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Dermoscopy – Total-body photography, digital dermoscopy and CT scans: indications and procedures

Chair: Josep Malvehy (Spain)

Speakers: Josep Malvehy (Spain) and Katrien Vossaert (Belgium)

I have to confess that I still use the good old method of manual photographic comparison in my practice. I'm a total has-been – it dates back to the 1970s. My image quality is very poor but I can probably detect changes of more than 2 mm.

To improve follow-up, I can now use digital dermoscopy (to obtain more sensitive and lesion-specific information), total-body photography (to detect new lesions in high-risk patients), or a combination of the two to reduce the number of benign lesions removed.

New technologies offer better image quality and shorter procedures.

Total-body photography makes sense in cases of atypical mole syndrome: in just one second, almost 100 images are acquired, providing information on the multiple lesions, whereas digital dermoscopy of each lesion is not feasible.

The sensitivity of the combination [total-body photography + digital dermoscopy] is very poor on initial acquisition (around 25%) but rises to 100% on subsequent visits.

Existing devices are not standardised. When they are subjected to the USAF microscopic optical resolution test, different results are obtained: it is

therefore necessary to know the state of the various dermatoscopic structures useful for diagnosis in order to determine whether a particular machine will be able to distinguish between them.

2D and 3D photographic systems do not allow us to see vessels, the pigment network, lines, dots, small globules or bright white structures correctly. However, they enable us to see colours, asymmetries, changes in diameter and pigmentation, pigmentation contrasts and pseudo-network aspects on the face, in order to target lesions for subsequent observation by dermatoscopy.

The latest full-body scanners use liquid lenses that enable the focus to be changed in just 1 ms, thereby greatly increasing the resolution.

There are also automated systems that combine total-body photography and dermatoscopic image-taking, which in around 10 minutes allow us to observe around 40 lesions dermoscopically with the same resolution as with a manual dermoscope.

Artificial intelligence (AI) tools can currently be used to segment lesions or dermatoscopic images, classify the morphology of individual lesions, detect changes, calculate melanoma risk scores and identify areas of interest or lesion similarity using explainable AI.

Explainable AI theoretically allows the user to check how an algorithm reached an answer. However, no authority is currently in a position to validate explainable AI tools!
As far as medical device legislation is concerned, obtaining the CE standard is legally necessary but not scientifically sufficient. Healthcare AI-based devices with machine learning must fall in Class II, a, b or III.

These tools have not yet been properly validated in terms of their clinical performance. They enable the patient's phenotype to be determined and the number of lesions to be counted in a reproducible way.

The models are able to perceive changes in symmetrical or asymmetrical growth, focal or overall hyperpigmentation, colour change or the appearance of new lesions.

However, it is important to be aware of their limitations despite their good sensitivity and specificity. The few studies comparing devices, software and algorithms show that there are many false positives and false negatives, and that for the same patient the answers will be different depending on the device used. Unfortunately, the detailed performance of each algorithm is not

available, which means that performance cannot be compared for different algorithms.

To test the performance of algorithms, Joseph Malvehy's team artificially modified naevi. Sensitivity was good – close to 96% for 3D devices – but there were many false positives: positional, specific location, clothing, hair. However, it is interesting to note that melanomas had a significantly greater amount of change than benign lesions, and that the decisions made by the dermatologist assisted by the tool were more relevant.
In terms of acceptance by the public and users: patients generally have confidence in these new technologies, provided they are supervised by the dermatologist, and more novice practitioners are more likely to trust the results provided.

In the specific population of patients with atypical naevi, the use of this technology is particularly attractive because it reduces the number of lesions to be treated (NNT) to remove melanoma to less than 3:1.

These images are interpreted based on the clinical and phenotypic information available and the genetic or mutational profile where appropriate.

In the absence of a medical context explained by the dermatologist, almost 50% of melanomas will not be identified by the system.

The integration of these multimodal data by AI solutions requires prior training with good-quality datasets annotated with the necessary information.

Doctor K. Vossaert, from Ghent, Belgium, told us about her very interesting experience using 3D total-body photography in the general population and for monitoring high-risk patients.
Observing that the current 2D devices available on the market are ill suited to private practice because they are too costly in terms of staff time and space, she presented data from one year's use of a 3D device by two dermatologists and four interns.

Because of the high cost, which would be insurmountable for an isolated practice, the device was installed in a stand-alone unit, with direct access for the patient or on referral, and with support provided only by an assistant who collected the necessary information. It performed dermatoscopic acquisition of lesions signalled after total-body photography by the algorithm via the pie chart, examining the skin folds, palms of the hands, soles of the feet and

scalp. Each acquisition was reviewed by the dermatologist, who produced a report and recommendations. Any lesion analysed as suspicious at the end of the examination constituted a reason for referral for a face-to-face consultation. AI assistance was provided at two levels: selection of lesions after total-body photography and assistance in examining suspicious lesions using the malignancy score.

The very high sensitivity of these exams must be balanced by the dermatologist's analysis, particularly for solar lentigines, blood vessels or tattoos, for example. The device therefore serves both as a diagnostic aid for high-risk patients and as a sorting aid for the general population.

