

## Reports on Scientific Meetings

### 9th World Congress of Melanoma

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In brown longitudinal pigmentation with parallel regular lines, the diagnosis of nail apparatus melanocytic naevus can be made. On the other hand, the presence of brown pigmentation overlaid by longitudinal lines irregular in their thickness, spacing, colour or parallelism is highly suggestive of melanoma.

Grey homogenous lines are observed in cases of lentigo, lentiginos, ethnic variation, drug-induced pigmentation and post-traumatic pigmentation. Blood spots are characterised by their round-shaped proximal edge and their filamentous distal edge, and are highly suggestive of subungual haemorrhage. However, other dermoscopic tell-tale signs must be ruled out.

#### **Clinical diagnosis: nail and acral dermoscopy**

Speaker: Thomas Luc  
Lyon Cancer Research Centre, France

Nail plate dermoscopy: a help in diagnosis of melanonychia striata.

The diagnosis of melanonychia striata or longitudinal nail pigmentation is often difficult and biopsy of the nail matrix is required in doubtful cases. However, dermoscopic examination of nail plate may reveal features that require histopathological examination of the nail bed/matrix.

#### **Learning points:**

With the use of dermoscopy, physicians can pick up useful features and proceed to biopsy of nail bed/matrix to rule out melanoma.

## Radiotherapy and immunotherapy in advanced stage melanoma

Speaker: Wang Tim

Australia and New Zealand Melanoma Trial Group (ANZMTG), Westmead Hospital, Sydney, Australia

BRAF inhibitors have been shown to synergise with radiation by increasing overall cell-kill in BRAF mutant melanoma cell-line studies. However, in routine clinical practice, BRAF inhibitors have been shown in multiple case series to increase the toxicity associated with radiation therapy in the treatment of melanoma, in particular cutaneous toxicity. A recent consensus statement from the Eastern Cooperative Oncology Group recommends withholding radiotherapy for three or more days before and after fractionated RT and one or more days before or after stereotactic radiosurgery (SRS). BRAF and MEK inhibitor combination therapy is now the mainstay of treatment for patients with BRAF V600 mutant advanced stage melanoma. This combination therapy showed an improvement in survival outcome as compared to BRAF inhibitor alone. The BRAF and MEK inhibitor combination therapy also demonstrated significantly less cutaneous toxicity. However, the toxicity of radiation therapy concurrent with BRAF/MEK inhibitor is still unknown. There is an ongoing Australian multi-centre prospective study evaluating the safety, efficacy and toxicity of concurrent palliative RT with BRAF and MEK inhibitors for treatment of metastatic melanoma with promising initial results.

### **Learning points:**

The emerging era of combined radiation and immunotherapy has provided new insight into the treatment of metastatic advanced stage melanoma.

## Clinical diagnosis: reflectance confocal microscopy: melanoma: different patterns for different types

Speaker: Pellacani G

University of Modena and Reggio Emilia, Dermatology, Modena, Italy

Reflectance confocal microscopy (RCM) is non-invasive imaging technique that produces horizontal images of the skin in a cellular level resolution and in real time. This instrument is of great value in the field of dermoscopically difficult-to-diagnose melanocytic lesions as it improves the diagnostic accuracy of melanoma and reduces the number of excisions of benign melanocytic lesions.

For melanocytic lesions, the classification of confocal patterns for the layer under evaluation must be taken into consideration. In the epidermis, the presence of atypical melanocytes, dendritic or roundish in shape, may be present. At the epidermo-dermal junction and upper dermis, we may find atypical cells and melanocytes clustered into non-homogenous nests.

In past few decades, the importance of RCM for diagnosis and subtype classification of melanoma has increased. Overall, four different subtypes of melanoma have been described: (1) pagetoid melanoma, (2) dendritic-cell melanoma, (3) large-clustered melanoma, and (4) mixed type. Each subtype is characterised by a predominant cell population, and each has been found to correlate with patient phenotype and sun-behaviour. For example, pagetoid and dendritic-cell melanoma are characterised by predominantly intra-epidermal proliferation of malignant cells and they usually correspond to superficial spreading melanoma type upon histopathological examination, with the difference that the latter is more frequently observed on chronically sun-damaged skin.

On the other hand, large-cluster melanoma usually corresponds to nodular melanoma with predominant vertical growth pattern. The mixed

type is a combination of the three subtypes with no predominance of single pattern and is probably derived from modifications of the cytological-architectural aspects during tumour progression.

### **Learning points:**

Expertise in the use of RCM technology will help reduce the number of benign melanocytic lesions excised. It also provides more information when delineating the extent of excision, especially in superficial spreading multifocal melanoma and facial lesions.

## **Field-directed treatments in the contest of therapeutic algorithms**

Speaker: Ketty Peris

University of L'Aquila, Italy

Topical therapies for actinic keratosis (AK) include 5% 5-Fluorouracil (5-FU), 0.5% 5-FU with 10% salicylic acid, 5% imiquimod cream, 3.75% imiquimod cream, ingenol mebutate, 3% diclofenac gel, and conventional or daylight photodynamic therapy, which all have a lesion clearance range from 54% to 92%.

