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WCCS 2022

Reports written by

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Dear colleagues,
I am extremely pleased to present you these summaries from the World Congress on Cancers of the Skin, held in Buenos Aires from 26–29 October 2022 with the support of Bioderma. The congress has been postponed several times since 2020, so when it finally happened, the opening session was really quite emotional.

Obstacles in melanoma prevention (why it does not work)

Following on from Prof. Boris Bastian's work to update the classification of the various types of melanoma (see the summary by Dr Manuela Martinez Piva), Prof. Claus Garbe listed the obstacles to the effective prevention of skin cancers, especially in Europe and the US (Garbe et al., EJC 2021).
He believes that Europe and the United States are struggling to see a reduction in skin cancer rates because there is not enough focus placed on prevention in the form of clothing as opposed to sunscreen. It appears that wearing just sunscreen encourages people stay in the sun for longer, which can ultimately be worse than not wearing it at all.
Whether they apply sunscreen or not, there is evidence that children get just as many naevi which progress with age (J Bauer et al., Am J Epidemiol 2005), but there is a significant fall in incidence when wearing a t-shirt, with or without shorts, and especially when wearing a hat. In practice, sunscreen is applied on average in the amount of 0.5mg/cm2 instead of 2mg/cm2.
Even low doses of UV (10% MED = minimal erythema dose) are mutagenic, irrespective of the presence of clinical sunburn. At these same doses, since there is no peeling of the skin, the keratinocytes (and of course the melanocytes) survive with their mutations. The best option is clothing and avoiding exposure.
Other countries have got the message: in Australia and New Zealand where people are strongly encouraged to cover up and seek shade, melanoma rates have been falling since 2010.
Prof. Garbe was controversial to the point of accusing the dermatologists present of being responsible for the rise in skin cancers if we ourselves only recommend sunscreen.

Update on the use of lasers for the Rx of photoaging and skin cancers

Next, Deborah Sarnoff (NYU) gave an update on the use of lasers for the treatment of photoaging. She recognises three main chromophores in the skin: haemoglobin, melanin and water.

For haemoglobin she recommends PDL (pulsed dye laser), KTP and YAG.
For melanin, lentigo can be treated with Q-switched laser (ruby or alexandrite).
For water, mainly laser treatment of wrinkles: ablative CO2, Erbium-YAG, based on the principle of creating micro-holes in the skin followed by neocollagenesis.
For all pre-cancerous lesions, Dr Sarnoff sometimes offers PDL, for example for actinic keratosis. For hard-to-operate in situ cancers (e.g. Gorlin syndrome or multi-operated XP), surgery remains the first-line option, but she described fairly good results with photodynamic therapy intensified with CO2 laser, known as LADD (laser-assisted drug delivery). This 2-in-1 method is highly effective but requires a longer recovery period and has not yet been tested in large-scale studies.
Finally, for in situ squamous cell carcinoma the treatment she offers is “fully” ablative (CO2 or Er-YAG), definitely not fractional, to obtain a complete response.
In the future, post-treatment verification of cancerous lesions using confocal microscopy would be ideal because simple clinical clearance is not always enough.

And that concluded the first day of the congress! See you tomorrow!

Dear colleagues,
The 2nd day of the WCCS started with two plenary sessions on melanoma, addressed in terms of its pathogenesis and treatment:

Pathogenesis of melanoma: evolution from precursor lesions

Prof Boris Bastian described the progression of “healthy” melanocytes to naevi, dysplastic naevi, and then melanoma. This progression is due to the gradual accumulation of UV-induced mutations for most cases of melanoma, but certain sub-types of melanoma (acral lentiginous, mucosal, and “blue naevus”-like) have a very different genetic profile that is independent of UV radiation.
He gave the example of a case of melanoma from a precursor naevus, for which he had conducted a histological and molecular evaluation: the benign part of this naevus harboured a BRAF V600E mutation, whereas the histologically cancerous part had acquired additional pathogenic *CDKN2A* (homozygous deletion), MAP2K1 P124L, and ARID1A P2161L mutations (Shain et al., NEJM 2015).
In his opinion, most melanomas start as a naevus through an early acquired activating mutation of the MAP kinase pathway (BRAF, NRAS, for example) and then progress to malignancy by accumulating *TERT* promoter mutations and then relatively late loss-of-function mutations in tumour-suppressor genes such as *PTEN* and *TP53*.
All this accumulation of mutations over time results in an increase in the TMB (= tumour mutational burden = number of non-synonymous mutations/Mb tumour DNA) between the naevus, dysplastic naevus, melanoma in situ, and (cutaneous) melanoma. At all these increasing TMB levels, the identifiable UV signature represents the large majority of the mutations. According to Professor Bastian, this research work suggests that it is particularly important to protect naevi from the sun.
Interestingly, he cited the work of Tang J, Feening E et al., Nature 2020, who sequenced human melanocytes biopsied from healthy skin and then amplified in culture.
The measured TMB was particularly high and was even correlated with the +/- photoexposed location of the biopsy (back > earlobe > buttock, etc.), displaying levels similar to the TMBs typically measured in authentic cases of melanoma. He suspects typical photo-ageing lentigines of being the clinical manifestation of these non-cancerous but mutated clones, a bit like, in haematology, a monoclonal spike can reflect the presence of a B-cell clone that is not necessarily cancerous.
Conversely, in acral lentiginous and mucosal melanomas, more gene amplifications are found than mutations. In his opinion, uveal melanoma and blue naevus melanoma, which typically harbour *GNAQ/GNA11* mutations, derive from the ventral migration of melanocytes from the neural crest,

giving rise to a mutational and evolutionary landscape that is very different from that of melanocytes deriving from classic dorsolateral migration (Adameyko et al., Cell 2009).

Neoadjuvant therapy for locoregionally advanced melanoma

Dr Jonathan Zager then described the growing relevance of neoadjuvant immunotherapy for locoregionally advanced melanoma, due in particular to the presence of tumour neoantigens upon initiation of treatment, as in the PRADO clinical trial evaluating ipilimumab 1 mg/kg + nivolumab 3 mg/kg, Reijers et al., Nature Medicine 2022, and in the S1801 trial. In the future, nivolumab 480 mg + relatlimab 160 mg every four weeks will probably even be favoured because this combination is better tolerated, but this still needs to be proven in a phase-3 clinical trial.

Skin cancer in the immunosuppressed patient

Immunosuppressed patients and HPV-induced genital lesions

Next, Dr Maria Ivonne Arellano Mendoza opened the session focusing on immunosuppressed patients and HPV-induced genital lesions.
Cell-mediated immunity enables HPV-induced genital lesions to be brought under control in immunocompetent individuals, but in transplant recipients, genital warts (including giant condylomata acuminatum or Bushke-Löwenstein's tumour) and anogenital carcinoma tend to proliferate.
In a retrospective study dealing with transplant recipients, these were found in 1.2% of patients, vs in 24% of patients as part of a prospective study, including 82% men. The prevalence of HPV lesions is therefore largely underestimated if they are not actively investigated (Nadhan KS et al., JAMA Dermatol 2018). It is important to inform patients that wearing a condom is not 100% effective at preventing transmission.
For primary prevention, the nonavalent HPV vaccine covers 63% of cervical HPV serotypes and 64% of anal HPV serotypes. For secondary prevention, in addition to the mucocutaneous examination, an annual Pap smear is recommended for transplant recipients.
Concerning the treatment of genital warts, among the various available local treatments such as trichloroacetic acid, podophyllin, photodynamic therapy, etc., the speaker strongly recommends imiquimod 5% cream, three applications/week, for up to 16 weeks, combined with cryotherapy every other week.

Merkel cell carcinoma in organ transplant recipients

Dr Carlos Garcia Rementeria then addressed the issue of Merkel cell carcinoma in organ transplant recipients, in whom it is more frequent and develops earlier (from age 65 vs 79 typically) and is more fatal than for immunocompetent patients (Ferrandiz-Pulido C et al., JEADV 2022).
The more HLA mismatching there is between the transplant donor and recipient, the greater the risk of skin cancer for the recipient, because the immunosuppressive treatment is intensified.
This type of iatrogenic immunosuppression is much stronger than that induced by HIV or the treatments proposed for an autoimmune disease.
If Merkel cell carcinoma is diagnosed, a PET scan (without brain imaging in the absence of symptoms) is recommended followed by excision with at least 1 cm margins (+/- sentinel node) and then radiotherapy.
In the event of immunotherapy, in 2022, in J Dermatol, Nakamura M. et al. published an article demonstrating the relevance of combining two predictive biomarkers for response: in particular, high PD-L1 expression and low G6PD (glucose-6-phosphate dehydrogenase) expression.

Role of systemic treatments for immunocompromised patients with skin cancer

Next, Dr Claas Ulrich had the tough task of discussing the role of systemic treatments for immunocompromised patients with skin cancer. As discussed at the 2022 EADO Congress,

preventive treatment with acitretin seems unanimously recognised as being more effective than nicotinamide (non-significant results) for the prevention of actinic keratosis and squamous cell carcinoma. Chemotherapy with capecitabine can help in extreme cases (Breithaupt et al., JAAD case reports 2015).
Regarding the curative treatment of advanced stages, he reported the results of a retrospective study focusing on 39 cases of (heart, liver or kidney) transplant recipients treated with PD-1 inhibitors and/or ipilimumab at the MD Anderson Cancer Centre. Organ rejection occurred in 41% of patients (15/39), including 40% treated with PD-1 inhibitors and 36% with ipilimumab. The rate of rejection was higher when the immunosuppressive treatment was simultaneously decreased during immunotherapy (50% vs 32%). However, responses were also reported in 36% of melanoma cases and 40% of squamous cell carcinoma cases.

Transplant recipients

Prof Kiarash Khosrotehrani shared his experience creating a fast-track clinic dedicated to transplant recipients where they can be clinically and dermoscopically diagnosed and also operated on. For actinic keratosis, in addition to acitretin, he underlined the relevance of cryotherapy (isolated lesions) and topical 5-FU (multiple lesions) and the need to adapt the immunosuppressive treatment with sirolimus/everolimus (mTOR inhibitors) for patients who have developed a high-risk squamous cell carcinoma or multiple squamous cell carcinoma of the skin (according to the expert consensus determined using the Delphi method, Massey et al., JAMA Derm 2021).
As oral mTOR inhibitors are relatively poorly tolerated, he demonstrated the relevance of topical sirolimus 1% as part of his randomised, double-blind, placebo-controlled clinical trial, on 30 patients for 12 weeks, for reducing the incidence of intraepidermal carcinoma and actinic keratosis.

Dermoscopy

Characteristics of melanoma according to the patient's phototype

Dr Susana Puig spoke more specifically about the characteristics of melanoma according to the patient's phototype. For example, **for patients with phototype 1**, where persons with red hair are homozygous for variants of the MC1R gene, the clinical appearance is less significant: melanoma is often pinkish, and the "ugly duckling" sign is less effective. Although dermoscopy makes a distinction between dotted and comma vessels, monitoring via confocal microscopy appears particularly appropriate: its sensitivity is not altered by the colour of the lesions.

Preoperative confocal microscopy in Dubreuilh's melanoma

Dr Cristian Navarrete-Dechent also highly recommends the use of preoperative confocal microscopy in Dubreuilh's melanoma (whether primary or recurring).

Combining total body photography with digital dermoscopy monitoring

Dr Gabriel Salerni talked about the relevance of combining total body photography with digital dermoscopy monitoring in patients particularly at risk for melanoma. This reduces the number of unnecessary excisions and enables thinner melanomas to be excised.

Skin Cancer Pathology

Recommended monitoring in the event of germline mutations in BAP1

Prof Richard Scolyer clarified the **monitoring that is recommended in the event of germline mutations in *BAP1***: ophthalmological (uveal melanoma?), radiological (mesothelioma?), dermatological + dermoscopic monitoring every six to 12 months from the age of 18 (melanoma?), renal ultrasound (renal carcinoma?) (interdisciplinary consensus of Star P et al., Eur J Cancer 2018).

He spoke about the trap of naevoid melanoma, also known as lawyer's melanoma, as it often gives rise to legal action. It can occur at any age, in any gender, on any site; it mimics a naevus because it is well circumscribed but asymmetrical; its pigmentation varies and the papillae appear stuffed ("puffy shirt sign"). The presence of mitoses, as well as FISH and/or CGH, can help with the diagnosis.

Relevance of molecular biology for melanoma patients

Lastly, Prof Boris Bastian explained the relevance of **molecular biology** (high-throughput sequencing, FISH, CGH) for melanoma patients, not only for **theranostic** (access to targeted therapies) but also for **diagnostic** purposes.

Histology of squamous cell carcinomas with a high risk of recurrence

To conclude, Dr Gabriel Casas ended this second day by addressing the **histology of squamous cell carcinomas with a high risk of recurrence**, like those of the lips, temples, and ears.
A Breslow thickness < 2 mm suggests a good prognosis without metastases, but a Breslow thickness > 5 mm gives rise to metastases in 20% of patients.
He argues in favour of including lymphovascular invasion and "satellitosis"/presence of in-transit metastases in the current AJCC classification.

And that's all for the 2nd day of the congress. I'll report back tomorrow for the next part!

Dear colleagues,

Cutaneous telemonitoring

In my opinion, the most interesting topic covered on the 3rd day of the WCCS was experience-sharing on **cutaneous telemonitoring** by Prof Peter Soyer, in Australia where melanoma is the most common form of cancer in 15- to 39-year olds. A network for the telemonitoring of naevi has been created as part of the **"ACEMID" (Australian Centre of Excellence in Melanoma Imaging & Diagnosis) cohort study**, benefiting from millions of dollars in funding.
To date, this cohort constitutes the world's largest repository of skin images and combines genetic, histological and dermoscopic data using an artificial intelligence approach.
Beyond its scientific and medical significance, this network is helping restore equitable access to dermatological expertise across Australia.
Patients are included in this cohort with personalised monitoring of their medical history and past sun exposure; they also undergo **3D total-body photography (via the assembly of 92 photos taken from a multitude of angles) and dermoscopy**, at variable rates. The patients are invited to complete quality-of-life, acceptability, and sun protection questionnaires.
According to Prof Soyer, due to the technological complexity associated with this type of monitoring, a new technical profession should soon emerge – that of a **"dermatological data technician"**, based loosely on the model of the technicians currently practising in the areas of radiology and nuclear medicine.

Cutaneous field cancerisation

A session was also dedicated to the **management of cutaneous field cancerisation**, which often occurs on the scalp of men over the age of 70 with a high level of past sun exposure.

Actinic keratosis

Dr Emilia Cohen Sabban reiterated that although 25% of actinic keratoses disappear spontaneously, these are extremely early forms of squamous cell carcinoma (SCC) in situ according to J Röwert Hubern, Br J Dermatol 2007.
From a genetic standpoint, actinic keratoses harbour the same oncogenic mutations as SCC, into which 0.1 to 20% of them progress (TP53 gene among others). Conversely, 80% of cutaneous SCCs derive from actinic keratosis.
In the context of field cancerisation, cryotherapy has the disadvantage of being a highly localised treatment that causes depigmented scars. It is therefore preferable to **favour broader treatments such as 5FU, imiquimod**, photodynamic therapy (PDT), +/- calcipotriol.
Some practitioners combine these treatments; for example, Dr Cohen Sabban frequently proposes 10 days of application of 5FU before using MAL (methyl aminolevulinate) PDT.

Advantages of PDT

Prof Rolf Markus Szeimies reviewed the advantages of PDT using natural or even artificial daylight to not be dependent on weather conditions and to improve patient satisfaction during treatment.

Evaluating the efficacy of these topical agents

Concerning the evaluation of these topical agents' efficacy, Prof Raul Cabrera warned against the simple counting of actinic keratoses: **taking photos is a more reliable** way to distinguish between treatment failure and a response accompanied by the onset of new neighbouring lesions.

Recently, **in a retrospective study, Brian Cheng et al., JAAD 2022, demonstrated the superiority of 5FU and imiquimod, in comparison with PDT** using ALA (5-aminolevulinic acid), for limiting the incidence of invasive SCCs within one year of treating actinic keratoses. There was no significant difference between 5FU and imiquimod. The authors conclude that clinical trials should include, as evaluation criteria, the subsequent onset of SCCs in addition to the simple clinical response of the treated actinic keratoses (which itself should be standardised using the actinic keratosis area and severity index (AKASI) score.

Transplant recipients

In **transplant recipients** as well, Dr Maria Ivonne Arellano Mendoza particularly recommended, for field cancerisation, the use of **topical 5FU** (Zeeshaan-Ul Hasan et al., BJD 2022).

Cutaneous toxicity of new cancer treatments

Next, the cutaneous toxicity of new cancer treatments was covered by Dr Monica Noguera, Dr Jade Cury-Martins, and Prof Reinhard Dummer.
Such toxic effects are frequent and often affect the quality of life of patients. Fortunately, they can be precursors of treatment efficacy (example of the toxic effects of EGFR inhibitors).
The context of **immunotherapy** in particular raises the issue of the **negative impact of high-dose corticosteroid therapy** (60 mg/day or more) on patient survival, especially when it is administered within the first eight weeks of immunotherapy (Xue Bai et al., Clin Cancer Res 2021).
It is worth noting that immune-induced cutaneous toxicity does not necessarily recur if immunotherapy is resumed. Future developments should focus on the **relevance of topical JAK inhibitors** for these immune-induced cutaneous drug reactions and on better understanding the related role of the digestive microbiome and the patient's genetic background.