Over one year of screening scans, 3,228 patients were photographed, including 64% with direct access and 36% who had been referred. This was not, of course, an organised, systematic screening programme in the strict sense of the term. Among the 2,059 patients who consulted spontaneously, high-risk patients were identified when there was a personal history of melanoma, or more than 100 naevi, including one atypical naevus. They represented 15% of patients.

Low-risk patients (59%) had to have fewer than 50 naevi and no personal history. The remaining 26% represented the median risk. In the low-risk group, 10% had suspicious lesions and the malignant lesion detection rate was 5.2% (i.e. 63 lesions for 1,208 patients within one year). The medium-risk group also had 10% suspicious lesions and a malignant lesion detection rate of 4%, i.e. 22 lesions for 545 patients. In the high-risk group, 18% of lesions were suspicious, with a detection rate of 4.2%, i.e. 13 malignant lesions. The total number of melanomas detected was one in the high-risk group, six in the medium-risk group and seven in the low-risk group.

The average detection rate of 4.8% is very interesting compared with data published 10 years ago in the literature, ranging from 0.8% to 3.2%.

The number of lesions that need to be removed to diagnose a malignant lesion is generally two, and three in the case of melanocytic lesions.

Seven melanomas were invasive, and the other seven *in situ*. Of these 14 melanomas, nine were incidental findings for the patient. The six other patients with melanoma had consulted a screening centre due to the lack of an accessible dermatologist. 1,590 of the 3,228 patients scanned did not require a subsequent dermatological consultation (all high-risk patients were referred, as were patients with suspicious lesions). In particular, 89% of the patients in the low- and medium-risk population did not require a consultation.

A comparative study between the automated total-body examination and the unassisted examination has also been planned.

Most melanomas occurred in the low-risk group of patients, due to their sizeable mass. For this reason, self-inspection is still recommended in this group, to look for new lesions or changes in existing lesions, with the CT scan potentially serving as a reference base.

The cost of the examination (around €100) was borne by the patient. A cost-effectiveness study is also required.

This model of fixed, expensive devices in practices may seem fragile in the face of proposals for mobile apps made to available to patients on their phones. However, while home-based solutions can reach certain groups who are unwilling or unable to consult a doctor, they are still limited by the quality of the images, the difficulty of autonomous acquisition, and the cost of the analysis required after the images have been taken.

Artificial intelligence in dermato-oncology

Chairs: Julia Winkler (Germany), Allan C. Halpern (United States), Konstantinos Liopyris (Greece)

Speakers: Harald Kittler (Austria), Allan C. Halpern (United States), Josep Malvehy (Spain), Peter Soyer (Australia), Konstantinos Liopyris (Greece), Julia Winkler (Germany)

Introduction to current and evolving trends in AI

Any symposium dealing with artificial intelligence (AI) is always a source of wonder and panic for me. Changes are always asymptotic. As I write these lines, the trend is towards transformative neural networks or transformer models. These are types of neural network architectures with no sequential structure and which use semi-supervised or unsupervised learning. They are the backbone of foundation models such as Le Chat and ChatGPT.

Foundation models are machine learning models trained with generalised, unlabelled datasets and capable of performing various tasks such as natural language processing (NLP), answering questions and classifying images.

A foundation model has now been created specifically for dermatological use, to interpret a variety of image sources. The aim is to use it for screening, diagnosis, data analysis and prognosis purposes. For example, the user can identify changes over time in dermatoscopic images. From a dermatoscopic

image, it can also generate a prediction about the characteristics of a given melanoma, which will be used to select an adjuvant or neoadjuvant treatment.

These dermatological foundation models are trained with datasets (sets of thousands or even millions of labelled images of dermatological diseases). As an example, since 2016 the International Skin Imaging Collaboration (ISIC) has been organising challenges aimed at improving the accuracy of melanoma diagnosis compared with other skin lesions. In 2024, hundreds of thousands of images were analysed and made available for more than seven different diagnoses. Databases are currently being enriched with images from a variety of sources (clinical photographs, dermatoscopy, histopathology, molecular biology, etc.). The current points of attention needed to minimise bias in dermatological image analysis are lesions that are underrepresented in databases, variations in skin colour, hair, and also markers placed on photos.

In Europe, explainable AI is required by legislation for AI in healthcare. This refers to artificial solutions for which the deep learning model can be understood by humans. While it may seem appealing, because it is more reassuring, it is currently mainly used to explain AI errors, but it does not provide any greater accuracy.

While it is now accepted that diagnoses are established more accurately by AI algorithms than by clinicians, the unresolved question is what to do with these new answers. People remain the holders of the information, and they choose when, where, how and to whom it should be transmitted. They must choose the useful fields of application for AI.
As far as training is concerned, various studies have shown that the information provided by AI is of benefit to less experienced users.
In research, AI is already being used in prospective real-life studies, such as the one where, in 2023 in The Lancet Digital Health, Menzies' team showed that an algorithm was as good as a specialist at diagnosing a suspicious pigmented lesion using remote expertise on a mobile phone.

Doctors are also responsible for optimising the responses provided by AI. In dermato-oncology, for example, a false negative in the diagnosis of melanoma has far more serious consequences than a false positive. Positioning this cursor is just as important as increasing accuracy. It is therefore crucial to use feedback loops in therapeutic decision support models, using asymmetric penalties, for example.

AI tools can also select relevant information flows, for example when sorting requests for remote expertise.

