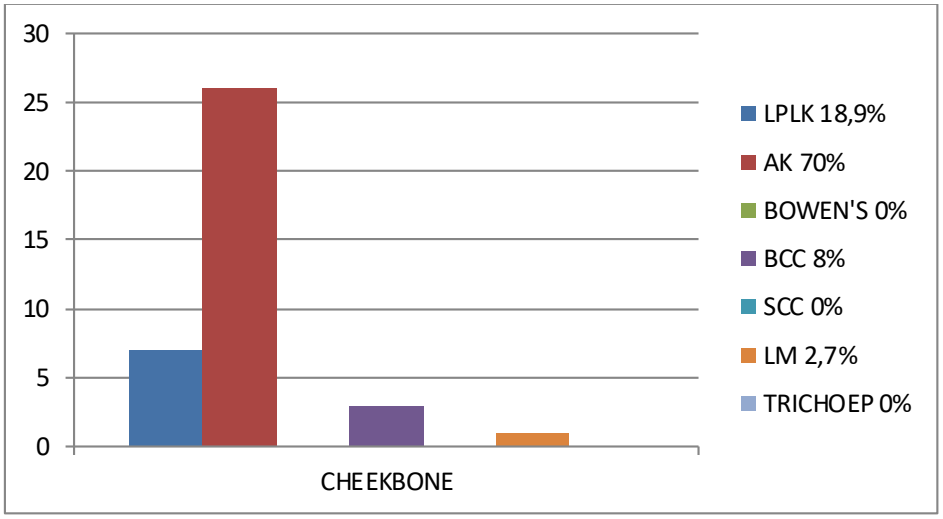

Figure 5 lesions in cheekbone region

CHIN

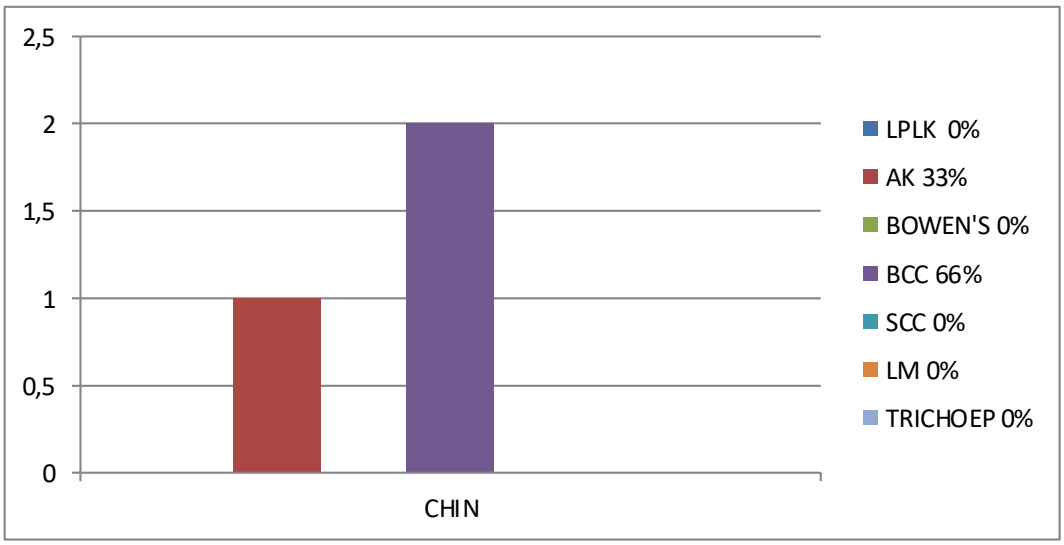

Figure 6 lesions in chin region

EYEBROW

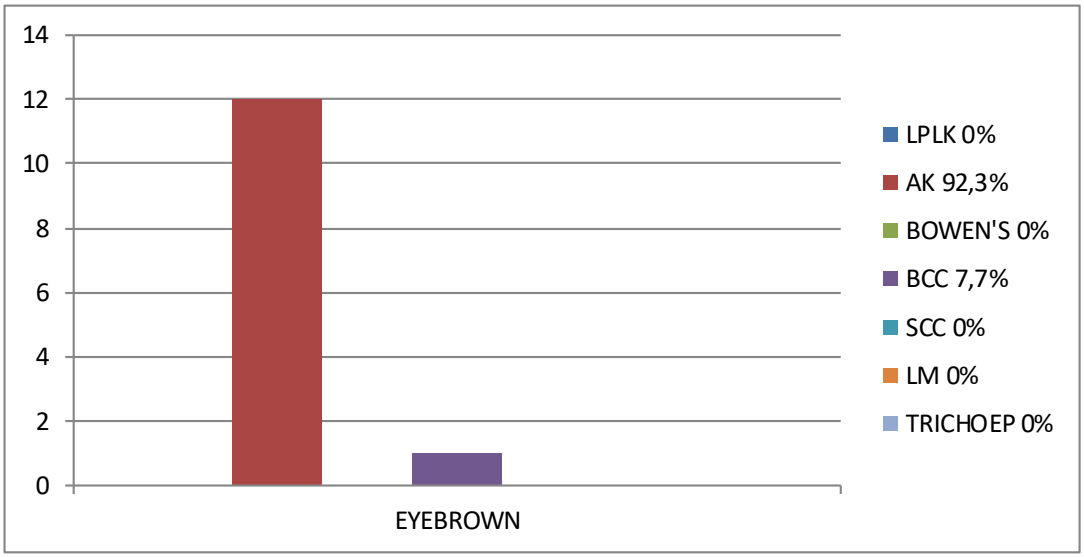

Figure 7 lesions in eyebrow region

EYELID

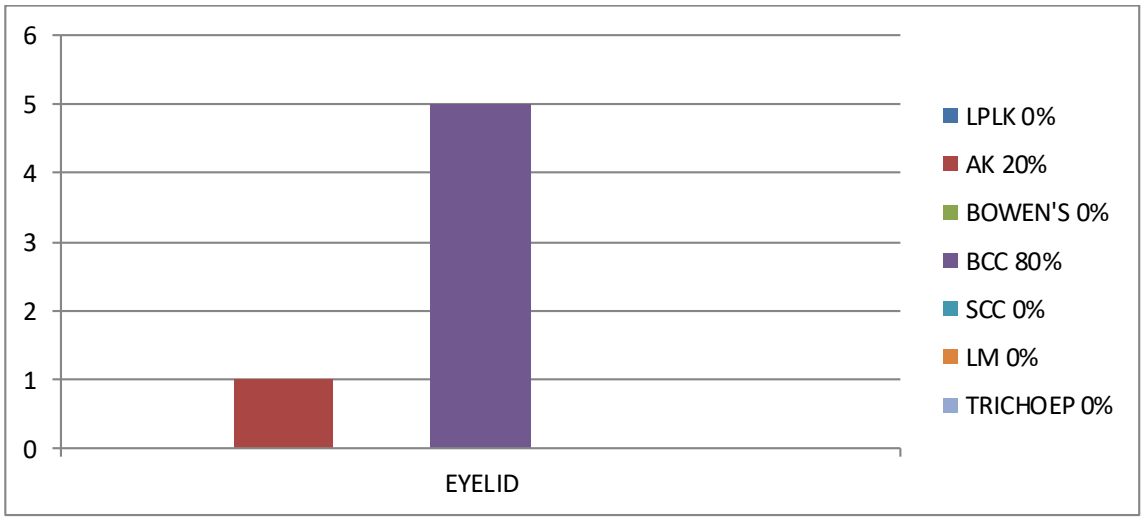

Figure 8 lesions in eyelid region

NOSE

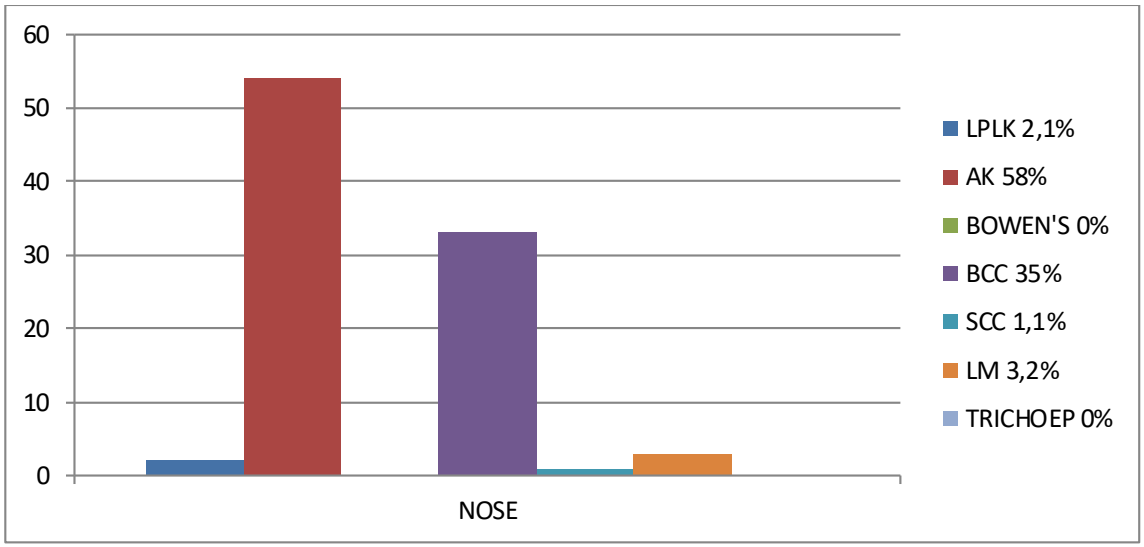

Figure 9 lesions in nose region

UPPER LIP

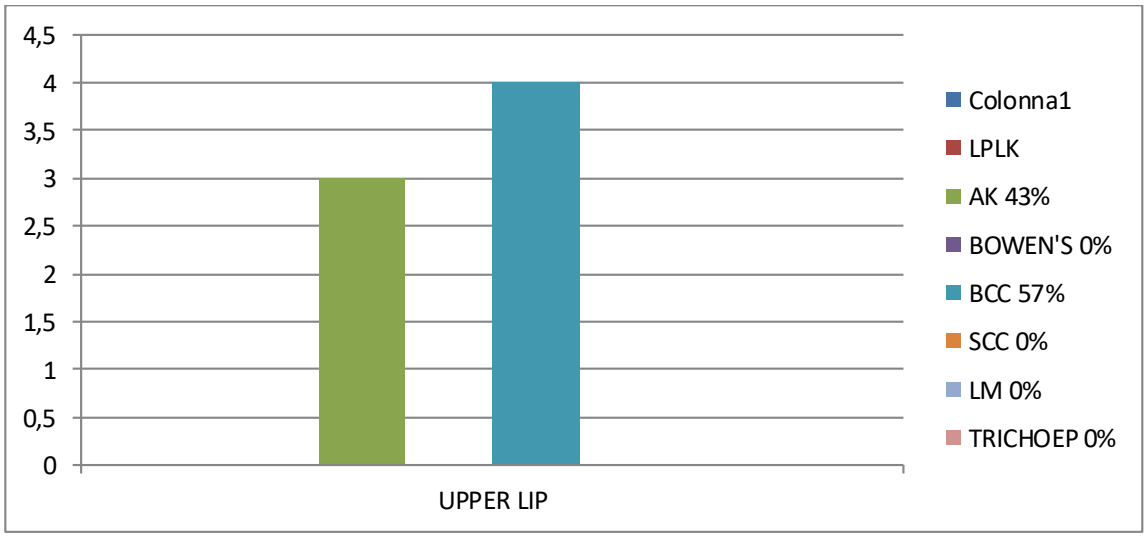

Figure 10 lesions in upper lip region

GLABELLA

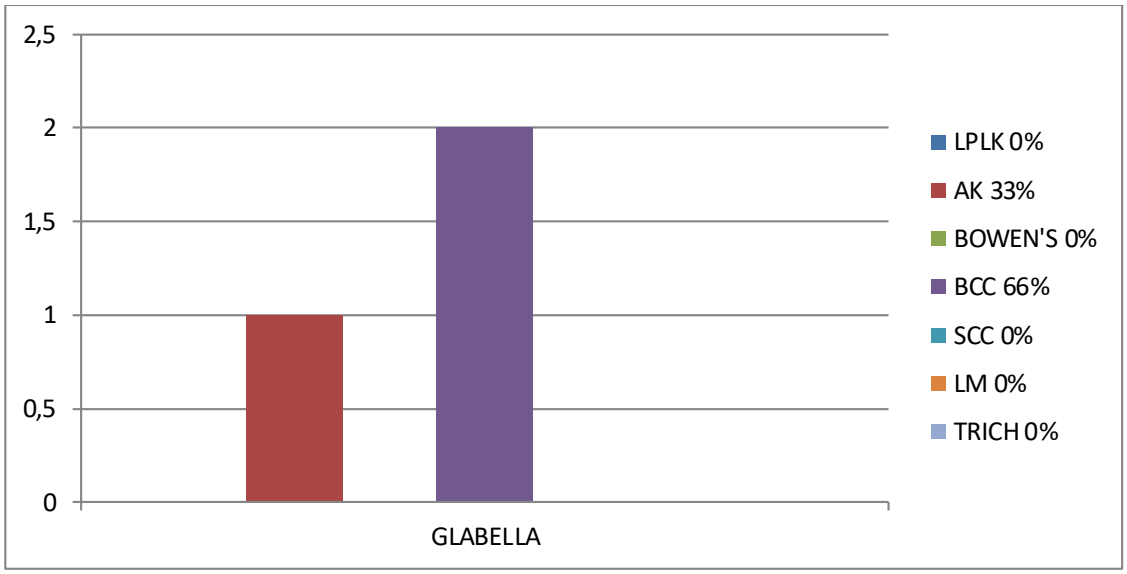

Figure 20 lesions in glabella region

NECK

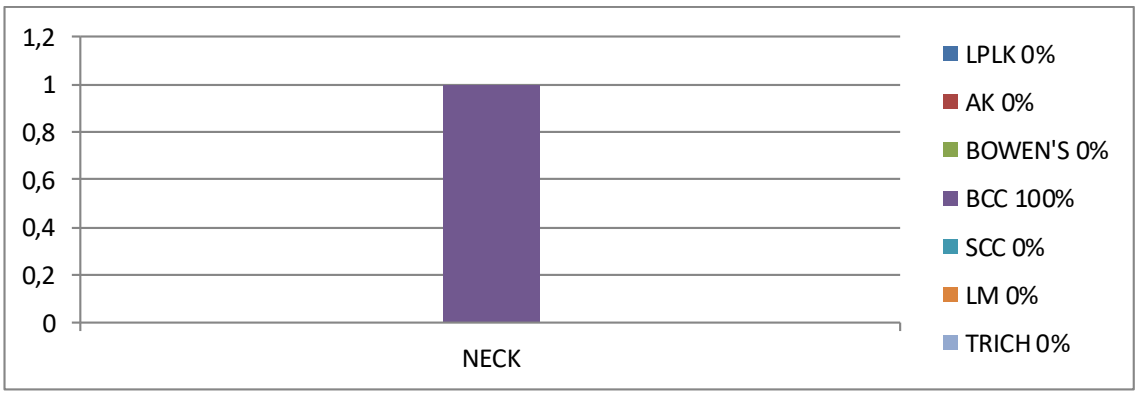

Figure 11 lesions in neck region