Rare cutaneous toxic reactions

Dr Jade Cury-Martins reported some rare cutaneous toxic reactions such as:

- a case of **facial lipoatrophy induced by a PD-1 inhibitor**, symptomatic of **lymphoplasmacytic panniculitis** and improved via lipofilling.
- a case of **eruptive pyogenic granulomas** observed during treatment with **encorafenib** + EGFR inhibitors, secondary to the **paradoxical activation of the MAP kinase pathway** with BRAF V600 inhibitors, in wild-type BRAF cells, as explained by Prof Reinhard Dummer.
- a case of **grade 3 pruritus, with hyper IgE > 2000**, during treatment with the **TIGIT inhibitor "vibostolimab"** +/- pembrolizumab as part of a phase I study (J. Niu et al., Annals of Oncology 2022).
The biopsy revealed perivascular dermatitis with eosinophils and negative immunofluorescence. The pruritus was so unbearable that the patient was withdrawn from the study and treated with **subcutaneous omalizumab 300 mg**, with rapid and complete regression of the pruritus: it is difficult to affirm whether this improvement was related more to treatment discontinuation or to omalizumab. This treatment had been proposed according to the publication by DM Barrios et al., Annals of Oncology 2021, showing an 82% response rate for omalizumab in recalcitrant pruritus induced by immunotherapy or anti-HER2 therapies.
New targeted therapies prescribed in particular for bladder cancer cause new cutaneous toxic reactions:
- **erdafitinib, an FGFR1-4 inhibitor**, is responsible for **calcinosis cutis, calciphylaxis, paronychia and onycholysis** after one to two months of treatment (ME Lacouture et al., The Oncologist 2021).
- **enfortumab vedotin (Padcev*), a nectin-4 antibody linked to a microtubule inhibitor**, leads to adverse drug reactions in 55% of patients from the 2nd week of treatment, including **13% grade 3-4 reactions**, as well as symmetrical drug related intertriginous and flexural exanthema **(SDRIFE)** (ME Lacouture et al., The Oncologist 2022).

Photoprotection

On the topic of photoprotection, Prof Henry Lim demonstrated the **association between the regular application of sunscreen or moisturiser and frontal fibrosing alopecia** (risk increased by 45% for sunscreen vs 26% for moisturiser for the face) in his systemic review and meta-analysis that he published this year, J Maghfour et al., JAAD 2022. However, the causal link has not been established. He also mentioned a study in 3418 adults that showed that **careful photoprotection does not have a negative impact on the presumed risk of osteoporosis/fracture**. On the contrary, people who protect themselves extensively from the sun appear to have fewer fractures, but this is probably related more to exacerbated caution (M Afarideh et al., JAMA Dermatol 2021).

Lastly, he and Prof Sergio Schalka explained how **tinted sunscreens** (containing iron oxide) have the advantage of also protecting against **high-energy visible light** (blue/violet, wavelength range of 400-500 nm), which also causes post-inflammatory pigmentation and melasma. Indeed, "opsin" photoreceptor proteins are found in the eyes and on the surface of keratinocytes and melanocytes. Opsin 3 is present in particular on the melanocytes of phototype 3 to 6 individuals. Therefore, protection against visible light is especially useful for these darker phototypes.

Despite the emergence of three new UV filters including MCE, BDBP and TRIASORB, **Uli Osterwalder**, a chemist specialising in photoprotection, reiterated that **nothing beats protective textiles**.

Cutaneous lymphoma

Concerning cutaneous lymphoma, Dr Mariana Arias spoke about **primary cutaneous anaplastic large cell lymphoma**, which affects 1.45 men for every one woman (median age at diagnosis of 59) and is often associated with a history of other cancers.

Often presenting as ulcerated nodules, it sometimes spontaneously regresses (10-40% of cases) and has a rather good prognosis.
However, 10% of cases show locoregional lymph node invasion and 20% progress to a multifocal distribution. Histologically, it is characterised by CD30+ > 75%.
A clinical, biological and radiological evaluation with a **PET scan** is recommended (+/- bone marrow biopsy depending on the case).
Treatment combines surgery and radiotherapy or consists of radiotherapy alone if there is a single lesion; it may include brentuximab in the event of multifocal progression. Long-term monitoring is recommended.

It was also reiterated that **pilotropic (or follicular) mycosis fungoides** may be either **indolent** (in the form of plaques, acneiform follicular papules, keratosis pilaris, with pruritus and follicular mucinosis) or **aggressive** (in nodular, tumoural or even erythrodermic form, with > 25% atypical cells in the dermis, > 10% ki67+ cells, > 10% blasts, with interfollicular epidermotropism, the presence of eosinophils and plasmocytes in the dermis, at an age > 60, or in the absence of a complete response). Treatment requires a multidisciplinary approach.

Now in terms of substance, I've finished summarising the 3rd day of the congress in Buenos Aires. With regard to "form", I do have a short anecdote from the congress to share with you. Today, in the middle of a slide show, a speaker said: "we shouldn't compare clinical trials with one another, but it's like with our ex-girlfriends – we shouldn't compare them, but everyone does! Hahaha". Aside from the fact that the comparison was rather awkward, it was quite funny to see him realise that he was addressing a mainly female audience, which didn't laugh at all at his joke! I think he'll remember that moment of solitude for a long time.
I'll check back with you tomorrow for the end of the show!

Dear colleagues,

Technological advances in the diagnosis and monitoring of melanoma patients

The last day of the WCCS started with technological advances in the diagnosis and monitoring of melanoma patients.

Future applications of "GEP" analyses

Dr Josep Malvehy set out some **futures applications of gene expression profiling (GEP) analyses**, which measure the differential transcription of a selection of mRNA. These GEP profiles will serve as biomarkers for malignancy, prognosis (predictors of melanoma recurrence) or the prediction of treatment response.
A 15-gene GEP analysis is already used in uveal melanoma to assess the risk of metastases (ditto for breast cancer).
On the skin, RNA can even be collected via a simple sticker applied to a suspicious lesion whose GEP analysis will help specify the degree of malignancy. This practice is not approved by the FDA but is already very popular in the United States.
To safely include this type of GEP test in the patient pathway, prospective trials are necessary (as in the trial by S Podlipnik, Cancers 2022, and the "NivoMela" trial which aims to test the relevance of nivolumab as adjuvant therapy in the event of a poor prognosis indicated by the "MelaGenix" test, T Amaral et al., EJC 2020).

Easier to apply, protein expression signatures in immunohistochemistry are also under development (R Reschke et al., Cancers, 2021).

Diagnosing melanoma in the digital age

To improve early diagnoses in the digital age, Dr Allan Halpern extolled the advantages of two-step monitoring, which is also popular among Australians, consisting of **total-body photography combined with prospective dermoscopic monitoring**. He encourages sharing the quantity of images thus generated with the ISIC public collection of melanoma photos, which will help improve the performance of artificial intelligence algorithms.

Public self-diagnosis apps

Dr Luis Mazzuoccolo criticised the **sensitivity and specificity of public self-diagnosis apps** (such as SkinVision, Miiskin, etc.), which are **overestimated in relation to real-life situations** (need for external confirmation). The performance of an artificial intelligence algorithm depends on the similarity of training data and test data, which vary depending on the population group and even depending on the type of smartphone taking the photo (Android vs iOS).

How to identify patients with a high risk of developing melanoma, and how to manage them

Prof Susana Puig reiterated that the people the most at risk of melanoma are those with a family or personal history of melanoma, and those with synchronous melanoma (a one in four chance of developing a subsequent 3rd melanoma), dysplastic naevus syndrome, or phototype 2 or 1, noting that all these factors accumulate one upon the other.
According to her **genotype-phenotype correlation** work, patients with ***CDKN2A*** mutations (= 20% of family melanomas) do not have more naevi than others but their naevi are more likely to be dysplastic. Conversely, patients harbouring an ***MITF*** mutation typically have a **large number of naevi** and tend to develop nodular melanomas.
According to her, a history of several spitzoid melanomas in the same individual should evoke a germline *TERT* or *POT1* mutation.

What's new in dermato-oncology?

To finish, on the topic of new therapies, Dr Fernando Stengel mentioned **tirbanibulin 1% (Klisyri)**, a new topical microtubule inhibitor for the treatment of actinic keratosis. This ointment is convenient in that it only has to be applied for **five days in a row**. However, its long-term efficacy, in comparison with the other topical agents available such as 5FU, remains to be determined.
Regarding systemic treatments for **advanced skin cancer** (melanoma, squamous cell carcinoma, Merkel cell carcinoma), all experts agree that the **role of surgery is gradually decreasing and giving way to neoadjuvant immunotherapy**. In the event of **inoperable metastatic melanoma in patients with a BRAFV600 mutation**, two recent clinical trials – SECOMBIT (phase 2) and DREAMseq (phase 3) – showed the **superiority of dual ipilimumab + nivolumab immunotherapy versus targeted dual therapy as first-line treatment** (except for symptomatic brain metastases, which are the exception).
It should also be noted that this year, the FDA and EMA approved **nivolumab + relatlimab (= an LAG3 blocking antibody)** as a first-line systemic melanoma treatment. In Europe, this new dual immunotherapy, which is better tolerated than **ipilimumab + nivolumab** but has a similar response rate, will be restricted to melanoma cases with a **low level of PD-L1 expression**.

All good things must come to an end – the WCCS is now over. I hope I helped you benefit from it, and I look forward to being in contact with you soon! Again, **a big thanks to Géraldine Fleury and**

Bioderma for giving me the opportunity to share this wonderful event with you.

Reports written by

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Mohs Society - LATAM

Clinical case presentations

In this session, experts in Mohs micrographic surgery gave presentations in which they talked about the challenges in oncological and reconstructive surgery on the various anatomical areas of the face.

Aluma Tenorio, Maria Soledad (Colombia)
Dr Aluma Tenorio presented various clinical cases relating to Mohs surgery and reconstruction in the lower third of the nose (nose tip, alas of the nose, soft triangle, and columella). While a skin flap in this area very frequently used and widely accepted is the frontomedial flap, it has some disadvantages that are worth mentioning: it adds a scar to the forehead, which is the area of skin from which the flap is taken; it can cause distortion to the brow; it requires a long pedicle, which causes more bleeding; it can give off an odour due to the accumulated blood; and it can even temporarily alter the field of vision. Additionally, the patient can lose the contours of cosmetic subunits and there can be transfer of hairs from the forehead to the nose. As such, other alternative skin flaps should be considered when it comes to repairing defects in the lower third of the nose, such as, for example, the interpolated melolabial flap. Often, if the surgical defect includes loss of cartilaginous support of the nose, you must first perform a graft of cartilage (whose donor site may be the auricular cartilage) to then be able to perform the melolabial graft. Often, for a better aesthetic result, you need a second round of surgery (which can be performed three weeks after the first round) whose purpose is to finish shaping the flap and harmonising the anatomy in the operated area. One important aspect when reconstructing the soft triangle of the nose is that the distal part of the flap should be thinner (so that the free edge of the nose doesn't turn out very enlarged) and the proximal part of the flap's pedicle should be thicker to ensure optimal blood flow. In her final conclusions, Dr Aluma Tenorio emphasised the selection of the melolabial flap as a good option for reconstructing defects of the lower third of the nose.

Cuellar Barboza, Adrian (Mexico)
Dr Cuellar Barboza presented the clinical case of a 78-year-old woman with ulcerate, infiltrative basal cell carcinoma with 2 years of progression on the right nasal wall and ala. Conventional surgery was done, but the anatomy of the pathology showed lateral surgical margins compromised by the tumour. As such, they decided to perform Mohs surgery with complete resection of the scar from the previous surgery. The surgery required two Mohs layers to obtain negative margins, leaving a surgical defect that compromised various cosmetic subunits of the right side of the nose: the nasal ala, tip, and wall. In this case, they had to perform a graft of cartilage from the auricular concha in order to be able to give structure to the posterior flap and prevent nasal valve collapse (which is the collapse of the nasal cavity when inhaling). Then, in two rounds of surgery, they placed an interpolated nasogenian flap with an inferior pedicle. In the second round of surgery (which was performed after three weeks), they freed the flap and placed transfixing sutures to shape the alar groove. In his final conclusions on the case, he mentioned: the need to completely remove the scar when dealing with tumoral relapse;

avoid defects of the nasal ala such as elevation of the nostril, erasure of the alar groove, or deceptive effects in reconstruction of defects of the nasal ala; lastly, you should consider the interpolated nasogenian flap as a good tool for defects of the nasal ala.

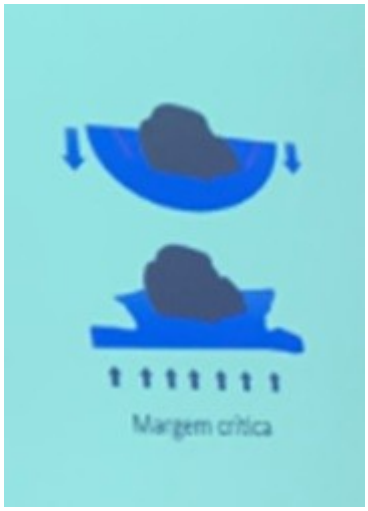
Etchichury, Dardo (Argentina)
Dr Etchichury presented the clinical case of a 73-year-old man with adenoid basal cell carcinoma that had returned twice after conventional surgery in the left pre-auricular region, on which Mohs surgery was performed. After three rounds of Mohs surgery, the deep margin was still compromised by tumoral cells. As such, they had to perform a superficial parotidectomy. The patient remained under periodic observation, and four years later, he presented another tumoral relapse in the area of the scar, of which the biopsy showed metatypical basal cell carcinoma. They decided to initiate treatment with normal doses of vismodegib. The patient received seven months of treatment with total response. Side effects experienced were severe cramping, moderate constipation, and mild fatigue. After finishing treatment with vismodegib, they decided to again perform Mohs surgery, which again produced evidence of remaining lobulated basal cell carcinoma in areas of fibrotic scarring, with superficial and deep margins free of lesions. They closed with a skin graft. In his final conclusions, Dr Etchichury emphasised the difficulty of treating patients with tumoral relapses, showed the range of therapy options, and stressed the importance of surgery after treatment with vismodegib.

Ferrario, Damian (Argentina)
Dr Ferrario presented the clinical case of an 85-year-old male patient with primary nodular and sclerodermiform basal cell carcinoma measuring 5 cm, with one year of progression, for which they decided to perform Mohs surgery due to the patient presenting high-risk criteria. Dr Ferrario showed the prior marking of the surgical margin to be taken with the Mohs surgery, which was done before injecting local anaesthetic. He also showed the antero-posterior dissection performed of the first Mohs layer to preserve unharmed the superficial temporal artery. Next, he showed how the sample was processed in the Mohs laboratory. He showed the relaxing cuts needed for good visualisation with the microscope of all of the superficial and deep surgical margins. He mentioned the care that must be taken when processing the sample to avoid false positives due to falling of the upper margin, caused by a lack of support of the sample on the slide. Three rounds of surgery were required to obtain negative margins. To close, they decided to use granulation and, by second intention, liquid bandages with vaseline and calcium alginate dressings. In his closing remarks, Dr Ferrario highlighted the importance of the anatomy and dissection planes for proper removal of Mohs layers, as well as the importance of proper handling of the surgical sample to avoid false positives. He also stressed that the secondary intention wound healing is an excellent option for patients with a large cancerised area and with high surgical comorbidities; however, its disadvantages include longer healing time with significant at-home wound care.

Paz Torres, Veronica (Uruguay)
Dr Paz Torres presented the clinical case of an 85-year-old male patient with infiltrative, moderately differentiated spinocellular carcinoma with perineural invasion on the external third of the lower eyelid with rapid growth (less than one month of progression). Mohs surgery was performed, which left a surgical defect with full density that involved more than 50% of the lower eyelid. For reconstruction, they performed a tarsoconjunctival graft, along with a Mustarde rotational cheek flap and advance of the homolateral cheek. Photos of the follow-up showed good cosmetic and functional results without relapse.