Current state of imaging in dermato-oncology

Digital medicine, which includes the use of AI, is a $57 billion market in 2025. It includes, in no particular order: remote expertise and consultations, diagnostic applications for patients and healthcare professionals alike, and various advances in imaging. Although dermoscopy is now a routine part of dermatology practice, other imaging techniques are still less readily available, such as optical super-high magnification dermoscopy (OSHMD), which enables 400x magnification of structures similar to those seen under a microscope.

Total-body 3D imaging enables individual lesions to be identified by their unique coordinates in three dimensions. Once again, the way in which this technology is used has yet to be perfected, since the latest publication by the team of H.P. Soyer in JAMA Dermatology has just shown that for practitioners with little experience and without the benefit of AI, melanoma screening was less effective using the 3D system (35%) than in the control group (64%).

Deep skin imaging (confocal microscopy and LC-OCT), which aims to increase diagnostic accuracy beyond dermatoscopic images, currently seems to be more widely used in Europe than in the United States.

Current state of AI marketing and implementation in dermato-oncology

The development of AI tools for healthcare is complex and currently goes through a number of stages: first of all, the problem to be solved must be defined and the programme designed; then comes the data collection phase to develop the model; the pre-clinical phase for technical validation; and the real-life clinical validation phase. The next stage is to obtain CE marking and, more recently, achieve compliance with the European AI Act (applicable from August 2025). The product must then prove its qualities in terms of cyber security, integration into the IT system and ethics. Using explainable AI is also a requirement. Then comes the phase of commercial use of the system, with implementation in daily practice, evaluation of the product and issues of reimbursement by health systems, as well as ongoing evaluation and post-market monitoring.

In 2022 in JAMA Dermatol, the ISIC for AI published the list of items needed to evaluate imaging devices using AI in dermatology.

The key point is the dataset used to train the algorithm. The quality of the dataset is paramount, and manufacturers have a duty to be transparent about its origin. The algorithm must also be assessable and accessible. The product must also have a defined target audience (healthcare professionals, patients, etc.), an end user and a defined use.

There are several devices available with Class IIA CE marking, but in light of recent studies (Rotemberg, JAMA Dermatology, 2024, etc.), the smartphone apps currently available for melanoma diagnosis have not shown any clear value in real life, due to the lack of sufficient robust and accessible data.

Class IIa CE marking is not a guarantee of sufficient scientific quality! And, as in the pharmaceutical industry, proof must be provided through clinical trials.

Artificial intelligence remains a tool: the assistance it offers enhances the user's intelligence. Studies have also shown that patients and doctors are more likely to trust a dermatologist aided by a machine than a human or AI alone.

Medical-legal and privacy issues related to the use of AI

The speaker discussed the ACEMID project, a network of three Australian states using fifteen 3D total-body photography devices, half of which are located in rural areas. The study has reached 16,000 visits from 7,500 participants; AI tools will soon be incorporated. The data currently being collected include 3D imaging and dermoscopic images, clinical data and patient questionnaires, Melanoma Institute Australia's melanoma risk, genetic and proteomic data, data from Australian cancer registries, virtual slides and histological reports.

The use of these computerised imaging techniques in dermatology raises questions in terms of legislation and data confidentiality. Discussions are currently underway to issue recommendations for data governance (classification, security, anonymisation and retention of data).

Limits to the use of AI in dermato-oncology

The applications of 3D total-body imaging are not limited to melanoma. It can be used to monitor all kinds of dermatological diseases (assessing responses to treatment, calculating PASI and BSA scores, etc.). Errors in the interpretation of images by the AI algorithm can arise from changes in the patient's morphology or position, areas of hair or tattoos or interpositions,

changes in position, a segmentation problem or simply a lack of reproducibility.

Opportunities and challenges of AI in dermato-oncology

It is an established fact that convolutional neural networks outperform humans when analysing images of pigmented skin lesions, even more so when the user is inexperienced. Currently, for a wider range of lesions, neural networks are as good as people, even when it comes to doubts about lesions that are difficult to diagnose, such as facial lesions!

However, AI performs poorly for mucous and nail lesions, as well as for vascular and adnexal lesions, lymphomas and all rare tumours.

Neoadjuvant treatment of melanoma

Chairs: Christian Blank (Netherlands), Georgina Long (Australia)

Speakers: Georgina Long (Australia), Christian Blank (Netherlands), Alexander Eggermont (Netherlands), Julie Stein-Deutsch (United States)

Clinical development of neoadjuvant immunotherapy in melanoma

Perfect is the enemy of the good in the realm of neoadjuvant treatment. A different immune response is obtained when immunotherapy is administered neoadjuvantly or adjuvantly.

Neoadjuvant treatment for melanoma is currently administered six to eight weeks before surgery, and the response is then assessed on histology. A complete histological response is defined as a maximum of 10% residual tumour. A partial response is defined as 10 to 50% residual tumour and a non-response as +50%. The sum of the complete and partial histological responses constitutes the major histological response.

The key SWOG and NADINA studies demonstrated the efficacy of neoadjuvant immunotherapy and enabled major responders to be exempted from further treatment. Event-free survival curves overlapped in the two trials, with SWOG (HR 0.58) showing a 42% reduction in the risk of events (progression, recurrence or death from any cause) and with NADINA

(HR 0.32) showing a 68% reduction. These results are gradually leading to treatment and reimbursement authorisations for these drugs worldwide.