According to this data, LPLK was located mostly on the cheek (n:7; 41,18%), AK on the nose (n:54; 32,34%), BCC (n:33; 37,93%) on the nose, SCC (n:5; 45,45%) on the cheek, LM (n:5; 41.67%) on the cheek.

Comparison of data according to the different age groups

Analysis of the collected data showed that there are two peaks in the incidence of dermatological pathologies taken into account, one in the group between 61 and 70 years and the other between 71 and 80 years.
In detail, in age group 61 and 70 years the following lesions were most commonly encountered:

- 2 lichen planus like keratoses
- 17 actinic keratoses
- 12 basal cell carcinomas
- 1 squamous cell carcinoma

In the age group 71 to 80 years the following lesions were found:

- 1 lichen planus like keratosis
- 33 actinic keratoses
- 24 basal cell carcinomas
- 4 squamous cell carcinomas

Comparing these two age groups, the incidence of precancerous and cancerous lesions (in particular AK and BCC and to lesser extend cSCC) doubled in the age group 71 to 80 years.
The parameter of a positive history of a previous facial pathology related to photodamage (precancerous or cancerous) deserves attention when analyzing the two age groups.
Of the 61-70 age group with a new facial lesion, 9 (12.16%), including 6 men and 3 women, had a previous history of skin cancer in this area.
Of the 71-80 age group, 22 persons (25,29%), of whom 14 men and 8 women had a previous facial pathology.

Inter-observer agreement
Overall, there was good agreement between both evaluators concerning the clinical diagnosis, 236 out of 296 lesions (80%). For the dermoscopic diagnosis the overall agreement increased to 248 out of 296 (84%).Table 4 shows details on the agreement and dis-agreement concerning the clinical and dermoscopic diagnoses:

Lesion	aggreement clin	non aggreement clin	Aggreement DS	non aggreement DS
AK	120	23	140	22
BOW	1	1	1	1
BCC	82	21	81	8
SCC	11	4	8	7
LM	6	7	6	8
LPLK	16	4	12	2
Total	236	60	248	48
Percentage	79,73%	20,27%	83,78%	16,22%