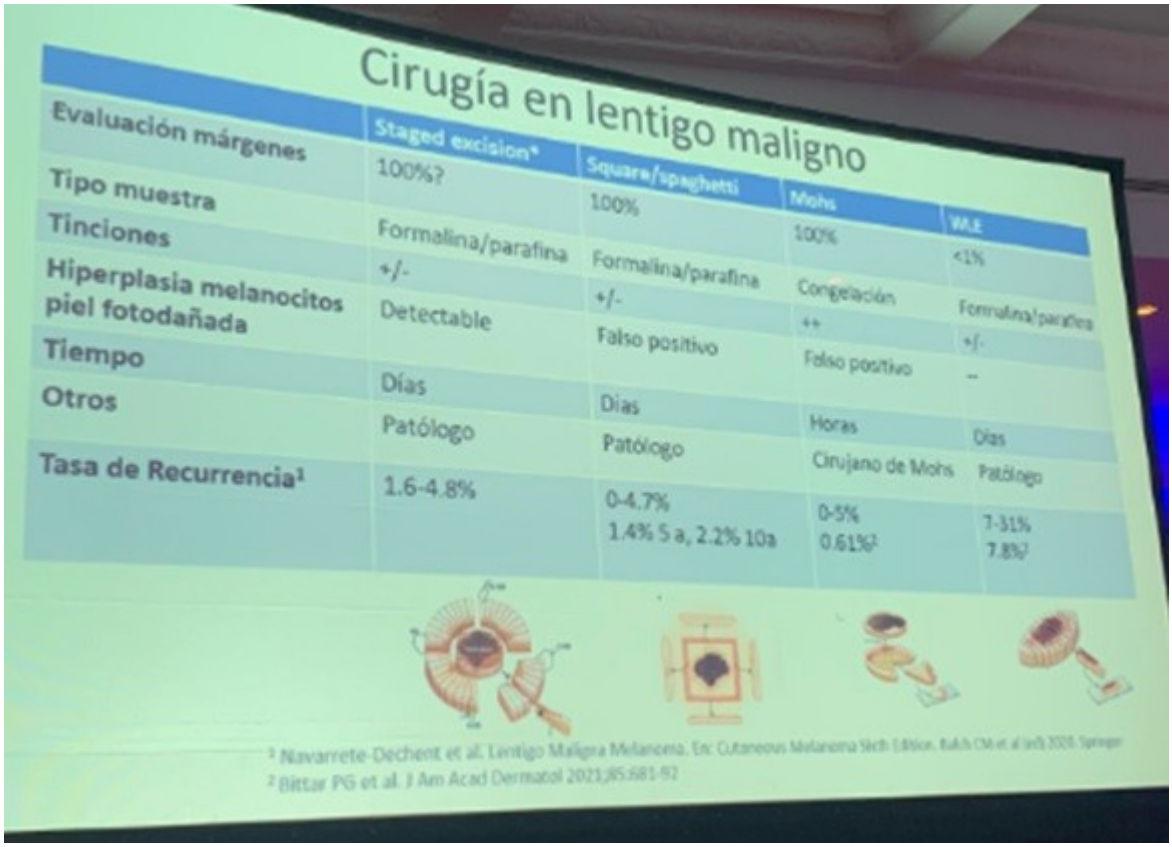
Gomes Tarlé, Roberto (Brazil)
Dr Gomes Tarlé started by talking about the difficulties of debulking for histological analysis during Mohs surgery in a thin area of skin due to the risk of compromising the deep margin of the surgical sample, whether that be due to perforation of the deep margin leading to a lack of tissue for

microscopic analysis or due to inadvertently removing cartilage, with a risk of chondritis or anatomical or functional alterations. He proposed, as an alternative, pseudobulking, which involves making a cut of partial thickness around the tumour without reaching the deep margin and without completely removing the tumour so that later, in the laboratory, the preparation of the surgical sample will be easier.



Terzian, Luis Roberto (Brazil)
Dr Terzian presented the clinical case of an 86-year-old male patient with basal cell carcinoma on his left lower eyelid. They performed Mohs surgery, which required two rounds to obtain negative margins and left a surgical defect with full thickness on 90% of the lower eyelid. For reconstruction, they performed a Hughes tarsoconjunctival flap advancement from the upper eyelid and then an inferior and lateral transposition flap. After two weeks, they cut the tarsal pedicle, with excellent cosmetic and functional results. Next, Dr Terzian presented the clinical case of a 43-year-old man with micronodular basal cell carcinoma who had undergone conventional surgery. They identified the deep margins compromised by the tumour. They performed Mohs surgery, which required three rounds to obtain negative margins and left a 3-cm surgical defect. It was reconstructed with a cheek advancement flap, with good cosmetic and functional results.

Uribe, Pablo (Chile)
Dr Uribe presented the clinical case of a 53-year-old male patient with a 1-cm lentigo maligna on his forehead. Lentigo maligna has higher rates of recurrence, subclinical spread, and upstaging, which makes treatment more difficult. Dr Uribe asked the audience how they would treat this patient according to normal practice, and he offered five options:
1 - Standard extension with 5 to 10 mm of margin
2 - Mohs surgery with cutting of tissue frozen with immunohistochemistry
3 - Staged excision with vertical radial peripheral cuts
4 - Staged excision using techniques like the spaghetti technique or square procedure
5 - Another way
He posed this same question to a group of 23 Chilean specialists of Mohs surgery, and they responded: 52.2% in favour of option 4, 26.1% for option 3, and 13% for option 1.
Dr Uribe explained a comparative table of these four surgical techniques for lentigo maligna.



In his final remarks, he commented on the great variability in existing surgical treatments for lentigo maligna. He also noted that the staged excision technique with vertical radial peripheral cuts allows you to better analyse the progression of the lentigo maligna within the margin, as well as to properly evaluate the actinic melanocytosis to differentiate it from the tumour, with favourable results.

Reconstruction

Malar reconstruction
Schuartz Cernea, Selma (Brazil)
When it comes to analysing reconstruction of the malar area, we have to take into account the anatomy of the facial nerve, of the parotid gland, and of the three cosmetic subunits that make up the area: the medial infraorbital, the pre-auricular-temporal, and the oral-mandibular. In the malar area, we can use direct closing, advancement flaps, rotational flaps, transposition flaps, or grafts.
Dr Schuartz Cernea showed multiple clinical cases in which, according to the size of the surgical defect, its location, and the experience of the surgeon, the doctors chose between the various alternatives for closing, from the simpler to the more complex.

Eyelid reconstruction
Devoto, Martin (Argentina)
Dr Devoto explained how you can close defects of the upper and lower eyelids according to their size. A small defect that compromises less than 33% of the eyelid can be closed with a simple closure, keeping in mind to first suture the tarsus on both sides with dissolvable sutures, and then the epithelium with mattress sutures to avoid furrows. For defects compromising 33% to 50% of the eyelid, you can perform a sliding flap procedure, and for defects compromising 50% to 100% of the eyelid, you need to perform a Hughes tarsoconjunctival flap procedure in two rounds. For the medial canthal area, we have several options: second intention, grafts, flaps, or combinations. The important thing here is to remember that the internal skin of the canthus is thinner and the external skin is thicker, and it’s important to account for these characteristics for an optimal post-surgical result. In his final comments, Dr Devoto said that the most important thing in the periocular region is to first

maximise the cure rate of basal cell or spinocellular carcinoma by performing Mohs surgery, and then preserve the function and cosmetics of the area.

Nose reconstruction
Vieira, Ricardo (Portugal)

Nasal defects can be classified according to:
1 - Location: lower third, middle third, and upper third, or multiple thirds of the nose
2 - Depth: only compromises the skin or compromises the entire thickness (skin and cartilage)
3 - Size: smaller or larger than 2 cm
The nose has various cosmetic subunits: the dorsum, tip, wall, ala, and soft triangle. We will get better results when the scar is hidden in the limits of the cosmetic subunits and when the entire subunit is repaired.

Reconstruction options for defects smaller than 2 cm: nose skin flaps or perinasal flaps as the donor area:
1 - Transposition: unilobulated, bilobulated, or trilobulated
2 - Advancement: east to west, semilunar, V to Y

Reconstruction options for defects larger than 2 cm: nasolabial transposition flap, nasolabial and frontomedial interpolated flap, or graft.

When is a cartilage graft required?
When structural support is needed and when there are functional and cosmetic implications. It is used for small full-thickness defects on the soft triangle of the nose, on the nasal ala, and larger defects on the nose tip or septum. Typically, cartilage from the ear is used as a donor area.

In his final conclusions, Dr Vieira noted that nasolabial, bilobulated, and trilobulated transposition flaps are very useful in this area. A cartilage graft is necessary for small full-thickness defects of the soft triangle of the nose and nasal ala. The frontomedial flap is the best option for large defects on the nose.

Large facial defects following Mohs surgery
Gonzalez, Abel (Argentina)
The principles to bear in mind for the repair of large surgical defects on the face are:
1 - Always take into account the cosmetic units when doing reconstruction.
2 - Try to replace tissue loss with tissues that have similar characteristics, giving preference to local flaps as they offer a better match.
3 - Usually, the number of surgical steps is correlated with the result, but you should consider a cost-benefit analysis and the preferences of the patient when deciding on this aspect.

Updates to the WHO classification: How many melanoma subtypes are there?

Bastian, Boris (United States of America)

We will discuss the various types of melanoma and their main characteristics.

Melanoma on sun-exposed skin

Depending on the level of cumulative damage caused by UV radiation (UVR), from less sun exposure to more:
1 - With low cumulative sun damage (CSD): BRAF V600E mutation, low mutational load, with a peak in incidence at 50 years old.
2 - With high cumulative sun damage (CSD): mutations NRAS, NF1 KIT, BRAF V600K, with a high mutational load (secondary mutations add up and lead to melanoma), increase in incidence in older age.
3 - Desmoplastic melanoma: NF1, high mutational load, with increasing incidence in older age.

Solar elastosis also increases with the accumulation of chronic sun damage.

Analysing the number of somatic mutations in various cancers affecting humans, we see that the mutational load, measured as the number of mutations per megabase, is very high for melanoma, being among the cancers with the highest numbers of mutations.
We also see that cutaneous melanoma in sun-exposed skin with high CSD has a high mutational load, whereas mucosal and acral melanomas (not exposed to the sun) have low mutational loads.

Melanoma on protected skin

1 - Acral melanoma: mutations NRAS, KIT, (BRAF V600E low), increasing in incidence in older age, very unique pattern of early genomic structural rearrangement.
2 - Mucosal melanoma: mutations NRAS, KIT, increasing in incidence in older age, also with structural rearrangement (BRAF V600E absent).
3 - Uveal melanoma: mutations in the Gαq pathway, GNAQ, GNA11, very different from other melanomas, with a low mutational load and no evidence of structural rearrangement; it also increases in incidence in older age.

The structural rearrangement in acral and mucosal melanomas is very complex, with fusion between chromosomes (for example, chromosomes 5 and 12) and intrachromosomal rearrangement.

Other melanoma subtypes
1 - Melanoma in blue nevus: Gαq mutations GNAQ, GNA11, increasing in incidence in older age
2 - Melanoma in congenital nevus: NRAS mutations (probably becomes melanoma through additional mutations induced by UVR)
3 - Spitz melanoma; HRAS mutations and fusions with BRAF, NTRK, ALK, RET, ROS, MET, MAP3K8, more frequent in young people and children, more favourable progression compared to other melanomas

Shared characteristics of uveal melanoma, melanoma in blue nevus, and melanoma in the leptomeninges
They have primary mutations: GNAQ, GNA11, PLCB4, CYSLTR2, which are later joined by secondary mutations: BAP1, EIF1AX, SF3B1, to ultimately develop into melanoma. They share a greater prevalence of metastasis to the liver.

Genetic evolution of melanocytoma
From a normal melanocyte ----1st mutation: nevus ----- 2nd mutation: melanocytoma (intermediate tumour) ------ 3rd mutation: melanoma

Melanocytomas according to the WHO
1 - With deep penetration: MAP kinase pathway + BRAF

2 - Inactivated BAP1: MAP kinase pathway + loss of BAP1
3 - Pigmented epithelioma: MAP kinase pathway + PKA pathway

Differences in WHO classification of melanoma

3rd edition
Superficial spreading melanoma
Nodular melanoma
Nevoid melanoma
Persistent melanoma
Childhood melanoma

4th edition
Melanoma with low CSD
Melanoma with high CSD
Nevoid melanoma does not exist
Persistent melanoma does not exist
Spitz melanoma

Brazilian Melanoma Group

Brazilian Dermoscopy Cases

Dr. Renato Marchiori Bakos

The first case presented corresponded to a phototype-IV patient, with a clinically ulcerated lesion, whose dermoscopic examination revealed peripheral pigmentation in the form of pseudopods (shaped as maple leaves). Given the above finding, a differential diagnosis of melanoma versus basal cell carcinoma (BCC) was proposed, with a biopsy confirming the diagnosis of BCC. The highlight message of this case is that dark-skinned subjects may exhibit unusual patterns that should be taken into consideration.
The second case was that of a patient with a pigmented, nodular, neoplastic lesion, with a proposed differential diagnosis of melanoma versus squamous cell carcinoma. A dermoscopic examination showed milky-red vascular areas and ulceration with a focus of perifollicular pigment. A histological study yielded a combined diagnosis of lentigo maligna and desmoplastic melanoma. The main takeaway of this case is to pay attention to atypical variants of melanoma.
The third case was a pigmented lesion that, viewed under dermoscopy, looked compatible with seborrheic keratosis with follicular pseudo-openings associated with peripheral pigment spots, which could be compatible with a melanocytic lesion. Its biopsy yielded a diagnosis of seborrheic keratosis.
The fourth case was a pigmented lesion of 15 years' evolution, with the clinical appearance of a nevus, albeit with a more pigmented area. A dermoscopic examination of this area revealed a network of pigment and pigment globules, and its biopsy yielded a diagnosis of melanoma with a Breslow depth of 2 mm. The core message of this case was its reference to a new dermoscopic structure to be analysed: a dermoscopic island sitting on a pigmented lesion.
The fifth case consisted in a pinkish lesion, which, under a dermoscopic examination, exhibited vascular polymorphism with areas of pigment and a peripheral network. The lesion was diagnosed as a naevoid melanoma. The key conclusion in this case was the need to consider different melanoma variants.
The sixth case report involved a lesion with a pigmented nodular area viewed under dermoscopy, with peripheral, granular pigmentation and areas compatible with milium pseudocysts. Its biopsy yielded a diagnosis of lichenoid seborrheic keratosis.

The seventh case was that of a transplant patient presenting with a nodular, erythematous lesion of 3 months' evolution, which exhibited an ulcerated area with vascular polymorphism and milky-red areas under dermoscopy. Its biopsy confirmed a diagnosis of Merkel cell carcinoma. The speaker emphasised on reminding the audience of the main AEIOU features of this carcinoma: Asymptomatic, Expanding rapidly, Immune suppression, Older than age 50, and UV-exposed site. The fundamental message of this case was to pay attention to melanoma simulators.
The eighth case was a pigmented foot lesion of 3 months' evolution, with pigmented spots and linear pigmented structures under dermoscopic examination, which was eventually diagnosed as tinea nigra. The main takeaway of this case was to use dermoscopy in general dermatology.

Recommendations for Sentinel Lymph Node Biopsies in Stage-IIB and -IIC Lesions

Dr. Joao Duprat

The current indication for the conduct of sentinel lymph node biopsies (SLNBs) in Brazil is:
- Melanoma with a Breslow depth greater than 0.8 mm or ulcerated melanoma with a Breslow depth below 0.8 mm
- Stages IB to IIC

The advantages of performing a SLNB are: regional control of the disease; it is a simple, low-risk surgical procedure with few side effects; it allows for correct staging of the patient's disease; and it is key in determining the indication for administering adjuvant treatment.

Mortality according to the T-stage: at stages I and II, Kaplan-Meier curves of the specific melanoma survival times according to the T-stage of the disease show a lower 5- and 10-year survival rate in stage T3b melanomas compared with T4a melanomas (86% vs. 90% at 5 years and 81% vs. 83% at 10 years).

Mortality according to the N-stage: at stages I and II, Kaplan-Meier curves of the specific melanoma survival times according to the N-stage of the disease show a lower 5- and 10-year survival rate in stage N1b melanomas compared with N1c melanomas (76% vs. 81% at 5 years and 71% vs. 75% at 10 years).

According to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system and the Kaplan-Meier curves of the specific melanoma survival times based on the stage of the disease, the 5- and 10-year survival rates of stage-IIB (87%/82%) and stage-IIC (82%/75%) patients are worse than in stage-IIA (93%/88%) and stage-IIIB (83%/77%) patients.

When comparing the seventh and eighth editions of this staging system, the survival time reported for stage-IIIA patients is greater in the eighth edition (93%) than in the seventh one (78%).

¿Are we ready to stop performing SLNBs?
According to a study carried out by Morton, Donald L. et al. in 2014, patients with intermediate or thick melanomas who underwent a SLNB had a longer survival time than those of the control group. However, those with thin melanomas of the control group had a greater survival time than those who underwent a SLNB. Hence, the results are controversial.

Keynote-716 study: a randomised, double-blind, phase-3 study analysing adjuvant therapy with pembrolizumab versus a placebo in 1182 patients with fully resected stage-IIB or -IIC melanomas during a total follow-up period of 27 months. In this study, pembrolizumab yielded favourable outcomes in terms of the recurrence-free and adverse event-free survival times, although without a significant impact.

CheckMate 76K study: this study, in which adjuvant therapy with nivolumab versus a placebo was evaluated in patients with fully resected stage-IIB or -IIC melanomas, showed that nivolumab was beneficial in all subanalyses (recurrence-free survival, overall survival, safety, quality of life, and side effects).

¿Why should a SLNB be performed if the patient is going to receive adjuvant therapy anyway? According to a paper published by Dr. Sondak, if we stop performing SLNBs, we will have to carry out many more lymphadenectomies. Furthermore, not all patients want to or can receive adjuvant therapy (50% of the US population), and SLNBs have proven to be very important, as survival rates drop drastically between patients with a stage-IIB or IIIC melanoma and those with a stage-IIIB or IIIC disease.