A pooled analysis of neoadjuvant checkpoint inhibitors showed that combinations (with anti-CTLA4 or anti-LAG treatments) were superior to anti-PD1 treatment alone in terms of event-free survival. The pooled analysis also showed that 61% of major histological responses were achieved in combination, compared with 50% with neoadjuvant anti-PD1 treatment alone. These patients, who therefore did not undergo any further treatment, had a lower risk of toxicity, better quality of life and less of an economic impact. For BRAF-mutated patients who do not respond, this non-response can help guide the choice of adjuvant treatment with targeted therapy. A major histological response augurs well, whatever the adjuvant treatment adopted. The overall survival of patients who received a neoadjuvant checkpoint inhibitor was better than that of patients who received adjuvant anti-PD1 therapy in the absence of a histological response.

Lastly, monitoring can be extended to six-monthly for patients with a major response. Histologically, the pathological response is estimated based on the percentage of viable tumour and the percentage of fibro-inflammatory territories (and secondarily of necrosis and melanophages). As far as pathologists are concerned, macroscopy of lymph nodes after neoadjuvant treatment is reduced by at least half under the new recommendations.

In terms of surgery, the results of the PRADO study (where, after removal of the index lymph node to establish the degree of histological response, no additional dissection is necessary in the event of a major response) will need to be confirmed by the ongoing MSLT3 study.

The pooled SWOG + NADINA results show that patients with high interferon gamma scores have a better fate. These good responder profiles could therefore be treated with neoadjuvant anti-PD1 therapy alone. The NéoIreni trial is about to begin, with the aim of determining whether neoadjuvant escalation (PD1-ipilimumab-relatlimab) can be reserved for patients considered to be future non-responders to anti-PD1 monotherapy, using a Neopredict composite baseline test.

Next steps towards fully personalised neoadjuvant treatment for melanoma

There are several extremely interesting avenues to explore with regard to biomarkers:

The five-year results of the PRADO study show that the 60% of patients with a major histological response have a specific survival rate for melanoma of 98%, so any aggressive strategy should be discouraged.

On the other hand, for patients with a low interferon signature, treatment escalation with a high dose of ipilimumab/nivolumab is recommended, with the aim of achieving a compensated histological response and an improvement in relapse-free survival curves.

In patients who remain with a low interferon signature after neoadjuvant anti-PD1 treatment, the addition of ipilimumab increases the signature and, at the same time, the anti-tumour response. In the group of patients with a low interferon signature, the response rate can even be improved by adapting the treatment, without increasing toxicity.

Another patient profile that is a candidate for therapeutic intensification is the group whose tumours express PD-L1 weakly and soluble LRG1 strongly.

LRG1 is a glycoprotein that increases neovascularisation by acting on the TGF-beta signal. It is induced by IL-6 and hepatocytes and plays a role in the diffusion of micrometastases. Expression of this molecule is a poor prognostic marker for response to immunotherapy, in the same way as the interferon signature, but also for the overall outcome of the patient (as clearly demonstrated in the PRADO and OpACIN-neo patient cohorts).

Stress-related adrenergic signals reduce the immune response. Patients exposed to stress have poorer response and event-free survival rates, and poorer metastasis-free survival.

Activated T cells express more surface receptors for adrenaline, and their stimulation exacerbates immune exhaustion. Blocking beta-1 and beta-2 adrenaline receptors with a beta-blocker such as propranolol improves patient outcomes.

On the other hand, it appears that patients subjected to stress have a lower incidence of Grade III and IV immuno-induced toxicity.

What can we learn from other cancers?

“More cures, shorter treatments, less surgery” seems to be the new paradigm when it comes to neoadjuvant treatment for all types of cancer. This talk set out a number of examples to be followed for other diseases.

Cutaneous squamous cell carcinoma is a tumour with a very high mutational load. The New England Journal article by Gross’s team in 2022 showed a

complete + near-complete response rate of 63%, which was underestimated by the imaging evaluation.

The arrival of subcutaneous anti-PD1 formulations (nivolumab-pembrolizumab-cemiplimab) will make their neoadjuvant use even easier.

For head and neck cancer, there is also a correlation between the pathological response (complete or near-complete) to anti-PD1 treatments, alone or in combination with ipilimumab or relatlimab, and cumulative survival (Li, Cancer Cell 2025). We are awaiting communications concerning Phase III studies on combined anti-PD1 and anti-LAG-3 treatment.

Neoadjuvant anti-PD1 treatments (pembrolizumab) are also proving useful in combination with conventional cytotoxic chemotherapy in the treatment of triple-negative breast cancer.

There is a significantly higher rate of complete histological response. Publications from 2024 showed an impact on overall survival following the authorisation of pembrolizumab as a neoadjuvant treatment. Use of the neoadjuvant nivolumab/relatlimab combination without cytotoxic therapies also shows an increase in major histological response.
For lung cancer, the combination of nivolumab plus chemotherapy as neoadjuvant treatment for locally advanced resectable tumours shows a 10-fold greater complete histological response than chemotherapy alone, even though trials have only shown a significant improvement in overall survival for tumours expressing PDL1.