Table 4: *Agreement between the two observers by Cohen's Kappa calculation*

Table 5 shows the results of the calculation of Cohen's Kappa coefficient

Table 5 - Cohen's Kappa calculated by comparing the results of the two assessors.					
Parameter	**Number of lesions**	**Cohen's Kappa**	**Confidence Interval (95%)**	***P value***	**Agreement**
Clinical assessment	338	0.72	0.66 – 0.78	<0.0001	Good
Dermatoscope assessment	338	0.78	0.72 – 0.84	<0.0001	Good
Assigned treatment	332	0.79	0.73 – 0.85	<0.0001	Good

Table n°5 The results show that the concordance between the two estimators can be classified as "Substantial".

7 DISCUSSION

Our records of patients presenting to a private dermatological clinic in Syracuse show a total of 296 lesions detected on the face. Actinic keratoses were the most frequent tumors (n=167; 56.4%), followed by basal cell carcinomas (n=87; 29.4%), lichen planus like keratoses (n=17; 5.7%), lentigo maligna (n=12; 4.1%), squamous cell carcinoma (n=11; 3.7%), Bowen's disease (n=1; 0.3%), trichoepithelioma (n=1; 0.3%).
It is well known that actinic keratoses generally occur in chronic photo exposed skin, most commonly in the upper limbs, face and scalp. These regions are responsible for 75% of the reported lesions. (166)
Our data are in line with previous published studies, in fact AKs detected during this research were most frequently located on photodamaged area such as the nose (32%), cheek (19%), cheekbone (16%), frontal (15%) or temporal area (7%), eyebrows (7%), upper lips (2%).

As regard to BCC, it can appear on any part of the body, but UV-exposed areas are frequently affected. Depending on the affected area specific histological subtypes are predominantly observed; superficial BCC is mostly found on the trunk, whereas nodular BCC is more frequently observed in the face and nasal area (88). Conforti et al also showed a predilection for BCC location on the lateral side of the forehead (12.7%), nasal dorsum (10.2%) and nasal ala (9.3%). (167).
Our study confirms this evidence because BCCs were most frequently tumor found on the nose (38%), cheek (17%), frontal area (16%). In contrast, Heckmann et al found no correlation between BCC in chronic sun-exposed areas: higher incidences of BCCs in pre-auricular crest and in the medial quadrant, as compared to the helix or to the lateral quadrant of the orbit. (168)
In our study, LPLK was located mostly on the cheeckbone (41%), cheek (35%), nose (12%), frontal area (12%). In contrast, Lyopiris et al (169) showed that lichen planus-like keratoses were most located on the trunk (52.1%, n = 185), and with evidence of chronic sun-damage (69.6%, n = 247), however as we focused only on facial lesions, a direct comparison with their data is not possibile.
In our study, LM was most frequently located on the cheek (42%), frontal area (25%), nose (25%), cheekbone (8%). This is in line with the study by Tiodorovic et al, who also repoted the cheek being the most common site especially in women, while scalp and non-cartilaginous areas of the nose were often seen in men. (110) Patients with LM typically present with a new, asymptomatic pigmented macule or patch localized in the head or neck area and incidence-wise, LM and LMM

account for approximately 4–15% of all melanomas, and represent approximately 10–26% of head and neck melanomas. (170)

SCC was the most frequent tumor located on the cheek (45%), frontal area (36%), temporal area (9%), nose (9%). However, a higher incidence of SCC was shown by Raasch et al in “less sun-exposed” areas of the face: forehead, pre-auricular, eyebrows, chin, and jaw, as compared to chronically sun damaged areas (171)

In conclusion, considering that the population with the highest incidence of skin cancer was between 71 and 80 years old, we can emphasize the importance of performing routine dermatological examinations even in the elderly because in this age group there is a high rate of keratinocytic tumors or melanoma subtypes as in the case of LM. The localization of the lesion helps in the diagnostic orientation although the dermatoscopic examination is essential for the correct differential diagnosis allowing an early diagnosis and ensuring the most appropriate treatment. Moreover, it has been shown that in 1 out of 10 persons aged 60+years, who present skin cancer suspicious lesions on sun-exposed areas, full body skin examination will reveal additional cancers on traditionally covered body sites such as the trunk and limbs (172); last but not least, this demonstrates the importance of a full body examination even if the patient has a solitary facial lesion with special attention to patients with a previous history of melanoma or NMSC and to patients older than 70 in which, as this research demonstrated, there is the highest incidence of cancerous lesions.

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