To conclude, I believe that SLNBs are important for both disease staging and patient follow-up, and it is a surgical procedure without major associated complications or comorbidities.

Excision with Histological Margin Control in Patients with BCC in Brazil

Dr. Flavio Cavarsan

It is estimated that around 142,000 new cases of BCC will be diagnosed in Brazil in 2022. Determining the high- or low-risk staging of BCC is crucial in defining the therapeutic approach to be followed. According to the National Comprehensive Cancer Network (NCCN), BCC is considered to be high-risk if it meets even one of the following clinical or histological criteria: located on the trunk or limbs with a diameter equal to or greater than 2 cm, the head and neck, the hands, the feet, the anogenital region, and the pretibial region with any diameter; poorly-defined edges; recurring; in a patient under immunosuppressive therapy or in an area previously subjected to radiotherapy; and of the sclerosing, cord-like, metatypical, micronodular, or adenoid histological subtype. The gold-standard treatment of choice for high-risk BCC is surgery with surgical margin control, such as Mohs surgery or a similar procedure. If this technique cannot be applied, a wide excision with ample safety margins can be performed. The problem in this case is that the specific width that these margins should have is unclear (a margin of 6 mm–10 mm is recommended), as only 5% of the margins are analysed in conventional surgery.
As final conclusions, it must be recalled that high-risk BCC is well defined in the NCCN guidelines, and that there are two possible surgical approaches available to treat high-risk BCC: Mohs surgery or conventional surgery with wide margins, the former being the preferred technique.

Toxicity of Immunotherapy and Targeted Therapy

Dr. Rafael Aron Schmerling

Some time ago we started discovering drugs that improved melanoma patients' overall survival (OS) and quality of life. The basis of immunotherapy is antigen presentation, whereby the antigen-presenting cells present the antigen to the T-cells, which start to fight the tumour. However, this same mechanism of action causing increased immunity generates toxicity against the host's own body. Any tissue in the body can be attacked if we lower the host's immune tolerance.
Ipilimumab was the first drug of this class to be discovered. It is known to have toxic effects on the skin, the digestive system, and the endocrine system, with its toxicity being greater at higher doses. Then, with programmed cell death protein 1 (anti-PD1) and programmed cell death ligand-1 (anti-PDL1) inhibitors, we saw less events of colitis and reduced hypothyroidism compared with ipilimumab, but increased fatigue and more events of pneumonitis.
In the kinetics of adverse events, rash and pruritus are the first to appear, followed by diarrhoea and colitis, then liver toxicity, and finally, hypophysitis.

Regarding the toxicity and efficacy of these drugs, there seems to be a correlation between OS and toxicity, as the former has been found to be greater with toxicity, and a higher likelihood of survival has been observed in patients developing a rash and vitiligo. In the case of anti-PD1, the greater its effect, the greater its toxicity, there even being a relationship between the number of events and their severity. If a patient needs corticosteroids, these can be administered without this having an impact on the treatment's efficacy.
Serine/threonine-protein kinase B-raf (BRAF) and mitogen-activated protein kinase kinase (MEK) inhibitors have a similar toxicity profile. Unlike with immunotherapy, the toxic effects of these drugs are not correlated with the treatment's efficacy, and a serious side effect that they can have is QT prolongation.

Skin Cancer in Latin America

Mohs Surgery: Are There Any Limits?

Dr. Ocampo Candiani, Jorge

Local Recurrences after Mohs Micrographic Surgery (MMS)
The incidence of these recurrences is of only 2%, with 75% of cases being due to technique application errors.
The mean time to recurrence is 38.5 months, with 20% of cases occurring after 5 years, especially in patients with a history of multiple relapses prior to undergoing the MMS and in those with high-risk locations, such as the ear.

¿In Which Cases Is MMS Indicated but Cannot Be Performed?
In patients with psychiatric disorders, those who are not cooperative or highly anxious, those in which sedation is not working, or subjects with cervical arthropathy. Other therapeutic options should be considered in these cases, such as cryosurgery, curettage and electrodessication, or radiation therapy, all of which offer acceptable healing rates.
To conclude, there ARE limits to when MMS can be applied, including: psychiatric patients or in the case of unresectable tumours affecting the parotid gland, the bones, the intranasal or intraorbital area, or the external auditory canal.

Systemic Treatment of Unresectable Squamous Cell Carcinoma (SCC)

Dr. Abel Gonzalez

The lecturer presented the case of a 37-year-old woman with a recurring SCC on the right sight of her upper lip. The lesion was excised through MMS carried out in two stages due to the presence of perineural invasion. The lip was reconstructed with three flaps: lip advancement + abbe cross + cheek island. Nine months later she presented with a new, contralateral nodule, for which the following therapeutic options were proposed: surgery, which was ruled out due to being considered excessively comorbid; radiotherapy, which was ruled out due to its non-curative intent and the fact that this was a young patient; and immunotherapy, which was the selected therapeutic option.

Chemotherapy regimens available for the treatment of advanced SCC included cisplatin, carboplatin, bleomycin, and 5-fluorouracil, with a combination of different regimens being more effective than the use of the drugs in monotherapy. The Food and Drug Administration (FDA) has approved these drugs for head and neck lesions. However, the duration of the response (which is initially very good) after discontinuing the chemotherapy is often questionable.

Treatments for advanced SCC based on targeted therapy and small molecule inhibitors include cetuximab, erlotinib, gefitinib, and panitumumab, many of which have been approved by the FDA for the treatment of head and neck tumours, but not advanced SCC. Response rates achieved with targeted therapy are lower than with chemotherapy, although the duration of the response and the incidence of adverse effects are better with the former. The most common side effect is an acneiform rash that could be suggestive of a greater progression-free survival.
Among immunotherapy treatments for advanced SCC, we have cemiplimab and pembrolizumab, both of which have been approved by the FDA for the treatment of advanced SCC. Half (50%) of the patients treated with these drugs achieve a partial response, and around 20% more maintain a stable disease. In addition, over 60% of these patients exhibit a long-lasting response at least 6 months after receiving the treatment. The adverse effects associated with these drugs are immune-mediated and generally well tolerated, and corticosteroids can be administered when necessary.

The use of neoadjuvant therapy with cemiplimab for stage-II and -IV SCC has been analysed in some studies, observing that around 50% of the patients respond to this treatment. In cases such as the one described, patients can first receive neoadjuvant immunotherapy, as they often do not require subsequent surgery, and, if they do, it would be carried out with less comorbidity.

Melanoma in Private Practice: Our Experience in Mexico

Dr. Mónica Ramos

In Latin America we face different challenges in relation to melanoma.
Challenge no. 1: Hispanic skin ranges from white to dark, with Fitzpatrick phototypes that not always fit this population due to its racial and ethnic heterogeneity.
Challenge no. 2: Physicians prescribe the use of sunscreen less often in people of colour, and 65% of Hispanics believe that they are not at risk of developing skin cancer and that they do not need to protect themselves from sun exposure.
Challenge no. 3: only 5% of Hispanic patients report having undergone a total skin examination performed by a physician compared with 49% of light-skinned patients. People of colour who develop melanoma are more likely to have metastases, not to mention the significant inequity in healthcare access.
In 2009 we published our first cases of melanoma treated in a private practice setting and raised the question of whether dermatologists make a difference. It was concluded that screening performed by these specialists indeed makes a difference by increasing the detection of early-stage melanomas.
Another article published in 2015 by the Mexican dermatology journal (Dermatología Revista Mexicana) was that concerning a 13-year retrospective study in which patients from two clinics were analysed, one in Guadalajara and the other in Ajijic (Mexico). A total of 165 melanoma cases with varying characteristics were detected in both men and women. Male patients often consulted due to having been sent by their wives after these detected something strange, while female patients tended to be more attentive and consulted earlier. Thus, men tend to have melanomas with a greater Breslow depth than women. As for the most frequently affected anatomical sites, acral melanoma is the most common type in Latin America.
Both American and Europeans tend to undergo screening exams, but Mexicans do not.
As a final conclusion, it must be noted that our Mexican patients can pay private medical clinics for clinical or cosmetic consultations. Most of our patients were diagnosed at early stages of the disease, with no differences being observed between our Mexican and non-Mexican patients. We observed lower Breslow depths when the melanomas were diagnosed through routine screening.

Epidermoid Tumours and Risk of Metastasis

Dr. Carlos Garcia Rementeria

In this lecture we will answer two questions:
1- How do we reach the diagnosis of actinic keratosis (AK) and SCC
2- How can we predict the risk of metastasis?

What is the risk of transformation?
We all know the theory about the different transformation pathways from AK to SCC in situ and then invasive SCC, from atypia involving the basal layer of the skin to its full thickness, and, from there, invading the dermis through different pathways. However, we now also know that this invasion can also take place directly from AK without intermediate steps. Dermoscopy, confocal microscopy, and optical coherence tomography (OCT) can aid in diagnosing these two conditions.
Dermoscopy findings of AK: erythematous pseudonetwork, superficial scales, wavy blood vessels, yellow follicular openings, and globules with white structures.
Dermoscopy findings of SCC: central keratin mass, scales and crusts, targetoid follicles, and multiform blood vessels.
Confocal microscopy: this is a non-invasive technology that enables in vivo visualisation of all layers from the epidermis to the papillary dermis with a resolution comparable to that of a histology examination.
OTC: this is a non-invasive technology that uses laser light to obtain images of the skin at a depth of over 2 mm, and can describe the characteristics of AK, SCC in situ, and BCC.

¿How can we predict the risk of metastasis?
High-risk factors associated with local recurrence and metastasis of SCC according to the following:
- Tumour characteristics: tumour of any size located in the central area of the face (eyes, nose, or mouth), the ears, the temples, the jaw, or the chin. Tumour larger than 1 cm located in the cheeks, the forehead, the scalp, or the neck, or tumour larger than 2 cm in any other area, with poorly-defined edges, rapid growth, associated neurological symptoms, and recurrence.
- Histology features: depth of over 4 mm, poorly-differentiated, aggressive pattern (such as acatolytic or desmoplastic), and with perineural or vascular invasion.
- Host factors: previous radiotherapy site, immunosuppressed, chronic wound site, and genetic predisposition, such as xeroderma pigmentosum.
Any of these high-risk features has an indication for Mohs surgery.

We have two staging systems available (the 8th edition of the AJCC and the Brigham and Women's Hospital tumour staging system) to predict which will be a high-risk tumour and determine its stage. SLNB is currently not recommended in these patients.

Merkel Cell Carcinoma: A Difficult Diagnosis

Dr. COHEN SABBAN, Emilia Noemí

An 81-year-old man presented with a painless, firm, red nodule on the lower eyelid of his left eye, with a diameter of 1 cm and of 4 months' evolution. A dermoscopy exam revealed milky-red areas, bright white lines, and vascular polymorphism, thus leading to a presumptive diagnosis of basal cell carcinoma (BCC) versus amelanotic melanoma versus Merkel cell carcinoma. The histological and immunohistochemical results of the biopsy were compatible with Merkel cell carcinoma. A sentinel lymph node biopsy was performed, obtaining a negative result. Staging according to the last consensus on Merkel cell carcinoma: Tis N0 M0.

Merkel cell carcinoma was first described in 1972 as a very aggressive, rare, primary, neuroendocrine tumour of the skin associated with high mortality. Its incidence is on the rise and there are two known types of this carcinoma: one affecting sun-exposed skin areas and the other related to poliovirus, the

latter representing 80% of cases. The risk factors for local recurrence of this condition are advanced age and male sex.
Its diagnosis is both clinical and histological, reached through a biopsy and immunohistochemistry analyses, in which antigen Ki67 acts as a risk marker, whereby the higher its levels the greater the mitotic index and the more undifferentiated the tumour. Sentinel lymph node biopsies and imaging studies are essential for determining the stage of this disease. Because it is a very aggressive tumour, a late diagnosis with metastasis is very common.
Treatment of the localised lesion involves a wide excision, and the indication of administering adjuvant radiotherapy is suggested, albeit controversial.

Dermoscopy in Dark Skin Types

Dr. BAKOS, Renato

Most nevi in dark skins exhibit a homogeneous, uniform, dark brown-black, reticular pattern. Hence, they entail a challenge in the differential diagnosis of melanoma. Fitzpatrick phototypes 5 and 6 tend to have less nevi, and, when present, these are more common on the face and acral regions, with high pigmentation and a reticulated pattern.
In the Latin American population, acral nevi tend to have a parallel, fibrillar pattern and a darker colour.
As for melanoma, in dark skins, these lesions tend to appear at older ages. It is more frequent among women, mostly invasive, and located in the lower limbs (probably acral).
Melanonychia-type nail alterations are very common among subjects with dark skin, and nail melanomas tend to manifest the Hutchinson sign.

Mohs surgery

Recommendations from the NCCN for Mohs/PDEMA

Dr Chrysalyne D. Schmults

The recurrence of squamous cell carcinoma (SCC) with perineural invasion after surgery with complete margin assessment (CMA) is 10%, versus 23% with standard excision.
According to the largest cohort of data from Cleveland and Brigham and Women's Hospital (BWH), the cure rate for high-risk SCC at 5 years was 10% greater with Mohs surgery (85% with Mohs vs 75% with conventional surgery, p=0.04).
Patients with high-risk SCC die mainly from recurrence and local metastasis to ganglions.
With Kaplan-Meier curves, we can see that in all classifications (BWH, CCF), the results on the risk of local recurrence are better with Mohs than with conventional surgery.
Peripheral and deep en face margin assessment (PDEMA), like Mohs surgery or the Tubingen technique, is the type of surgery of choice for high-risk or very high-risk SCC, according to the NCCN.

According to the NCCN, the very high-risk factors for local recurrence and ganglial compromise (only one factor is required for it to be considered very high risk) are:
- Clinical factors: size greater than 4 cm
- Histological factors: poorly differentiated, desmoplastic subtype, more than 6 mm of invasion depth or invasion below the fat, tumour cells on nerve sheaths greater than or equal to 0.1 mm in diameter or below the dermis, vascular or lymphatic invasion.

In Dr Schmults' final comments, she noted that the NCCN recommends PDEMA and Mohs as the gold-standard treatment for very high-risk SCC given that these techniques offer the greatest

possibility for local control of the disease and present a lower rate of local relapse, as well as minimise the risk of death.

Mohs surgery for melanoma and Merkel cell carcinoma of the head and neck

Dr Vishal A. Patel

The objectives of this talk were to:
- Discuss the evidence for the usage of Mohs surgery in the treatment of melanoma and Merkel cell carcinoma
- Discuss the usefulness of complete margin assessment for the treatment of high-risk tumours of the head and neck
- Describe a multidisciplinary approach for the treatment of Merkel cell carcinoma and melanoma of the head and neck

It's important for us to ask ourselves these questions:
- What is complete margin assessment (CMA)?
- What is the difference between CMA and standard surgery?
- What is the benefit of CMA over standard surgery?

Standard surgery consists of creating a range of margins pre-established according to the Breslow thickness of the melanoma, but the margins can be modified according to the anatomy or functional considerations of the area.

Now, we are at a point where we need clarity as to what we're talking about and the abbreviations used as they are often confused (CMA gets equated to CCPDMA and PDEMA) and all are surgical techniques with complete margin assessment. This descriptive term, CMA, can be applied to Mohs surgery, as well as the Tubingen muffin or torte technique.

According to the NCCN guide on melanoma, the data used to define the margins for standard excision are from trials relating to melanomas of the trunk; very little of the data pertained to melanomas of the head and neck, and none of the melanomas were acral. For this reason, it can be difficult to define the margins according to the location.

Which surgical technique for margin assessment is superior? According to various studies, the techniques using complete margin assessment on 100% of margins are superior (CMA, CCPDMA, and PDEMA).

According to the NCCN, for Merkel cell carcinoma, if the patient has a localised disease without ganglial compromise and without other risk factors, it can be removed with standard surgery with ample margins; however, if there are other risk factors, adjuvant radiotherapy offers greater coverage. If adjuvant radiotherapy is previously planned, narrower margins can even be sufficient to leave the patient disease-free.

Multiple retrospective analyses have been done to compare the results of Mohs surgery versus standard excision with ample margins for the treatment of Merkel cell carcinoma. Mohs surgery proved to be the most effective method for overall survival from Merkel cell carcinoma. Patients with Merkel cell carcinoma of the head and neck progress better with Mohs surgery.

Why is it necessary to have a multidisciplinary focus?
Melanoma and Merkel cell carcinoma are multifaceted diseases that require experience from many subspecialities and coordinated efforts. In Dr Patel's facility, they do complete planning with Mohs

surgery and sentinel node biopsy (SNB) all at the same time, and the patient can return home the same day.

In conclusion, Dr Patel suggests that you start making a list of the various techniques for complete margin assessment to avoid confusion. This type of surgery can be preferable over standard surgery. The SNB should be done at the same time as the surgery with margin assessment. You need to do complete planning with the patient before starting interventions. Melanoma and Merkel cell carcinoma of the head and neck should be treated and cared for in leading medical facilities with multidisciplinary approaches.