Neoadjuvant pembrolizumab/chemotherapy outperforms adjuvant pembrolizumab, which in turn outperforms chemotherapy alone, this time with a gain in overall survival!

Neoadjuvant immunotherapy is, of course, effective at treating cancers caused by microsatellite instability (MSI). The NICHE 1 study showed 100% histological response, including 60% complete response in dMMR colorectal cancers.

Studies testing the anti-CTLA4 + anti-PD1 combination (botensilimab + balstilimab) show response rates of around 30% in cancers with repair anomalies and 93% in MSI+ cancers, all without recurrence at one year. For bladder cancer, which also has a high mutational load, neoadjuvant durvalumab plus chemotherapy shows a benefit in terms of event-free survival and overall survival and drastically reduces the number of cystectomies required. Reducing morbidity will be the main objective of pivotal trials.

Neoadjuvant anti-PD1 therapies have also been shown to improve survival in recurrent glioblastoma, even after a single dose.

Making pathological response criteria more effective and pan-cancerous

Since 2020, there has been a histological anti-PD1 response score for all tumours combined. The speaker described the three components of the regression bed: residual tumour, necrosis and regression.

The histological response after adjuvant treatment is the equivalent of RECIST by imaging in patients with metastatic cancer.

The establishment of these scores requires that pathologists draw up new recommendations for macroscopic management and report writing, to be able to reduce this new workload in the future.

The latest harmonisation presented at ASCO in 2024 shows that the results are reproducible regardless of the type of cancer and the type of sample (primary tumour, sentinel lymph node, biopsy), both for the estimated percentage of residual tumour and for the percentage of regression.

The results of the lymph node or tumour analysis following neoadjuvant treatment are therefore given for three parameters (residual tumour, necrosis, regression), expressed in 10% increments, with mention of complete histological response, major histological response or near-complete response, but there are no current recommendations for partial responses or lack of response at this stage.

Management of mucosal melanoma

Chairs: Paul Lorigan (United Kingdom), Jun Guo (China)

Speakers: Jun Guo (China), Bin Lian (China), Paul Lorigan (United Kingdom), Paul Nathan (United Kingdom)

Neoadjuvant and adjuvant therapies for mucosal melanoma and therapeutic options and challenges in advanced mucosal melanoma

The Chinese teams presented their work on mucosal melanoma. **Although mucosal melanoma is uncommon in our patient cohorts (less than 1%), it**

accounts for a quarter of all melanomas encountered in the Chinese population.

It is mainly found in the anal and sinus regions, and the survival rate of patients with mucosal melanoma is much lower than that of patients with cutaneous melanoma. It has a low mutational load, a BRAF mutation in only 16% of cases and a CKIT mutation in 15%. In these tumours, there is less infiltration by the immune system and the efficacy of checkpoint inhibitors remains limited, with a maximum overall response rate of 19% depending on the study, compared with 30% to 40% for SSM. The combination with ipilimumab does not change progression-free survival or overall survival, and the addition of relatlimab and the triple combination do not show any improvement in overall survival.
In BRAF-mutated cases, however, efficacy matches the data for SSM in all Asian population studies (Korea, China, Japan). The NRAS mutation is present in around 18% of patients, and the overall response rate reaches 25% with MEK inhibitors (compared with 10% in SSM and 43% in acral melanoma). In CKIT-mutated patients, the combination of imatinib + toripalimab achieves disease control in 80% of cases, with an overall response rate of 55%.

High endothelial VEGF expression is a poor prognostic factor, and trials combining axitinib (a tyrosine kinase inhibitor with anti-VEGFR action) and toripalimab (anti-PD1) showed an overall response rate of 48% in chemotherapy-naive patients. Three-year survival data published in 2022 showed median progression-free survival of 7.5 months and median overall survival of 20 months, leading to FDA approval as an orphan drug.

Lastly, while the combination of pembrolizumab + lenvatinib did not show superiority over pembrolizumab alone for SSM, for the 64 Chinese patients with mucosal melanoma, the overall response rate was 26% with pembrolizumab alone. The data will be presented at ASCO this year.

The Chinese recommendations for the treatment of advanced mucosal melanoma therefore include the following as first-line treatment: a combination of cytotoxic agents (carboplatin + paclitaxel) or an anti-PD1 agent with an antiangiogenic agent (axitinib or bevacizumab), or the combination of anti-BRAF + anti-MEK agents when there is a BRAF mutation; and as second-line treatment they include: anti-PD1 monotherapy or tunlametinib, a MEK inhibitor, when there is a NRAS mutation.

In Stage II and III mucosal melanomas, adjuvant treatment (cisplatin + temozolomide for six cycles) is better than observation or interferon alpha for one year, in terms of overall and recurrence-free survival.

Ipilimumab 10 mg/kg every three weeks four times, then every two weeks, is also better than nivolumab 3 mg/kg.

Based on retrospective studies or comparisons with the literature, adjuvant chemotherapy is proposed for mucosal melanoma in China, after complete excision and dissection if there is macroscopic lymph node involvement. In the neoadjuvant setting, a Phase II trial studied the efficacy of toripalimab combined with axitinib: the response rate was 33% (with a relatively small number of around 30 patients); in these patients, the tumours appeared to be infiltrated by more lymphocytes after treatment. Another trial tested the combination of pembrolizumab + lenvatinib as neoadjuvant therapy: the response rate was 38%, again with a small number of 21 patients. However, the Chinese teams currently have open adjuvant trials recruiting over 600 patients!

Clinical guidelines for the management of mucosal melanoma

In the Caucasian population, mucosal melanoma accounts for 1.3% of melanomas. It occurs later in life, with a median age of 70. 55% are located in the sinuses, 24% in the anorectal region and 18% in the vulvar region.
The United Kingdom has published recommendations: surgery for anorectal, penile and vulvovaginal melanomas should aim for complete excision while preserving sphincter, urinary and genital functions; sentinel lymph node biopsy is not routinely recommended outside clinical trials. For sinus melanomas, adjuvant radiotherapy should be discussed if there is a risk of local recurrence.
Mucosal melanomas have a low mutational load and fewer somatic mutations; however, they tend to have structural or copy number changes. The rate is around 10% for each mutation: BRAF, NRAS, CKIT, NF1.

Intralesional therapies for skin cancer

Chairs: Christoph Höller (Austria), Mario Mandala (Italy)

Speakers: Michael Midgen (USA), Adil Daud (USA), Christoph Höller (Austria)

State of the art

Intralesional treatment is:

- An alternative to the intravenous route to increase the local tissue concentration when there is no evidence of distant metastasis

- An option in the neoadjuvant setting, for specific locations or high-risk lesions

The intralesional immunotherapy may be an antibody such as anti-PD1 therapy, an oncolytic virus, a viral vector (delivering interferon gamma, for example) or an antibody conjugated to a cytokine.

The Phase I study testing intralesional cemiplimab in squamous or basal cell cutaneous carcinoma resulted in dose escalation to 5 mg with an objective response rate of 77%, all with complete responses. The Phase III study is currently open.

A Phase IB/II study is underway in solid organ transplant recipients, testing an oncolytic RP1 virus that will express GCSF and a fusogenic GALV-GP-R protein, leading to the formation of immunogenic syncytia. Previously, intratumoral RP in combination with intravenous nivolumab had shown complete responses in immunocompetent patients in the IGNYTE study.

The overall response rate was around 35% in this small group of 23 patients. There were no Grade III to IV treatment-related side effects and, above all, there was no graft rejection.

Adenovirus is another viral vector modified by deletions to render it incapable of replication. With Sp002, the infected cell will then produce interferon gamma for two weeks.
A Phase II study is using three weekly injections of this viral vector after four weeks of vismodegib.

Conjugated antibodies contain a proprietary fraction that binds to a protein specifically expressed by tumours (e.g. fibronectin L19) fused to a cytokine fraction (e.g. TNF or IL2). These are therefore selective immunomodulatory therapies that can be combined in a single injection. Data from the DAROMUN Phase III pivotal trial in patients with operable locally advanced melanoma were presented at ASCO 2024: recurrence-free survival was increased to 57.5% in the treatment group compared with 23.6% in the surgery alone group, with an HR of 0.59. The side-effect profile was an injection site reaction with signs of classical immune response (fever).

We are currently awaiting the results of two Phase II trials testing the same therapy (Daromun) in non-melanocytic malignant skin tumours.

Lastly, a peptide shuttle can be used to deliver an antisense oligomer that will block the intracellular translation of messenger RNA (e.g. Gli1 in basal cell carcinoma). These molecules will adhere to cells electrostatically and then generate endocytosis.

The intratumoral injection technique itself is very important in achieving effective treatment. The target must be both the peritumoral dermis and the tumour itself, infiltrating to a depth of 1 mm at the centre, base and periphery, to ensure treatment of the entire tumour. The injection must be extremely slow with multiple fractions and should ideally be ultrasound-guided in order to visualise the distribution.

New targets and systemic immunological activity

In the tumour microenvironment, molecules such as STING and GAS lead to the maturation of dendritic and antigen-presenting cells which migrate to the lymph node, where they activate T cells via receptors (PD1 as a checkpoint in the tumour microenvironment, CTLA4 as a costimulation signal at lymph node level, LAG3, etc.).

In the tumour microenvironment, lymphocytes inexorably end up being exhausted. They definitively lose their ability to produce interferon gamma and IL2; they then express the surface molecules PD1 and LAG3. Immunotherapies temporarily suspend lymphocyte exhaustion; so that the response to immunotherapy lasts, new lymphocytes must be recruited from the lymph nodes or peripheral circulation.

In order to generate local vaccination, therapeutic agents can be injected using electrochemotherapy (injection of plasmid containing interleukin, followed by electroporation using a needle electrode).

When it was administered to patients identified as non-responders to anti-PD1 therapy (due to low expression of costimulation receptors by their lymphocytes), the addition of IL12 to systemic PD1 by electroporation enabled the lack of response to anti-PD1 therapy to be overcome in 40% of cases.

One of the problems with intratumoral treatment is identifying which of the post-procedural inflammatory responses trigger an anti-tumour response.

In the Keynote-665 study, patients progressing on anti-PD1 therapy and subsequently treated with PD1 + IL12 plasmid achieved median survival of 23 months (instead of the expected 10 months); the overall response rate was 27.8%, and in particular 25.9% in M1 b, c or d patients, and responses were observed for non-injected systemic lesions.