A multidisciplinary focus for Mohs surgery

Dr Abel Gonzalez

Mohs surgery is the best option for non-melanoma skin cancer treatment because of its precise analysis of the surgical margins. In some cases, Mohs surgery cannot be performed in an ambulatory setting with local anaesthesia (as is done for the majority of patients) and it requires general anaesthesia or sedation.
A multidisciplinary approach is indicated when there is compromise of an intracranial nerve, bone, an orbit, a parotid gland, the vulva or the perianal region, or when very complex reconstruction is required.
The multidisciplinary team can include the Mohs surgeon, a head and neck surgeon, a plastic surgeon, a craniofacial surgeon, or an oncological surgeon. During processing of the tissue from the Mohs surgery, the rest of the team can proceed with flap advancement, parotidectomy, or SNB as needed, which minimises the time required for general anaesthesia.

Standard surgery and Mohs surgery for primary SCC

Dr Ricardo Vieira

For conventional surgery for squamous cell carcinoma (SCC), the 2020 European guidelines recommend a range of peripheral margins according to whether the SCC is low or high risk to achieve a 95% cure rate, with 5 mm for low-risk SCC and 6 to 10 mm for high-risk SCC, but recommendations are lacking for the deep margins that may include subcutaneous fat or galea aponeurotica on the scalp. The recurrence rate for conventional surgery for invasive SCC ranges from 4.4% to 7.5%, correlating with high-risk factors for SCC.

There is a lack of prospective studies comparing the recurrence rate for Mohs surgery vs conventional surgery for SCC. The data we have from retrospective studies are:
Conventional surgery: Primary SCC: 5.7% - Recurring SCC 17.3%
Mohs: Primary SCC: 2.6% - Recurring SCC 5.9%

Frozen tissue is harder to interpret than tissue in paraffin, with a high risk of false negatives. There are immunohistochemical techniques for frozen tissue, but they are not widely available.
There is no clear benefit of adjuvant radiotherapy for fully removed SCC, but it can be beneficial for perineural invasion and should be considered.

In conclusion, there is not much evidence regarding the selection of MMS for low-risk SCC, but MMS is practically obligatory for high-risk SCC, especially with perineural invasion, given that there is conclusive evidence of its superiority. MMS is also the intervention of choice for recurring SCC and SCC in higher-risk anatomical locations in order to maximise preservation of the healthy peritumoral tissue.

Merkel cell carcinoma: Updates and challenges

Dr Rafael Aron Schmerling

Merkel cell carcinoma (MCC) is a difficult disease often found in older patients, with a prognosis that is not always favourable.
Traditionally, the metastatic disease is treated with chemotherapy, with a response rate of 55%, which is considered good.
The mutational load of the MCC tumour is very high and can be used to estimate the response to immunotherapy. At the same time, we know that the more mutations there are, the greater the chance of having more immune-mediated adverse effects. There are two causes of Merkel cell carcinoma: the first is related to accumulated exposure to UVR and the second is related to polyomavirus, with a totally different molecular profile and a lower tumoral load; however, we can also use immunotherapy as a treatment in the second case because the immune system can recognise the virus within the affected cell.

Avelumab interferes with the activity of lymphocytes and triggers the destruction of the tumour. Additionally, it has been observed that the duration of benefit is much greater with this treatment and thus we can judge that the long-term benefits justify use of this therapy. The great challenge in oncology is how to select patients for this treatment. The use of biomarkers such as PDL1 may help, with PDL1+ patients getting greater benefit from this treatment than PDL1- patients; although these differences were not statistically significant, that may have been due to a small sample size.
Avelumab is effective in patients who have previously received treatment and in patients who did not previously receive first-line treatment. While the disease may continue to progress with this treatment, the patient will remain alive for a longer period of time and we can add surgery or radiotherapy to counter the progression.

With pembrolizumab as a first-line treatment, we see a reduction of the tumour and good rate of survival without progression and good overall survival. Nivolumab is another option with fairly similar data in patients who previously received treatment. And what do we do with patients for whom anti-PD1 therapy fails? One option is to combine ipilimumab and nivolumab.

When we compare treatment suspension to treatment maintenance, we can see that 73% of patients who had a total response remained progression-free at 5 years versus 44% of patients who had a partial response and for whom treatment was suspended due to toxicity or elective suspension. The progression-free time at one year was greater among those patients who had toxicity and then switched.

The drug combination IPI + NIVO can be used as a salvage therapy for recurring or metastatic MCC. One group received IPI + NIVO as a first-line treatment with radiotherapy and the other group received IPI + NIVO as a first-line treatment without radiotherapy. All patients showed a good response to the combined IPI + NIVO treatment; as such, we are unable to analyse the isolated benefit of adding radiotherapy to it. MCC is a tumour that’s fairly sensitive to radiation; as such, when considering IPI + NIVO for patients with a metastatic form, it would be better as a first-line treatment so that you don’t lose the option of doing radiotherapy later.
Post-surgery adjuvant treatment with nivolumab should be considered given that patients with metastatic cancer have a fairly poor prognosis and it has been shown that nivolumab adjuvant treatment improves the rate of disease-free survival versus just observation.

Risk stratification and optimising management of CSCC

Dr Chrys Schmults

The objectives of this session were to use appropriate staging criteria for SCC, to understand how proper staging can impact the patient's prognosis, and to apply appropriate treatment and follow-up based on the risk of recurrence and ganglial metastasis.

Given that the majority of SCC cases can be easily cured, why do we need to do prognostic staging? Because some SCCs are unusually aggressive. In the U.S., there are 1.5 million SCC cases per year; that is too many to be able to use controls and perform statistical studies of all cases. As such, the numbers are not as well-known as they are for melanoma, but we know that in the U.S., 1% to 4% of patients have SCC metastasis and 1% to 2% of patients die from SCC. That means approximately 15,000 deaths from SCC per year in the U.S. That number is probably higher than the number of deaths from melanoma in this new era of immunotherapy treatments, with an estimated 7,300 deaths per year from melanoma.
We need to do proper staging to identify that small group of patients with SCC at high risk of recurrence and death.
The eighth edition of the AJCC staging system expanded T3 to include patients with any of these factors: 4 cm in diameter, invasion with a depth greater than 6 mm, invasion of a nerve with 0.1 mm of diameter or located below the dermis, or superficial bone erosion. The problem with the eighth edition of the AJCC staging system is that T2 and T3 have similar risk levels (although not equal) and represent 25% of patients with SCC. On the other hand, for Brigham and Women's Hospital (BWH), they consider high-risk parameters to include a diameter of 2 cm or more, invasion below the fat, poor differentiation, and perineural invasion of a major nerve or a nerve with 0.1 mm in diameter. Patients are considered to be at high risk when they have two to three factors (T2b) or four factors or invasion of bone (T3).
BWH performs better than AJCC at staging the risk for patients with SCC, while both capture most patients with risk of metastasis and death; however, according to the AJCC system, 18% of patients would be considered high-risk, while the number is 9% in the BWH system.
The surgical treatment of choice in these cases is surgery with control of 100% of the margins, like Mohs surgery and peripheral and deep en face margin assessment (PDEMA) given that they have reports of higher cure rates for SCC, especially when there's perineural invasion, with a 10% risk of recurrence, versus 23% for conventional surgery.
According to the NCCN, the factors for very high risk of recurrence and metastasis with SCC are:
- Clinical factors: size greater than 4 cm
- Histological factors: poorly differentiated, desmoplastic subtype, more than 6 mm of invasion depth or invasion below the fat, tumour cells on nerve sheaths greater than or equal to 0.1 mm in diameter or below the dermis, vascular or lymphatic invasion.

Local radiation to treat a positive margin is not reliable to finish cleaning up the margin, attempting to obtain free margins with surgery with control of 100% of the margin.

What do we do with ganglia? In 30% of T2b cases in the BWH classification that underwent SNB, the tests came out positive, but the risk ranged from 6% to 21%. Using a method of analysis for 100% of the margin should not be sacrificed in favour of SNB given that SNB does not have conclusive proof of its benefits, whereas Mohs surgery, for example, does have conclusive proof behind it.

Adjuvant radiotherapy should be considered when you are unsure about obtaining negative margins due to perineural invasion or due to SCC that has relapsed multiple times, given that the radiotherapy improves local control, although it does not impact the risk of metastasis.

In conclusion:
- AJCC staging comes with difficulties given that many cases end up being inappropriately upstaged.
- Inappropriate upstaging is less of a problem with the BWH system.
- You should use echography and tomography for the initial ganglial staging of SCC and for follow-up every 6 months for 3 years in cases staged T2b and T3 under the BWH system.
- You should consider adjuvant radiotherapy according to the risk of recurrence and presence of comorbidities in the patient.

Systemic Management of Advanced Melanoma

Long-Term Results of Standard Treatments

Dr. Martín Greco

In this lecture we will discuss the classification of melanomas, the evolution of melanoma treatment over time, the long-term results of immune checkpoint inhibitors and targeted therapy, the drugs achieving good responses, and the long-term quality of life of melanoma patients.

Because different subtypes of melanoma have a different molecular composition and mutations, their treatment should also differ.

In a timeline of the evolution of treatment for malignant melanoma (MM) and the approval of different drugs for this disease, we can find dacarbazine among the first chemotherapy treatments approved in randomised clinical trials, with an overall survival rate of nine months.

This drug was followed by interleukin 2 (IL2) at high doses, which was tested in a clinical trial with 270 patients with MM who exhibited a good response to the treatment, a high survival rate of 16%, and few recurrences after 2.5 years among responders (deemed virtually cured). In 1998, the Food and Drug Administration (FDA) approved this drug for the treatment of melanoma. However, although it yields a good response, it causes significant toxicity.
Ipilimumab and vemurafenib subsequently appeared in 2011.
BRIM-3, phase-III study comparing vemurafenib and dacarbazine in melanoma: 4-year overall survival (OS): this OS was greater among patients treated with vemurafenib and with a lower grade of toxicity than IL2.
In 2013, dabrafenib and trametinib were available as monodrug therapies and, in 2014, dabrafenib was used in combination with trametinib, pembrolizumab, and nivolumab.

Keynote-006 trial: comparison of the 5-year (later extended to 7 years in follow-up SMR2021) OS and progression-free survival (PFS) between pembrolizumab and ipilimumab, revealing a significantly greater OS and PFS with pembrolizumab.

CheckMate-66 trial: comparison of nivolumab versus dacarbazine, demonstrating a greater 5-year OS and PFS for nivolumab.

MSKCC study: retrospective analysis of treatment with pembrolizumab: a decrease in the likelihood of treatment failure was observed after starting treatment with pembrolizumab.

Intralesional talimogene laherparepvec (T-VEC) therapy emerged in 2015. In addition to ipilimumab + nivolumab, ipilimumab as adjuvant therapy, and vemurafenib plus cobimetinib.
CheckMate 067 trial: nivolumab + ipilimumab versus nivolumab in monotherapy versus ipilimumab in monotherapy as first-line treatment for melanoma. Primary endpoint: OS and PFS. The statistical power achieved in this trial was insufficient. A long-term follow-up (7 years) revealed a response rate of 58% for ipilimumab + nivolumab, of 45% for nivolumab in monotherapy, and of 19% for ipilimumab in monotherapy. The melanoma-specific survival achieved with the combination of ipilimumab + nivolumab, nivolumab in monotherapy, and ipilimumab in monotherapy was 56%, 48%, and 27%, respectively. In general, adverse effects were of grades 3 to 4 and appeared in 40%, 8%, and 19% of patients treated with the ipilimumab + nivolumab combination therapy, the nivolumab monotherapy, and the ipilimumab monotherapy, respectively.

Phase-III study: BRAF and MEK inhibitors in advanced melanoma without prior treatment. Two groups of patients with stage-IIIC/IV, unresectable melanomas were analysed. Primary endpoint: OS.
1st group: BRAF V600E/K wild-type treated with two therapeutic lines, one consisting of a combination of dabrafenib + trametinib and the other of vemurafenib in monotherapy. A greater OS was achieved with the combined therapy with dabrafenib + trametinib (34% at 5 years).
2nd group: mutated BRAF V600 treated with two therapeutic lines, one consisting of a combination of vemurafenib + cobimetinib and the other of vemurafenib + placebo. A greater OS was achieved following combination therapy with vemurafenib + cobimetinib.

A significant difference between the combined therapy with ipilimumab + nivolumab and nivolumab in monotherapy was observed in patients with a BRAF mutation. The curves almost overlap in patients with wild-type BRAF, and their response to immunotherapy was better.
The problem with the combination of ipilimumab + nivolumab is its high toxicity. In fact, 50% of patients treated with this combination have to discontinue the treatment after just 4 to 5 cycles.
Targeted therapy with dabrafenib + trametinib yields a complete response rate of 7% and a PFS of 50%.
Another important prognostic factor is the patients' level of lactate dehydrogenase (LDH).

Adjuvant combination therapy with encorafenib + binimetinib and dabrafenib + trametinib surfaces in 2018.
In 2019, adjuvant pembrolizumab starts to be used in patients with nodal involvement.
In 2022, adjuvant pembrolizumab is being used to treat patients with stage-T3b and -T4 melanoma.

In this molecular era of limited clinical and analytical data, the only outcome predictor is the Breslow depth. No molecular testing can be performed, patients with vitiligo respond better to immunotherapy, and PTEN loss can be a cause of resistance to BRAF inhibitors.

In terms of the quality of life of patients with long-term survival, this Netherlands trial showed an economic impact, as patients have to pay for their treatments.

To conclude, thus far we have sufficient data on these new treatments for melanoma obtained from the 5-to 8-year follow-up of these patients. We can affirm that any of these therapies (immunotherapy or targeted therapy) results in an OS of at least 50%. This is why it is important to understand the biological mechanisms underlying the lack of response in the remaining 50% of patients. With these data we hope to achieve a more personalised treatment.

Which Is the Best Way to Sequence Systemic Treatments?

Dr. DUMMER, Reinhard

According to the European Society of Medical Oncology's (ESMO) clinical practice guidelines for the diagnosis, treatment, and follow-up of cutaneous melanoma, the main points that should be considered are the patients' symptoms, subtype of melanoma, age, LDH levels, tumour burden, organ involvement, mutational burden, T-cell infiltration, and the presence of programmed cell death ligand-1 (PD-L1).

In the DREAMseq trial, patients with a BRAF mutation and melanoma metastases were divided into two treatment arms: one received IPILIMUMAB + NIVOLUMAB followed by DABRAFENIB + TRAMETINIB upon exhibiting signs of disease progression (2-year OS rate of 72%), and the other received DABRAFENIB + TRAMETINIB followed by IPILIMUMAB + NIVOLUMAB in the face of disease progression (2-year OS rate of 52%).

SECOMBIT was a randomised, open-label, phase-II study with three treatment arms for patients with metastatic melanoma and a BRAF mutation.
Arm 1: treated with encorafenib + binimetinib, followed by ipilimumab + nivolumab, achieving a 4-year PFS of 29%.
Arm 2: treated with ipilimumab + nivolumab, followed by encorafenib + binimetinib, achieving a 4-year PFS of 55%.
Arm 3: treated with encorafenib + binimetinib, followed by ipilimumab + nivolumab, then encorafenib + binimetinib (called SANDWICH), achieving a 4-year PFS of 54%.

TRICOTEL: a multicentre, open-label, single-arm, phase-II clinical trial for patients with melanoma brain metastases treated with ATEZOLIZUMAB, VEMURAFENIB, and COBIMETINIB.

Treatment options for patients with PD1-resistant metastases. Combination therapy with IPILIMUMAB + NIVOLUMAB is recommended for low-risk patients with normal LDH levels and no liver or brain metastases. Targeted therapy (DABRAFENIB + TRAMETINIB, ENCORAFENIB + BINIMETINIB) is recommended for high-risk patients with a BRAF mutation. Combination therapy with ATEZOLIZUMAB, VEMURAFENIB, and COBIMETINIB is recommended in high-risk patients with a BRAF mutation and symptomatic brain metastases.

To conclude, there are many therapeutic options available, with IMMUNOTHERAPY being the preferred option as a first line of treatment in stage-IV melanoma. In high-risk patients with a BRAF mutation, Sandwich therapy should be considered. Options available for patients resistant to PD1 include combination immunotherapy and, in carriers of a BRAF mutation, targeted therapy.

Systemic Treatments for Rare (Or Not So Rare) Melanoma Subtypes

Dr. SCHMERLING, Rafael Aron

Melanoma subtypes were not given importance in the past, but it is now known that different types of melanoma are linked to different mutations and have different mutation profiles.

Cutaneous melanoma represents 90%–95% of melanomas, is induced by ultraviolet (UV) radiation, and usually predominates in patients with fair skin aged 59–65 years. Uveal melanoma has completely different characteristics, as it only represents approximately 5% of melanomas, is rarely induced by UV radiation, originates in the choroid in 90% of cases, predominates in light eyes, and tends to affect the liver secondarily. Mucosal melanoma represents merely 1% of cases, is rarely induced by UV radiation, has a poor prognosis, and tends to affect locoregional lymph nodes. Mucosal melanoma has a significant impact on the patient's quality of life due to its location and treatment. It tends to appear in adult patients, mostly affecting the vaginal, anorectal, or sinus regions,

and has a high rate of local recurrence. It is treated with conservative or wide excision surgery associated with radiotherapy. Although surgical treatment of mucosal melanoma enables a good local control of the disease, the same is not true for the systemic disease and the appearance of metastases, as these are not as well controlled in patients with this subtype. Mucosal melanoma has a worse prognosis than cutaneous melanoma and is more sensitive to immunotherapy, such as combination therapy with ipilimumab + nivolumab. Its 5-year OS is 36% with combined treatment, 17% with nivolumab in monotherapy, and 7% with ipilimumab in monotherapy.