Similar responses were obtained in triple-negative breast cancer (IL12 treatment induced the appearance of CD8+ T cells and sensitivity to anti-PD1 therapies) and in Merkel cell carcinoma.

Intralesional neoadjuvant approaches: ready for prime time?

Not quite, but...

T-VEC is a therapeutic agent derived from the HSV1 herpes virus, modified so that its replication is preferential in tumour cells, so that it increases their lysis, and so that it expresses GM-CSF, which promotes an anti-tumour response.

Although its efficacy had not been demonstrated in the curative treatment of advanced stages, its use as neoadjuvant therapy for Stage IIIB to IV M1a melanoma showed a complete histological response in 17% of cases (ITT), with the overall and recurrence-free survival curves reaching a plateau.

The DAROMUN study showed a significant increase in metastasis-free and recurrence-free survival in patients who, in more than a third of cases, had already received prior systemic treatment, mainly curative or adjuvant immunotherapy. The complete pathological response obtained was 21%.

These intralesional therapies are showing interesting results, but are obviously not on a par with the systemic neoadjuvants (ipilimumab + nivolumab) used in Phase III trials.

However, they have their place for patients who are eligible for systemic immunotherapies (organ transplant patients, patients on immunosuppressants, comorbidities) or when all immunotherapies have failed.

For non-melanocytic tumours, we have seen Phase II results with neoadjuvant cemiplimab in locally advanced cutaneous squamous cell carcinoma, with 50% complete histological responses.

A Phase II study is testing neoadjuvant T-VEC in locally advanced but operable basal cell carcinomas with scarring. The main objective is to see whether the carcinomas become resectable by direct suturing after

treatment. The preliminary study with 18 patients showed 50% direct suturing, 33% complete histological response and 33% complete clinical response.

The neoadjuvant approach to Stage III resectable melanoma in 2025: current data

Chair: Axel Hauschild (Germany)

Speakers: Axel Hauschild (Germany), Caroline Robert (France), Susana Puig (Spain)

Currently, the only treatments validated for Stage III resectable melanoma since September 2024 have been nivolumab, pembrolizumab and the trametinib/dabrafenib combination. Despite these treatments, around one in two patients will have a recurrence five to seven years later.

The current approach is adjuvant: the lesion is surgically removed, then immunotherapy is administered for one year. In this situation, we have removed the cells against which we would like to create an immune response and potentially we obtain fewer activated T cells and cytotoxic T cells targeting tumour neoantigens.

In a purely neoadjuvant situation, immunotherapy is administered before surgery to obtain as many activated T clones as possible. Surgery is then potentially optional, depending on the histological response obtained.

The regimen used in SWOG with pembrolizumab was hybrid and called perioperative. It consisted of dividing the year of immunotherapy into three pre-surgical cycles and then completing the rest of the year with 15 post-surgical cycles. Two-year event-free survival was 72% in the neoadjuvant arm.

This scheme uses the waiting time that is often necessary to organise surgery. Compared with the current recommendations, the total duration of treatment is the same: there is no additional cost or toxicity.

The NADINA trial with nivolumab + ipilimumab in its neoadjuvant arm made the postoperative continuation of immunotherapy conditional on the absence of a major histological response.

Event-free survival at one year was 83.7% in the neoadjuvant arm. The two-year data will be published next year.

The histological response predicts recurrence-free survival: 60% of patients had a major histological response, and virtually all of these patients remained free of recurrence at one and then two years. Just under half of histological non-responders experienced a recurrence at around one year. Partial responders had an intermediate future.

The new ESMO and EADO 2025 guidelines therefore include neoadjuvant treatment as first-line therapy for Stage III resectable melanoma: depending on the patient, this may be either pembrolizumab alone + adjuvant, or ipilimumab plus nivolumab +/- adjuvant.

The other recent news relating to neoadjuvant treatment concerns intralesional neoadjuvant therapy. Daromun, administered by intratumoral injection, is currently awaiting authorisation by the European Medicines Agency. It is a cocktail of mixed molecules combining an antibody directed against fibronectin (expressed in tumour vessels), IL2 or TNF-alpha, in a single injection. In the pivotal study and the neo-Dream study, unlike the NADINA and SWOG systemic neoadjuvant trials, patients could have received prior immunotherapy or radiotherapy, and adjuvant treatment was left to the discretion of the investigator.

It should be noted from all these studies that cutaneous and subcutaneous metastases appear to respond less well to immunotherapies than lymph node metastases. The literature shows that patients with multiple cutaneous metastases frequently have rapid recurrences of new lesions.

Unlike surgery, radiotherapy and electrochemotherapy, intratumoral immunotherapy aims to achieve an abscopal effect.

A few comments for the road:

NF1 mutations are more frequently present in desmoplastic melanoma and melanomas associated with chronic sun damage and with a high mutational load; they therefore respond more frequently to anti-PD1 immunotherapies.

Intratumoral injections are unpleasant, even painful, but they should not be combined with local anaesthesia, as this could potentially alter the response to treatment.