Acral melanoma predominates in the Asian and Central American populations, usually has a high Breslow depth at diagnosis, a high rate of nodal involvement, and there tend to be significant delays in its diagnosis. It has a lower response rate than cutaneous melanoma and responds better to the combination of anti-PD1 drugs + ipilimumab.

Desmoplastic melanoma generally affects sun-exposed areas, has a low rate of distant metastasis, but a high rate of local recurrence. The typical mutation seen in this type of melanoma is NF1. A 70% response rate is achieved with pembrolizumab. Treatment should be chosen based on the mutations that are present. The NTRK mutation is present in 20% of cases of desmoplastic melanoma.
It is important to pay close attention, and the pathologist will be key in providing information that can help us. Therefore, it is important to take a good sample to be able to perform an adequate histopathological analysis.
Multidisciplinary treatment is fundamental in these patients with rarer melanomas, as it is a well-known fact that patients achieve better results with a multidisciplinary approach.

Pathology as the Gold-Standard for Melanoma Diagnosis: How Much Does It Glitter?

SCOLYER, Richard A.

The role of the pathologist in diagnosing melanoma is crucial. In fact, 5% of melanoma diagnoses change after a histological re-examination.

Some lesions may have borderline characteristics that combine features of both benign and malignant lesions. There is currently an overdiagnosis of fine benign lesions, such as melanoma in situ. However, this is an even greater challenge in deeper lesions, because the difference between a nevus and a thick melanoma has major implications for the patient in terms of their prognosis and the approach to follow. An atypical melanocytic proliferation can range from a dysplastic nevus to a melanoma in situ, melanocytic hyperplasia, or lentigo maligna.
The histological diagnosis is subjective, as different pathologists can have different interpretations and opinions about what they are observing. Nevertheless, there are tools that can help the pathologist reach the correct diagnosis: the clinical history of the lesion, it being very important for us to provide information to the pathologist when sending the sample for analysis; the discrimination of whether this is a new or pre-existing lesion; and a description of the symptoms, as the pathologist’s interpretation of the lesion can vary depending on the clinical information we provide. A study carried out in Australia revealed that more than half of the specimens are sent for histological analysis without useful information for the pathologist in the histopathology order. The Australian guidelines recognise the importance of the clinicopathologic correlation.
Given that a pre-existing lesion can have a focal area of change, it is important that the biopsy (e.g., punch biopsy) be performed of the most representative area of that lesion.

We must work closely with the pathologist to ensure fluid communication and share any clinical images. Other techniques can be used to aid in reaching the histopathological diagnosis, but these are not always definitive. Borderline tumours have both benign and malignant characteristics, and a pathologist who is aware of these features will be more likely to reach the correct diagnosis.

The molecular pathogenesis of these lesions consists in an accumulation of genetic events that eventually lead to the transformation of a benign lesion to an intermediate one, and, finally, a malignant one. The World Health Organisation (WHO) considers this paradigm of intermediate tumours and calls them MELANOCYTOMAS. Each of these nine pathways define a benign, borderline, or malignant tumour.

Sentinel lymph node biopsy (SLNB) was used in the past as a tool when the diagnosis of intermediate tumour was unclear and, in those cases in which the biopsy was positive, we were reliably sure that the lesion corresponded to a melanoma.
The idea that these intermediate tumours can result in nodal but not systemic metastases is unreasonable, therefore, a SLNB does not have the same prognostic implications in these cases than in conventional melanoma. Hence, a SLNB is not recommended in these intermediate melanomas (or, better said, intermediate lesions), while an ultrasound aimed at examining the lymph nodes is.

A practical approach for the management of these intermediate lesions would be as follows:
1. In definitely benign lesions, complete excision, wide excision, and SLNB are not indicated.
2. In probably benign, but uncertain, lesions, complete excision is indicated, but wide excision and SLNB are debated.
3. In definitely uncertain lesions, complete excision is indicated, but wide excision and SLNB are debated.
4. In probably malignant, but uncertain, lesions, complete excision, wide excision, and SLNB are indicated.
5. In definitely malignant lesions, complete excision, wide excision, and SLNB are indicated.

In conclusion, pathological diagnosis is fairly straightforward; however, in certain cases it can be difficult to provide the clinical information of the tumour sent for analysis to the physician and the pathologist can rely on tools that can help them clarify the diagnosis of these 1000 intermediate tumours.

Management of High-Risk Early-Stage Melanoma

Targeted Therapy and Immunotherapy in Stage III Melanoma

Dr. SCHMERLING, Rafael Aron

According to the 8th edition of the American Joint Committee on Cancer (AJCC) classification system, the likelihood of 10-year survival among melanoma patients is 95% in case of stage-I melanoma, 84% in case of stage-II melanoma, and 69% in case of stage-III melanoma.
A greater percentage of survival 8 years after the initial diagnosis is observed among patients treated with adjuvant ipilimumab compared with a placebo, although this drug has a high degree of toxicity. The same is found when administering pembrolizumab, as well as combination therapy with dabrafenib + trametinib (in the latter, a greater benefit is observed for a stage IIIB-C-D disease compared with stage IIIA).
Compared with ipilimumab, nivolumab achieves a better response.

To conclude, adjuvant therapy is effective for stage-III melanoma. The magnitude of its benefits exceeds that observed in the case of other tumours. The choice between anti-BRAF/MEK versus anti-programmed cell death protein 1 (PD1) therapy in patients with BRAF mutations must be individualised, particularly focusing on the potential toxicity. The magnitude of benefit of this therapy for stage-IIIA melanoma requires further discussion in terms of the absolute risk reduction.

Redefining High-Risk Patients: Stage IIB/C

Dr. CINAT, Gabriela

According to the 8th edition of the AJCC classification system, the 5-year overall survival (OS) rate is 87% in stage-IIB melanoma, 82% in stage-IIC melanoma, 93% in stage-IIIA melanoma, and 83% in stage-IIIB melanoma.

Keynote-716 study: a randomised, double-blind, phase-III study analysing adjuvant therapy with pembrolizumab versus a placebo in 1182 patients with fully resected stage-IIB or -IIC melanomas during a total follow-up period of 27 months. In this study, pembrolizumab yielded favourable outcomes in terms of the recurrence-free and adverse event-free survival times, although without a significant impact.

CheckMate 76K study: this study, in which adjuvant therapy with nivolumab versus a placebo was evaluated in patients with fully resected stage-IIB or -IIC melanomas, showed that nivolumab was beneficial in all subanalyses (recurrence-free survival, overall survival, safety, quality of life, and side effects).

Therefore, adjuvant treatment is supported by the evidence. However, its relative and absolute risk must be discussed, particularly for certain subgroups. We must consider the patient's personal history, its associated toxicities, and their access to the treatments. Despite the dramatic improvement in the survival of patients with advanced melanoma, which currently exceeds 50%, patients still die from this disease.
Patients with a stage-IIB or -IIC melanoma have a worse prognosis than those with a stage IIIA disease. The AJCC needs to improve.
Anti-PD1 therapy can reduce the risk of recurrence of this disease.
As for neoadjuvant therapy, treatment used for stage-IV melanoma is successful when used in stage-II/III diseases. A careful analysis of the risks and benefits must be carried out. Using neoadjuvant treatment is a powerful strategy and its implementation in daily clinical practice should be expected.

Free Papers II

COVID-19 lockdowns and their impact on melanoma diagnosis

Ferraresso, María Guillermina, Hospital Italiano De Buenos Aires

Introduction and Objectives: Due to lockdowns caused by the COVID-19 pandemic, certain scheduled medical activities were postponed, both as a result of national directives and by patients who were afraid to go to hospitals. With regard to melanoma, certain histopathological characteristics such as Breslow depth, mitotic index and presence of ulceration are key factors in determining staging and prognosis. Because delays in diagnosis may lead to increased morbidity and mortality, it is pertinent to assess whether melanoma characteristics in patients treated at the Hospital Italiano de Buenos Aires changed as a result of the preventive lockdown (PL) established by the national government.

The objective was to describe the histological and clinical characteristics of melanomas diagnosed after the end of phase 1 of the PL, and to compare them with diagnoses from before the PL.
Materials and methods: A retrospective observational study was conducted, including patients with a melanoma diagnosis at the Hospital Italiano de Buenos Aires between 01/04/2019 and 30/04/2022. All patients with melanoma pathology results were included in two periods: period 1, from 04/12/2020 to 30/04/2021, when phase 1 of the PL ended, and period 2, from 04/01/2019 to 19/03/2020, when the PL began. We compared tumour aggressiveness based on histological characteristics: Breslow depth, tumour size, mitotic index, ulceration, and lymph node or distant metastasis.
Results: A total of 273 patients with melanomas were included, with 114 in period 1 with an average age of 67 years and 159 in period 2 with an average age of 61 years. The histological subtypes of melanoma were as follows in periods 1 and 2, respectively: in situ 42% vs. 47%, superficial spreading 26% vs. 34%, nodular 19% vs. 13%, lentigo maligna melanoma 6% vs. 2%, acral lentiginous 4%, and average Breslow depth was 1.7 mm in period 1 and 1.1 mm in period 2. Ulceration was observed in 20% of melanomas in period 1 and 12% in period 2. The mitotic index rate was 2/mm2 for period 1, and 0 for period 2. Metastasis to lymph nodes was observed in 23% of cases in period 1 and 16% in period 2. Distant metastasis was observed in 7% of cases in period 1 and 4% in period 2.
Conclusion: In the present study, we observed that melanomas diagnosed after the lockdown had a higher percentage of invasive subtypes than those diagnosed before the lockdown. We also encountered greater Breslow depth, a higher mitotic index and a higher ulceration rate. In addition, higher frequencies of lymph node involvement and distant metastasis were observed after the lockdown. The delay in diagnosis lead to an increase in negative prognostic factors for melanoma.

Extrafacial lentigo maligna. Dermoscopic characteristics of 24 cases.

HANSMAN, Daniela, Cutaneous Oncology Unit. Instituto Alexander Fleming.

Introduction and Objectives: Lentigo maligna is usually located on the face. Extrafacial lentigo maligna (EFLM), a variant of lentigo maligna found on non-facial skin with chronic sun damage, is less common. It can be difficult to diagnose. The dermoscopic characteristics of EFLM have recently been described, and tend to detect early melanomas. The objective of our study is the describe the dermoscopic characteristics of our EFLM series.
Materials and methods: The inclusion criteria consisted of EFLM confirmed via biopsy with dermoscopic images. Twenty-four lesions were found in nineteen patients. The patients were diagnosed and treated between March 2017 and June 2022 at the Cutaneous Oncology Unit at the Instituto Alexander Fleming in Buenos Aires, Argentina. Data were recorded on the following parameters: sex, age, location and dermoscopic characteristics.
Results: Sex: male 11/19, average age: 71.8 years (range: 54-80), location: trunk 12/24. Dermoscopic characteristics: angulated lines 16/24 (66%), peripheral tan structureless areas 13/24 (54%), granularity or peppering 7/24 (29%), atypical pigment network 7/24 (29%), aggregated dots 4/24 (16%), shiny white structures 6/24 (25%), blue-white veil 4/24 (16%), vascular structures 2/24 (8%), circle-in-circle 1/24 (4%), no pattern 1/24 (4%), asymmetric perifollicular hyperpigmentation 0/24 (0%), negative network 0/24 (0%), criteria of seborrhoeic keratosis 10/24 (41%).
Conclusion: The structures most frequently observed were angulated lines and peripheral tan structureless areas. Dermoscopy allows for early diagnosis of EFLM and is useful in the differential diagnosis of pigmented lesions on non-facial skin with chronic sun damage.

Addressing the gaps in differential diagnosis of acral lentiginous melanoma

ROBERTS, Michelle – Hospital Italiano De Buenos Aires

Introduction and Objectives: Acral lentiginous melanoma (ALM) represents less than 5% of all melanomas. Nevertheless, it is a common error to confuse ALM with melanomas that occur in acral

areas (hands, feet and ungual areas). Our goal was to explore melanomas at this anatomical location and their characteristics.
Materials and methods: We conducted a retrospective study in which we analysed electronic clinical histories of patients older than 18 years of age with a histopathological diagnosis of melanoma from 2007 to 2016. Melanomas located on the hands and feet were selected. Stage 0 melanomas were excluded.
Results: Of 530 melanomas, 30 (5.6%) were located in acral areas. Of these, 14, 10 and 6 tumours had a histopathological result indicating nodular melanoma (NM), surface spreading melanoma (SSM), and ALM, respectively. Staging was described for 23 tumours: 8 were in stage I at the time of diagnosis (7 SSM and 1 ALM), 5 in stage II (4 NM and 1 ALM), 4 in stage III (3 NM and 1 ALM), and 6 in stage IV (4 NM, 1 SSM and 1 ALM).
Conclusion: The majority of our acral melanomas were NM. This suggests that acral topography may not match the histopathology.

Characterisation of melanoma and non-melanoma skin cancer in a Colombian dermatology centre, 2016-2020

CASTILLO MOLINA, David - FUNINDERMA

Introduction and Objectives: Melanoma and non-melanoma skin cancers are the most common forms of neoplasia. Our objective was to describe the epidemiological characteristics of a group of patients with melanoma and non-melanoma skin cancer treated in a Colombian dermatology centre.
Materials and methods: A retrospective observational study was conducted at a dermatology centre in Bogotá, Colombia. We characterised all cases of skin cancer treated at this institution from January 2016 to January 2020. We analysed age at diagnosis, gender, occupation, phototype, histotype, anatomical location and treatment. We used relative and absolute frequencies to describe the patients. Clinical factors were compared using the chi-squared test and the t test. The data analysis was performed in Microsoft Excel version 16.34 and SPSS26.
Results: Of 396 patients, 52.8% (n=209) were women. The average age at diagnosis was 70.4 years (SD±13.8). The characteristics of the study population are presented in Table 1. Table 2 presents a comparison between patients with melanoma and those without melanoma. The frequency of melanoma cases was higher in patients with phototype II (23.1%) vs. phototype III (3.8%) and phototype IV (5.5%) (p=0.007). Nodular BCC (n=94), infiltrating SCC (n=49) and lentigo maligna (n=38) were the most common histological subtypes for each variant of skin cancer.
Conclusion: In the studied population, BCC was the most common, followed by SCC and melanoma, as reported in the literature. We also found that the frequency of melanoma cases was higher in patients with phototype II than in any other phototype. Further studies are needed to prioritise direct health policies and improve both diagnostic and therapeutic procedures.

Melanoma in a child with moderate congenital melanocytic nevi

MONTES María Victoria - Hospital Universitario Austral

Introduction: Malignant melanomas in the paediatric age range are quite rare, representing 0.9% of malignant paediatric neoplasias. Congenital melanocytic nevi are among the lesions most commonly seen at birth, with an incidence of 1 in 100 newborns. Their clinical relevance is based in their association with the development of malignant melanoma and with central nervous system involvement in the form of neurocutaneous melanosis. However, very few cases have been described of malignant melanoma derived from congenital nevi, and it is believed that the risk is directly proportional to the size of the nevus. We present a case of malignant melanoma in a 9-year-old girl who presented with a moderate congenital nevus with no family history of skin cancer.
Case presentation: Female patient 9 years of age being monitored for a moderate congenital melanocytic nevus at the tip of the nose. Upon the appearance of new raised lesions on the nevus, a

skin biopsy was performed on one of the lesions, and came back as a compound melanocytic nevus with congenital characteristics and moderate binding dysplasia. Since the incisional biopsy identified a moderate dysplastic nevus with no urgent indication for removal of the lesion, it was decided to take two biopsies of the remaining nodular lesions. Both were came back with results indicating a compound melanocytic nevus with congenital characteristics and mild lentiginous dysplasia, one with a central sector of fibrosis with melanophages and angiogenesis. In agreement with the dermatology, paediatrics and plastic surgery departments, a complete resection was performed of the lesion with its margins, followed by reconstruction with a medial forehead flap and auricular conchal cartilage graft. The second stage of surgical reconstruction was performed later with a medial forehead flap and nasal restructuring. Pathological anatomy results for this pattern indicated a melanoma focus in the vertical growth phase associated with a compound melanocytic nevus with congenital characteristics, Breslow depth 1 mm, non ulcerated, with free margin 1 cm from the lesion. Before the melanoma diagnosis in the context of congenital nasal nevus, discussions were held with the dermatology, plastic surgery and paediatric haemato-oncology departments. It was determined that the safety margins of the malignant lesion were sufficient, and the decision was made to request staging studies, the results of which ruled out secondary involvement, and to perform strict clinical monitoring of dermatology and mucosa. As the extension surgery had already been completed and lymphatic drainage had deteriorated, it was decided not to perform a sentinel node biopsy. Finally, the third stage of nasal reconstruction was performed with a medial forehead flap, pediculated section and refinement of the nose tip, with excellent aesthetic results.
Discussion: The prognosis for single congenital melanocytic nevi of small and moderate size is usually excellent, and its risk of developing into melanoma over the patient's lifespan is estimated at around 1%, and is extremely rare before puberty. In patients with large or giant congenital melanocytic nevi, the risk is estimated at around 5%, and increases with increasing size. In the latter case, melanomas tend to arise earlier in life (during childhood). Dermoscopy is vital in evaluating these, as it is an inexpensive, rapid and non-invasive method that can provide the doctor with very useful information for the diagnosis of early malignant transformation. However, it is not always this easy. Whenever there is clinical suspicion of melanoma or in case of any change in the nevus, it is urgent to perform a biopsy with histopathological exam. Early diagnosis and rapid treatment is needed to prevent metastasis. Tumour stage is the principal prognostic factor in both paediatric and adult melanomas. The case considered here highlights the role of clinical suspicion of malignancy and the need for strict monitoring with this type of nevus.

Genetics of melanoma of the perianal mucosa

WARSHAUER, Emily Mira - Paediatric, Adolescent and Adult Dermatology

Introduction: Mucosal melanoma is a rare and aggressive subtype of melanoma that remains poorly understood. It has a poor prognosis, often due to diagnosis at an advanced stage and a lack of effective therapies. The biology and oncogenic promoters found in mucosal melanoma are distinct from those of cutaneous melanoma, and a better understanding of the mutation panorama of mucosal melanoma will be essential to identifying new therapeutic targets and improving clinical results.
Case presentation: A 68-year-old woman with a history of endometrial and thyroid cancer presented at our dermatology clinic in October 2020 with a large pedunculated perianal nodule. Her gastroenterologist initially identified it as an atypical anal lesion, leading to the dermatology referral. Biopsy of the lesion revealed advanced perianal melanoma (pT3b with ulceration, 5 mitosis/mm2 and positive margins). A second biopsy of a smaller satellite lesion came back positive for melanoma in situ. A PET/CT scan showed no evidence of distant lymph node metastasis; however, it did reveal an FDG avid nodule (+) in the lateral left breast. A brain MRI showed no evidence of metastasis. An ultrasound-guided breast biopsy confirmed a diagnosis of intermediate to high-grade (pT1c) ER+ invasive ductal carcinoma (IDC). A multifocal ER/PR+ HER2- IDC lumpectomy was performed in December 2020 and re-excision in January 2021 due to positive margins. A wide local excision of the

perianal melanoma was performed with clear margins, together with a negative SLNE of the L groin. Adjuvant therapy was initiated for the resected primary high-risk anorectal melanoma with a PD-1 inhibitor, nivolumab, as well as an aromatase inhibitor for the IDC of the breast. Molecular diagnostic tests were positive for the following somatic alterations: CDKN2A, CDKN2B, NF1, ANKRD11, MSH6, PTPRT and SF3B1.
Discussion: Increased understanding of the genomic panorama of mucosal melanoma, combined with the advent of directed therapies, has revolutionised the range of treatment options for this rare and aggressive melanoma. In our patient's case, alterations were identified in the CDKN2A, CDKN2B, NF1, ANKRD11, MSH6, PTPRT and SF3B1 genes. Mutations of the germ line covering both CDKN2A and CDKN2B have been associated with a cancer predisposition syndrome which constitutes an increased risk for multiple cancers. The loss of these two tumour suppressors, as confirmed in our patient, may partially explain the diagnosis of endometrial, thyroid and breast cancer, in addition to the perianal melanoma. Although ANKRD11 mutations have not previously been identified in melanoma, it has been shown that ANKRD11 is regulated downward in breast cancer cell lines and activates the expression of CDKN1A. Frequently known for being mutated in melanoma, PTPRT is also altered in our patient. The patient responded well to the PD1 inhibitor Nivolumab, and to date, imaging shows no evidence of melanoma. Similarly, it has been found that PD1-directed therapy is more effective in MMR-deficient melanomas, as found in this case with the mutated MSH6. The arsenal of predictive biomarkers is crucial in effective management and treatment of melanoma patients. In patients with a mucosal melanoma as in our case, mutations in SF3B1 have been specifically identified as the most frequent and may have a negative prognostic effect. NF1 co-mutations are sometimes found as well, as seen in this patient. Allelic loss of NF1 may result in deregulation of the RAS/MAPK pathway, acting at least in part as a tumour-suppressing gene in the development of malignant melanoma. Curiously, the SF3b spliceosome complex has become a potential therapeutic target and has the potential to improve treatment options for both mucosal melanoma and breast cancer.

Acral melanoma: retrospective analysis of 13 cases

MILLER ROVTAR, Romina - Hospital Universitario

Introduction and Objectives: Acral melanoma is an uncommon pathology, defined as a melanocytic neoplasia located in the distal part of the extremities, independently of the clinical/pathological variant. These melanomas are characterised by their aggressiveness and poor prognosis, due to the fact that they are typically detected at an advanced stage. The purpose of this study is to describe the epidemiology and the clinical and histopathological presentations that this neoplasia showed in our population.
Materials and methods: We retrospectively reviewed all the clinical histories of 30 patients who had presented with cutaneous melanoma from January 2019 to January 2022, evaluated at Hospital Dr. Federico Abete, and included only those with acral locations. Epidemiological characteristics, personal case history, clinical presentations and histopathological variants.
Results: A total of 30 patients with cutaneous melanoma were diagnosed at our institution between January 2019 and January 2022. Patients with cutaneous melanoma located in acral areas represented 43.3% (n=13) of this group. The majority of cases (n=8) affected the feet, primarily the hallux (n=4) and soles (n=3), but also the lateral region of the feet (n=1). Cases on the hands affected only the fingers (n=5). Men (n=9) were more commonly affected than women (n=4). The patients' ages ranged from 17 to 89 years, but the majority of patients were over age 60 (n=11). Skin phototypes were primarily III (n=7) and IV (n=3), while 3 patients were of phototype II. None of them reported a personal or family history of melanoma, but some (n=4) reported a local trauma where the melanoma was located. One distinctive feature was a concomitant diagnosis of vitiligo in 3 patients. The predominant histopathological diagnosis was nodular melanoma (n=6), vs. the acral lentiginous variant (n=4) and indeterminate diagnosis for the remaining cases.

Conclusion: Independently of the fact that patients tend to avoid medical check-ups in our sociocultural context, we find the number of cases seen in this study to be very much worth highlighting, given that acral melanoma is an uncommon finding compared to other melanomas. In addition, we find it interesting that some patients had a concomitant diagnosis of vitiligo and a history of local trauma at the site of the tumour, and that none of them reported a family history of melanoma.

High-Risk Squamous Cell Carcinoma

Consensus and Disagreements Concerning High-Risk Squamous Cell Carcinoma among Skin Cancer Experts

Dr. PATEL, Vishal A.

According to the National Comprehensive Cancer Network (NCCN), factors associated with a very high risk of local recurrence and nodal involvement (only one factor is needed for it to be considered of very high risk) are:
- Clinical factors: size greater than 4 cm.
- Histological factors: poorly differentiated, desmoplastic subtype, invasion to a depth greater than 6 mm or below the adipose tissue, tumour cells in the nerve sheaths with a calibre equal to or greater than 0.1 mm or located below the dermis, and vascular or lymphatic invasion.

Eighth edition of the American Joint Committee on Cancer (AJCC)
T1: below 2 cm.
T2: between 2 cm and 4 cm.
T3: greater than 4 cm, or superficial bone invasion, or perineural nerve invasion greater than 0.1 mm or below the dermis, or invasion to a depth greater than 6 mm or below the adipose tissue.
T4a: invasion of the cortical or medullary bone.
T4b: invasion of the skull or the foramen at the base of the skull.

Brigham and Women's Hospital (BHW) Classification
T1: no high-risk factor.
T2a: one high-risk factor.
T2b: two or three high-risk factors.
T3: four or more high-risk factors, or bone invasion.
Although all staging systems can be used, the BHW classification offers greater sensitivity, specificity, and a higher positive predictive value (PPV), i.e., a greater statistical value.

Below we will analyse the areas of consensus among expert specialists according to the disease stages.

AJCC T2N0M0:
Areas of strong consensus: surgery is recommended as a first line of treatment. A sentinel lymph node biopsy (SLNB) during surgery to detect the existence of metastasis is not advised. Preoperative imaging studies to detect distant metastasis are not recommended.
Areas of moderate consensus: Mohs surgery is the first therapeutic line of choice.
Areas lacking consensus: 59% of experts do not recommend performing a preoperative ultrasound to detect nodal metastases in these patients, while the remaining 41% do.

AJCC T3N0M0:

Areas of strong consensus: surgery is recommended as the first therapeutic line. Preoperative imaging studies to detect nodal metastasis are recommended.
Areas of weak consensus: preoperative imaging studies to detect distant metastasis are not recommended. Mohs surgery is the first therapeutic line of choice.
Areas lacking consensus: the conduct of a SLNB during the surgery to detect subclinical nodal metastasis is not recommended by 59% of experts and recommended by 41% of them. Additional therapy with clean surgical margins is recommended by 57% of the experts, while 43% of them recommend no additional therapy. In case of administering additional therapy, radiotherapy should be administered locally on the primary site (61%) versus also on the lymph node (31%).

AJCC T4N0M0:
Areas of strong consensus: surgery is recommended as the first line of treatment (Mohs surgery 40% versus conventional surgery 60%). A preoperative ultrasound to detect nodal metastases is recommended. Postoperative adjuvant radiation is recommended despite the surgical margin being clean.
Areas of moderate consensus: preoperative imaging studies to detect distant metastasis are recommended.
Areas of weak consensus: a SLNB combined with surgery to detect nodal metastasis is recommended.

To conclude, although the experts reach a consensus on the management of an advanced disease, there is significant variability in the consensus concerning a high-risk disease. Additional trials are needed to clarify the role of the imaging studies, follow-up, SLNB, and adjuvant therapy in cases of a high-risk, resectable, advanced disease.

Therapeutic Options for Stage-N0 High-Risk Neck Squamous Cell Carcinoma

Dr. Abel Gonzalez

Although the overall prognosis of patients with head and neck SCC is good, 4% of patients with this condition develop nodal metastases and 2% die from this cause. Nodal and systemic involvement is the most important prognostic factor, as it reduces the survival rate by half. Most deaths from head and neck SCC occur due to an advanced locoregional disease.
The rate of nodal and distant metastases varies depending on the compromised site, with the lips and ears being the most affected locations. This more aggressive behaviour might be explained by the unique anatomy of these areas, characterised by thin skin, minimal subcutaneous tissue over cartilage or muscle structures, and their proximity to lymphatic pathways.
Within the lips, the vermillion has a greater risk of metastasis (7.6%) than the cutaneous lip (1.5%).
Different approaches have been proposed for the management of neck lymph nodes:
elective lymphadenectomy (more studies are required to indicate this treatment);
a SLNB, which can allow for identifying occult metastases in high-risk patients, although its usefulness has yet to be confirmed;
and active surveillance. A follow-up should be performed every one to two months during the first two years. Patients should be educated on how to self-palpate their lymph nodes on a weekly basis and instructed to contact their physician in case of doubts.

Management of Squamous Cell Carcinoma Beyond Surgery: Current and Emerging Indications for Immunotherapy

Dr. Chrys Schmults

The goals of this lecture are to carefully analyse which cases of SCC are deemed unresectable, to understand the current information available on immunotherapy for SCC, and to determine when to

consider referring patients for immunotherapy.
Around 1.5 million cases of SCC are diagnosed per year in the United States, which are too many cases to be able to perform statistical controls and studies of all of them. This is why these figures are not as well-known as those of melanoma, but it has been determined that 1%–4% of patients in the US with SCC develop metastasis and around 1%–2% die from this disease. This sums up to approximately 15,000 yearly deaths from SCC in the US, a rate that is probably higher than that of deaths caused by melanoma in this new era of immunotherapy treatments, which is estimated at around 7300 deaths per year.
The NCCN recommends administering a programmed cell death protein 1 (PD1) inhibitor for SCC unlikely to be cured by surgery or radiotherapy. But, how can we know which cases are unlikely to be cured? Locally advanced SCC is deemed inoperable when it is unlikely to be cured, its reconstruction would be too risky, or its treatment would result in an intolerable loss of function for the patient.
Anti-PD1 immunotherapy, such as cemiplimab, a drug approved in the US in 2018 that offers a response rate of 50% and a disease control rate of 72%, can be used in these cases.
Pembrolizumab is another drug that was approved in the US in 2020, offers a response rate of 34%, a disease control rate of 52%, and has been used in most trials as a second line of treatment for patients.
The complete response rate achieved with these treatments is less than 20%, but still possible.
Do all metastatic vessels need anti-PD1 therapy? Many nodal metastases do not require systemic therapy. For example, N1 tumours have a 92% 5-year cure rate with surgery ± radiotherapy, but greater N-stages have a worse outcome, and immunocompromised patients with a stage-N2 nodal disease have lower survival rates.
Two trials are currently being developed to analyse adjuvant treatment with anti-PD1 versus a placebo following surgery and radiotherapy.
A recent publication of the New England Journal of Medicine (NEJM), dated 27 October 2022, analysing neoadjuvant therapy with cemiplimab for stage-II to -IV SCC in 79 patients, 60% of whom had nodal metastases, reported a complete histological response in 51% of the patients treated with four doses of cemiplimab and subsequent full resection therapy, as well as grade-3/4 adverse effects in 18% of them.
Who should receive neoadjuvant anti-PD1 therapy?: unresectable tumours, patients with high surgical morbidity, and cases with a high risk of recurrence despite the surgery.

To conclude, SCC kills approximately 10,000 US citizens per year. Cemiplimab and pembrolizumab are the only approved treatments for unresectable SCC, yielding a response rate greater than 50%, a disease stabilisation rate greater than 70%, and a complete response rate below 20%. Because transplanted patients have a 50% chance of experiencing organ rejection with these treatments, these drugs are not recommended in their case. Neoadjuvant therapy offers promising results, with a complete response rate of 50%.

Dystrophic Epidermolysis Bullosa

Dr. MAYOR, Ander

Epidermolysis bullosa (EB) is a disease associated with a cumulative risk of developing SCC of 7.5% at 20 years, 67.8% at 35 years, and 90% at 55 years, and a cumulative risk of death from SCC of 57.2% at 35 years and 87.3% at 45 years.
Squamous cell carcinoma associated with EB manifests a high mutational burden unrelated to ultraviolet light exposure. The microenvironment of SCC in these cases is characterised by high doses of an inflammatory component and fibrosis, with high doses of transforming growth factor beta-1 (TGF-β1) and interleukin 6 (IL-6).
Some clinical considerations of SCC related to EB: the mean age of onset is around 32 years; it generally affects the upper and lower limbs; at least three tumours tend to be present simultaneously,

often with a diameter greater than 2 cm and well-differentiated in a histological examination; it has high recurrence rates; and its risk of metastasis is estimated at 38%.
A complete skin examination every 3 to 6 months is recommended in severe forms of EB, every 6 months in other forms, and every 3 months if the patient already has a history of SCC.
Special attention must be paid to non-healing wounds and areas of hyperkeratosis or with increased paresthesias and pain. Because it is hard to differentiate this condition from benign hyperplasia, involvement of an expert pathologist is recommended. There are no data available on Mohs surgery, but we personally suggest using this technique in these cases. There is no evidence either that amputation improves overall survival.
To conclude, we would like to mention that SCC is an important problem for EB patients. The chronic fibrosis state generates a pro-neoplastic microenvironment, which is the main cause of onset of SCC in these patients. Information available on the management of advanced disease in these patients is limited.

Managing Advanced Squamous Cell Carcinoma

Role of Neoadjuvant Therapy and Therapeutic Accuracy in Advanced Basal Cell Carcinoma

Dr. Susana Puig

Basal cell carcinoma (BCC) is the most common type of skin cancer, accounting for 80% of non-melanoma cancers and representing 25% of all cancers worldwide (possibly being underestimated).
Among the molecular mechanisms underlying BCC, mutational signature resulting from ultraviolet radiation (UVR) exposure is known to be important, and the number of mutations per megabase is greater than in the case of melanoma. Over 90% of cases of BCC are activated through the hedgehog signalling pathway, 80% due to mutations in PCTH1 and other genes, such as SMO, GL1, SUFU. There are different molecules that inhibit this pathway, such as vismodegib or itraconazole.
We know that the best treatment for this condition is surgery and that a different technique should be chosen depending on the location of the disease and its subtypes. However, because advanced cases might not be candidates for surgery and not respond to radiotherapy, other options, such as systemic therapy, should be used. Hedgehog signalling pathway inhibitors are currently the only systemic treatments approved for advanced BCC: vismodegib has been approved for locally advanced and metastatic BCC, and sonidegib has been approved for locally advanced BCC and, only in Australia and Switzerland, for metastatic BCC.