Rare tumours (adnexal, sebaceous, dermatofibrosarcoma protuberans)

Chairs: Philippe Saiag (France), David Adams (United Kingdom)

Speakers: David Adams (United Kingdom), Thomas Jouary (France), Philippe Saiag (France)

The genomic landscape of rare adnexal tumours: The DERMATLAS project

The aim of this project is to characterise the genome of the 70 rare skin tumours identified by the WHO, using paraffin material collected all over the world. Each case is reviewed centrally and the transcriptome and exome are sequenced after RNA and DNA extraction. The aim is to identify somatic and germline variants, copy number changes, pathogens, mutational signatures and fusion genes. More than 3,000 tumours have been analysed, with over 50 of each type, whether benign or malignant, from all skin structures. These data will be used to train deep learning algorithms.

In this context, 286 sebaceous tumours (benign sebaceomas and adenomas, and malignant adenocarcinomas) have been analysed. They may be sporadic (with or without abnormal DNA repair by alteration of the MSH2, MSH6, MLH1 or PMS2 genes) or associated with Lynch or Muir-Torre syndrome. All these tumours have mutations in genes such as NOTCH1, RREB1 and HRAS, with the exception of peri-ocular tumours which are genetically different, with P53 and ZNF750 mutations.

Tumours with altered DNA repair genes have a high mutational load, even more so than melanoma, suggesting the efficacy of anti-PD1 treatments, and in particular a high deletion-insertion rate.

Constitutional mutations in MUTYH are also equivalent to Lynch syndrome.

The data analysed have led to practical recommendations for clinicians and pathologists: for example, the probability of having Lynch syndrome is 98.5% in the event of multiple sebaceous tumours, including locations outside the head and neck, or cancers associated with Lynch syndrome.

Recent clinical advances in adnexal tumours

The WHO currently classifies 40 subtypes of adnexal tumours into four main groups: eccrine and apocrine sweat gland carcinomas, follicular carcinomas, sebaceous carcinomas and site-specific carcinomas. The CARADERM

database now includes 5,620 patients (49% sweat gland tumours, 37% follicular tumours and 11% sebaceous tumours).

Surgery remains the standard treatment for localised adnexal tumours. The risk of recurrence is partly related to the quality of the excision margins. Well-delimited lesions do not require any particular precautions in the histological analysis of the margins, but Slow Mohs and Mohs are indicated for poorly delimited tumours (such as microcystic adnexal carcinoma, trichoblastic carcinoma, invasive porocarcinoma, hidradenocarcinoma or mucinous carcinoma), tumours with a high risk of recurrence, and peri-orificial locations.

The role of adjuvant radiotherapy has yet to be defined, as the studies undertaken are contradictory. However, radiotherapy is proving useful in palliative situations for locally advanced carcinomas, increasing progression-free survival.

Trichoblastic carcinoma shares some common features with basal cell carcinomas, and a series of 16 cases of patients responding to vismodegib has been reported (62% ORR), leading to it being discussed as a first-line treatment. Treatment with immunotherapy has proven effective, with 54% disease control at three months in a small series of 12 cases. Anti-PD1 agents have also been tried in isolated cases of trichilemmal carcinoma or microcystic adnexal carcinoma.

Dermatofibrosarcoma protuberans: update of the EADO-EORTC guideline

The new EADO recommendations were published in January 2024.

Dermatofibrosarcoma protuberans (DFSP) involves a t(17;22) reciprocal translocation resulting in a COL1A1-PDGFB fusion. Around 10–15% of DFSPs develop into fibrosarcomas, the cells of which frequently retain the translocation, often during recurrence, and are therefore at risk of further recurrence and distant metastases.

DFSP is currently the most common cutaneous sarcoma in France, and its incidence has recently been rising. It usually occurs between the ages of 20 and 59, most often on the trunk, with no gender predominance. Growth is slow, and any signs of exacerbation should raise suspicions of progression into fibrosarcoma. A biopsy is essential beforehand; it reveals a storiform pattern of CD34-positive cells infiltrating the hypodermis and along the fascia. Atypia and mitosis raise the suspicion of transformation.

Molecular analyses, including FISH or sequencing secondarily, are recommended to search for the rearrangement, which is present in over 90% of cases. In 8% of cases, the fusion is cryptic or the partners are different.

The extension assessment should include an MRI of the area, to rule out transformation (peritumoral oedema, T2 hypointensity, multinodular appearance, absence of flow in vessels). A distant CT scan is only recommended in the event of recurrence or suspected metastasis.

A classification appears in the recommendations: Stage 1: no nodular component, Stage 2: nodule (a: without fascial involvement, b: extension under the superficial fascia), Stage 3: lymph node involvement, Stage 4: distant metastasis.

Surgical treatment should aim for initial complete excision, using micrographic surgery with lateral margins of 1 to 1.3 cm and deep margins to the deep fascia, removing the latter in the event of a deep lesion. Reconstruction should be simple, and in all cases carried out only after checking that excision is complete.

Monitoring is not codified and imaging is not systematic.

Imatinib (a PDGF inhibitor) is indicated in cases of inoperable or metastatic lesions, with efficacy of around 55% (often with partial responses) and for neoadjuvant purposes. Cytological changes on imatinib may interfere with the histological analysis.

There are no recommendations for radiotherapy for DFSP.

In cases of fibrosarcoma, the treatment recommendations are the same, but with irradiation if complete excision is not possible.