Two studies have been carried out on the use of hedgehog signalling pathway inhibitors for advanced BCC: vismodegib (ERIVANCE) and sonidegib (BOLT), both reporting similar, important response and toxicity profiles. Some adverse events related to these drugs can be serious, some appearing within the first few weeks of treatment and others at a later date, such as hair loss, asthenia, and weight loss. Dysgeusia and muscle spasms are the most frequent side effects. There is some resistance to these treatments and many patients discontinue them due to experiencing adverse effects.

Many authors suggest using hedgehog signalling pathway inhibitors as neoadjuvant therapy.
A multicentre, open-label, phase II study on the use of vismodegib as neoadjuvant therapy for locally advanced BCC, administered at a standard dose for 4 to 10 months, demonstrated that it could benefit the surgical treatment and result in a less comorbid surgery. The authors of this study classified the potential surgical approach applied prior to the treatment into different stages from higher to lower severity, observing that most patients exhibited an improvement and a decrease in their surgical stage after receiving this treatment.

The VISORB trial, which analysed the use of vismodegib to preserve the visual function of patients with advanced periocular BCC, was an open-label, non-randomised, phase IV study evaluating this drug in patients with locally advanced ocular BCC with a risk of involvement of the eyeball and the lacrimal ducts. A score was developed to evaluate the patients' visual function and participants were administered 150 mg/day of vismodegib for 12 months. After this period, their surgical samples were subjected to a histological examination. The conclusions reached in this study were that vismodegib was effective in protecting the eye and visual function either administered alone or as neoadjuvant therapy. This treatment should be considered for periocular BCC potentially requiring exenteration of the eyeball or associated with a significant loss of visual function, in addition to major facial deformity.

These types of carcinomas tend to exhibit great mutational burden and a high expression of programmed death-ligand 1 (PDL1). Tumours with a high mutational burden tend to be more responsive to PD1 inhibitors. Checkpoint inhibitors, such as cemiplimab, are another option for patients in whom hedgehog signalling pathway inhibitor therapy has failed.

To conclude, neoadjuvant therapy with hedgehog signalling pathway inhibitors for difficult-to-operate, advanced BCC is effective, as it allows for preserving structures and functions, and its adverse effects are manageable. The duration of this treatment prior to performing surgery is not yet well established. Although some tumours may be primarily resistant and progress to non-surgical stages, immunotherapy can be used in these cases. Documented tumour recurrence at 36 months is greater than 30%.

Resistance to Hedgehog Signalling Pathway Inhibitors

Dr. Mazzuoccolo

There are three main resistance mechanisms:
- Genetic mutations: SMO mutation, SUFU deletion, and GLI amplification.
- Activation of the non-canonical hedgehog signalling pathways.
- Primary cilia loss.

The STEVIE trial is one of the pivotal, open-label, multicentre, phase II trials evaluating the safety and efficacy of vismodegib in patients with locally advanced or metastatic BCC. In this study, over 20% of the total diameter was considered intrinsic resistance and contraction of over 30% and new growth was considered acquired resistance. Genomic evidence was searched in patients with primary resistance, identifying a significant mutational burden in subjects with intrinsic resistance compared with those responding to vismodegib. Patients who had received a previous line of chemotherapy or radiotherapy had a higher risk of treatment resistance.

Smoothened variants (SMO) explained most cases of drug resistance in BCC. The researchers found mutations that were not present in the patients' biopsies before starting treatment with vismodegib; that is, that new mutations had appeared.

Activation of non-canonical hedgehog signalling pathways. In this case, TGF-β1 is a potent inducer of GLI1 and GLI2.

There are studies on how primary cilia loss acts as a mechanisms of resistance to SMO inhibitors.

An exchange in hedgehog signalling pathway inhibitors can be used as a strategy to address resistance when advanced BCC is a threat.

To conclude, different mechanisms may explain resistance to these treatments. Although there are some strategies available to overcome this resistance, additional studies are needed to customise these therapeutic regimens.

Experience with Vismodegib in LATAM and Argentina

Dr. Roxana del Aguila

The Food and Drug Administration (FDA) approved vismodegib in 2012 and, in Argentina, two studies led to its final approval by Argentina's National Administration of Drugs, Food, and Medical Technology (ANMAT, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica) in 2017.
One of these studies was the STEVIE trial, a pivotal, open-label, multicentre, phase II trial evaluating the safety and efficacy of vismodegib in patients with locally advanced or metastatic BCC.
The other one was an observational study evaluating the efficacy and safety of vismodegib in real-world settings in an Argentinian cohort of patients with advanced BCC.
In addition, the results of another multicentre (Hospital Roffo, Hospital Italiano, and Hospital Eva Perón), retrospective, observational, and descriptive study on VISMODEGIB administered at a dose of 150 mg/day for 4 years in standard dermatology practice are also available.
To conclude, we observed a high response rate to vismodegib, with a good safety profile and mild-moderate adverse effects. Vismodegib is used in Argentina for locally advanced or metastatic BCC, and as neoadjuvant therapy administered before Mohs surgery.

Neoadjuvant Therapy with Vismodegib for Locally Advanced Periocular Basal Cell Carcinoma

Dr. Abel Gonzalez

Locally advanced periocular BCC is the most frequent cause of ocular exenteration.
Mohs surgery is the gold-standard treatment for periocular BCC, with cure rates ranging from 95% to 99%. Preservation of the eye with negative margins is possible in very few patients and the reconstruction outcome is usually suboptimal.
Neoadjuvant therapy with vismodegib has proven to decrease the size of the tumour in these patients and, as a result, enable a less morbid surgery. Subsequent Mohs surgery allows complete resection of the tumour with histological confirmation of the efficacy of vismodegib and safe reconstruction with an improved functional and cosmetic outcome.

The VISORB trial, which analysed the use of vismodegib to preserve the visual function of patients with advanced periocular BCC, was an open-label, non-randomised, phase IV study evaluating this drug in patients with locally advanced ocular BCC with a risk of involvement of the eyeball and the lacrimal ducts. A score was developed to evaluate the patients' visual function and participants were administered 150 mg/day of vismodegib for 12 months. After this period, their surgical samples were subjected to a histological examination. The conclusions reached in this study were that vismodegib was effective in protecting the eye and visual function either administered alone or as neoadjuvant therapy. This treatment should be considered for periocular BCC potentially requiring exenteration of the eyeball or associated with a significant loss of visual function, in addition to major facial deformity.

Controversies in Skin Cancer

Skin Cancer Screening

Leads to Early Diagnosis of Melanoma and Improved Mortality Rates

Dr. PUIG SARDÁ, Susana

Who is considered a high-risk patient for melanoma? According to different publications, the presence of 20 nevi on the arms is a simple rule to identify young patients under the age of 50 at a high risk of being diagnosed with melanoma.

In which subjects is it advisable to perform a full-body examination? Risk factors are age over 50 years, number of nevi, a personal history of melanoma or non-melanoma skin cancer, significant chronic sun exposure for several years, and actinic keratoses.

In the DERMA RISC study, in which a total of 400 adult patients participated, 26 of whom had skin cancer, 12% of the participants reported a family history of skin cancer and 6% a personal history of this disease. A full-body skin examination was performed in 20% of the participants. Of these, 44% had 10 or more pigmented lesions on one arm, or more than 20 lesions between both arms, and 21% of them exhibited signs of chronic sun damage. Over 80% of the melanomas, 95% of the basal cell carcinomas (BCCs), and 100% of the squamous cell carcinomas (SCCs) were diagnosed in the group of patients over the age of 45 years.
This tool (risk assessment questionnaire and physical examination of the skin of the arms and other exposed areas) has a negative predictive value of 98% and a sensitivity of 92% for detecting skin cancer.

According to a meta-analysis published in the Lancet, dermoscopy improves the diagnostic efficacy of melanoma by 35% in comparison with a naked-eye examination.

To conclude, although skin cancer screening among different populations is minimal and controversial, we must improve access to appropriate treatment for patients with melanoma and skin cancer. Empowering the population about their own health includes educating patients to try to recognise suspicious skin lesions and taking responsibility in attending skin consultations with a dermatologist so as not to miss the opportunity for an early diagnosis.

Leads to Overdiagnosis and Increases the Incidence of Melanoma
Dr. SANCHES, José Antonio

Is melanoma overdiagnosed?
In 1997, Swerlick and Chen were the first authors to suggest that the “Cutaneous Melanoma Epidemic” is more apparent than real. This rapid increase continues to be debated and lack consensus more than two decades later.
The impact of the increase in the diagnosis of melanoma has been widely discussed from the perspective of an early diagnosis, which can improve patients’ survival outcomes. However, from the point of view of an overdiagnosis, it can actually harm patients, as a diagnosis of cancer can lead to excessive medical treatments and psychological stress, as well as result in increased costs and resource consumption for the healthcare system.

If we compare the incidence and mortality rates of this disease over the past years, we can see that the incidence and mortality of melanoma increased by 73% and 29%, respectively, between 1975 and 1989. From 1989 to 2013, the incidence of melanoma increased by 77%, but its mortality remained unchanged, and from 2013 to 2017, its incidence increased by 6.6%, while its mortality decreased by 22%.

According to a study carried out in the United States, over the past 10 years, between 2007 and 2016, the incidence rate of melanoma increased an average of 1.5% per year, while the mortality rate

decreased an average of 2.5% per year.
Thus, the incidence of melanoma is now six times higher than it was 40 years ago. Many questions have been raised as to whether this increase actually reflects a true epidemic of melanoma or rather an epidemic of melanoma overdiagnosis. This increase in the number of diagnoses only affects cutaneous melanoma, as the rate of non-cutaneous melanomas remains stable. It is hypothesised that this discordance between the incidence of both types of melanoma is due to the different accessibility to a visual skin examination, which makes cutaneous melanoma more accessible to its diagnosis, as the patients' skin is more exposed than non-cutaneous melanoma sites.

Potential factors associated with this increased incidence of melanoma are a greater exposure to ultraviolet radiation; the increased number of skin biopsies performed by dermatologists; the increased number of histopathological diagnoses owing to a legal issue of the pathologist; the failure to diagnose many melanomas in the past, which causes us to believe that the current incidence is greater; and the ageing population.

Concerns about diagnosis: screening proponents argue that it allows for reaching an early diagnosis and for taking the opportunity to counsel patients on photoprotection. However, screening might lead to overdiagnosis and overtreatment of clinically unremarkable diseases. Cancer overdiagnosis refers to the detection of tumours that do not cause a clinically significant disease if left untreated. Around 25% of melanoma-specific deaths are caused by thin melanomas, so they cannot simply be ignored. Melanoma in situ could be indicative of a patient's predisposition to develop secondary invasive melanoma.

The Screen Study carried out in Germany compared melanoma mortality rates in a region of Germany where screening was performed versus surrounding regions in which it was not, reporting a 48% lower mortality linked to melanoma in the former. However, another independent study in which the study participants were followed for an additional 5 years found that these findings did not persist over time (although 37% of the subjects were lost to follow-up). Based on the results of this trial, Germany implemented a national melanoma screening programme for patients over 35 years of age. The incidence of melanoma was higher after launching this programme, but its associated mortality remained stable.

To conclude, additional research is needed to fully understand the impact of screening on melanoma. According to the US Preventive Service Task, there is not enough evidence to indicate population screening and the American Cancer Society recommends that adults over the age of 20 years have their skin checked as part of their routine check-ups. It is a well-known fact that some populations are at a greater risk of developing melanoma, including patients over the age of 50, with a family history of melanoma, with over 100 nevi, with dysplastic nevi, and immunocompromised patients. In this group of patients, screening is considered to be beneficial.

2022 Margins in Melanoma. What Should We Do?

Standard Margins
Dr. GONZÁLEZ, Abel

Standard surgery for local treatment of primary melanoma is wide excision including the tumour, the normal skin surrounding it, and the underlying subcutaneous cell tissue in order to remove any potential microscopic satellitosis that may be present around the main tumour. Failure to correctly remove the melanoma or microscopic satellitoses results in local recurrence or metastasis.

Satellitosis, as a manifestation of regional, lymphatic, intracutaneous or subcutaneous spread of the disease, is found in 4% of melanomas and is related to poor survival, and local recurrence is linked to a survival rate below 10%. Until they began to be correlated with the Breslow depth, surgical margins for melanoma excision were more radical in the past. According to the National Comprehensive Cancer Network (NCCN):
Melanoma in situ: surgical margin of 0.5 cm to 1 cm.
Breslow depth equal to or lower than 1 mm: surgical margin of 1 cm.
Breslow depth between 1 mm and 2 mm: surgical margin of 1 cm to 2 cm.
Breslow depth between 2 mm and 4 mm: surgical margin of 2 cm.
Breslow depth of over 4 mm: surgical margin of 2 cm.
It does not recommend Mohs surgery as primary treatment for invasive melanoma when standard margins can be achieved.

In 2021, the European Journal of Surgical Oncology (EJSO) published an abstract on the surgical margin recommendations provided by different guidelines of all over the world. Although all these guidelines recommend slightly different margins, the local recurrence rate observed in all trials was lower than 5%.

The MelMart trial aims to determine the safety of a surgical margin of 1 cm compared with 2 cm in patients with lesions with a Breslow depth greater than 1 mm and who have been subjected to a sentinel lymph node biopsy. The primary endpoints of this trial are local recurrence and melanoma-specific survival. The proposed sample size for this trial is 10,000 patients, so it will take several years to be completed.

To conclude, we base our decisions on the findings of systematic reviews and randomised, controlled trials.

Personalised Margins
Dr. PELLACANI, Giovanni (Italy)

In vivo is applied with the patient lying in bed prior to a surgical procedure and exclusively in the case of superficial margins, such as lentigo maligna.
Ex vivo is applied to tissue recently resected during surgery and enables examination of the full sample thickness, for example, in the case of BCC.

In vivo confocal microscopy is indicated for all types of superficial skin cancers located on areas of skin that are not excessively thick.
Ex vivo fluorescence confocal microscopy is indicated in cases in which rapid detection of the intraoperative tumour margin is needed. Acridine orange 1mM stain is applied for 10–30 seconds and subsequently rinsed with saline solution.
It is useful for Mohs surgery, can potentially replace classic freezing of the surgical specimen, and the digitally stained image can be interpreted by a pathologist.

The Future of Sunscreens

Dr. OSTERWALDER, Uli

My lecture is based on this review on the fate, exposure, and effects of sunscreens in aquatic environments and the implications of the use of photoprotectors on human health.

The desirable characteristics of a photoprotector are:
1. It protects from the harmful effects of ultraviolet radiation.
2. It is safe for human use.
3. It is cosmetically acceptable.
4. It has a low environmental risk.
5. It is affordable.

1. Does sunscreen prevent melanoma? We cannot affirm this yet, but we believe that we are on the right track. What we are seeing is that it is extremely important to apply sunscreen on sunny days and to wear shirts, pants, and hats to protect the skin from sun exposure.
Sunscreen is known to work and help prevent the most common form of skin cancer.

There are different protection profiles available, some with increased ultraviolet B (UVB) protection, others with higher ultraviolet A (UVA) protection, and others offering a more uniform protection, known as spectral homeostasis, which are the type that we must look for. Not all sunscreens with the same sun protection factor (SPF) are the same, not all of them offer adequate protection against UVA or blue light, and not all of them use the same concentration of the filters needed to reach said SPF.

2. Safety in humans and skin absorption. Benzophenone 3: at a concentration of 6%, it is deemed safe for small areas, such as the face or the hands, but not for large areas of the body. Homosalate: the current law defines 10% as a safe concentration.

3. The market defines what is cosmetically acceptable: the current trend shows a preference for mineral and coloured filters.

4. Low environmental risk: the National Academy of Science (NAS) recommends that the Environmental Protection Agency (EPA) perform an ecological risk assessment for all filters that are currently available on the market and any new ones, and to share such information.

5. In the United States there are filters costing over 20$ an ounce and Germany is working on developing cheaper filters costing less than 2$ an ounce.

Ex Vivo Confocal Microscopy for Rapid Evaluation: Mohs Surgery

Dr. MALVEHY, Josep

Confocal microscopy is a quick technique, does not require a complex laboratory, and can guide Mohs surgery for the treatment of non-melanoma skin cancer.
Acridine orange staining is used to generate significant contrast between the nucleus, the cytoplasm, and the dermis, without being affected by subsequent freezing of the specimen, if required.
It results in less surgery time, a lower rate of biopsies, a lower rate of incorrect tissue extractions, and replaces other less sensitive and specific modalities.

Procedure: the specimen is stained with acridine orange 0.6 mmol for 20 seconds, rinsed with saline solution, soaked in 50% acetic acid for 20 seconds, rinsed again with saline solution, and finally examined under a confocal microscope.

It allows for reaching a rapid diagnosis of skin tumours and assessing surgical margins in skin cancer (cbc, cec, dfsp), including special sites, such as the eyelids, conjunctiva, and nails, and can be used to diagnose other tumours, such as breast, prostate, brain, thyroid, and colon tumours; infections, such as mucormycosis, dermatophytosis, herpes, or aspergillosis; other diseases, such as vasculitis, blistering disorders, psoriasis, or lichen planus; and even to detect hyaluronic acid fillers.

Ex vivo confocal microscopy allows for a rapid pathological examination and telediagnosis between the operating room and the laboratory.