Three new guidelines or algorithms for treatment of actinic keratosis have been published in 2017 from British Association of Dermatologists (BAD) in British Journal of Dermatology, by Dirschka et al in Journal of Dermatology Treatment, and by Calravarapinton et al. in the Journal of Cutaneous Medicine and Surgery respectively. The BAD guidelines do not recommend treating all AKs but the other two guidelines concur on treating all AKs; however, the most important message is that all three guidelines agree that actinic keratosis are premalignant lesions, and field treatment instead of isolated lesions treatment in multiple actinic keratosis cases, especially in photo-damaged skin is advisable.

Actinic keratosis field treatment sites most commonly are the face and scalp, and sometimes may be the chest or back. In multiple AKs on small fields (area  $\leq 25$  cm<sup>2</sup>), for example in localised areas of the face, 5% imiquimod cream, 5-FU, 0.5% 5-FU with 10% salicylic acid, ingenol mebutate, or photodynamic therapy are recommended. For large areas of actinic damage, 3% diclofenac gel, 3.7% imiquimod cream, 5-FU and photodynamic therapy are recommended. When treatment area is large, clustered directed therapies may be used in successive treatment cycles.

However, age of patient, ability to perform home-based treatment, compliance, patient immune status, history of previous treatments and availability of therapy need to be considered when deciding on treatment modality.

Recommendations for use of 5% imiquimod cream in treatment of AK vary from three days a week for four weeks (one or two courses) in Europe to twice weekly for 16 weeks in the United States and even three times a week for 16 weeks in Australia.

The treatment regimen can be either field treatment followed by cryotherapy to any remaining AKs; or lesion-directed treatment followed by field directed therapy like cryotherapy followed by 5-FU or imiquimod cream.

### **Learning points:**

New guidelines in 2017 for actinic keratosis recommend field treatment to actinic skin damage in those with multiple AKs.

## **New approaches in the treatment of advanced SCC (immunotherapy)**

Speaker: Axel Hauschild

Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany

In advanced or unresectable squamous cell carcinoma (SCC) of the skin, chemotherapy is usually the treatment of choice. However, patients may not undergo further chemotherapy due to lack of response or side effects. In these cases, anti-PD1 antibodies are an alternative treatment for skin SCC and have shown promising results. In one study, out of four SCC and one basosquamous basal cell carcinoma, two cases showed a partial response and three were stabilised with a response duration of over six months with excellent tolerability.

There is an ongoing pivotal phase II cutaneous SCC study involving metastatic or locally advanced cases treated with anti-PD1 antibodies, and preliminary response rate is 46.2%. This excellent result has prompted pivotal studies of anti-PD1 antibodies given every three weeks as an intravenous infusion in cases of cutaneous basal cell carcinoma (BCC) refractory to hedgehog inhibitors.

However, anti-PD1 has certain serious adverse effects such as immune-mediated neuropathy, pneumonitis in which may be lethal. PD1 is also essential in keeping transplant organs intact and is therefore contraindicated in organ transplant patients. Unfortunately the same group of patients are prone to developing cutaneous malignancy due to immunosuppression. The speaker here shared his case of an off-label use of pembrolizumab in a kidney transplant patient on cyclosporin A and steroid with treatment-resistant cutaneous SCC. The patient developed irreversible organ rejection two months post pembrolizumab but she achieved 85% reduction in tumour burden after eight months of treatment and continued with dialysis. Therefore, the decision to treat advanced SCC with immunotherapy with contraindications is based on the balance between risk and benefit.

### **Learning points:**

Treatment response in chemotherapy for advanced cutaneous SCC is short and uncommon, responses with no proven impact on overall survival. Immune checkpoint modulators, namely anti-PD1 antibodies are promising treatment options for advanced SCC, BCC and even Merkel cell carcinoma.

## **2017 Australian Guidelines for digital dermoscopy monitoring: evidence and recommendations**

Speaker: Scott Menzies

University of Sydney, Central Clinical School, Discipline of Dermatology, Australia

Digital dermoscopy monitoring for melanoma can be classified into short-term monitoring and long-term monitoring. Short-term monitoring is to observe for changes three months later, in stable atypical lesions, or unstable but only mild atypical lesions, in which any change will lead to excision. Diagnostic sensitivity could be up to 94% whereas specificity is about 84%. In contrast, long-term monitoring is a standard surveillance tool in melanoma detection varying between from 6 to 12 months. The aim is to monitor any melanocytic lesions in patients with multiple atypical naevi, or follow up of short-term monitored lesions. The sensitivity is about 95-96% but specificity is unknown.

Long-term digital dermoscopy monitoring can also identify dermoscopic featureless melanoma over time: the featureless melanoma is monitored for the eventual appearance of suspicious morphology, leading to its diagnosis.

The speaker stressed that long-term monitoring is less efficacious in low-risk patients. Studies have shown that 150 patient visits are needed, or 3000 lesions are needed to be monitored to diagnose one melanoma in low-risk patients. Therefore, long-term monitoring is only recommended in high-risk patients.

Long-term monitoring is also a cost effective intervention in melanoma management as it reduces the benign to malignant excision ratio and number of benign lesions excised. This was illustrated in a study in which the general practitioners were instructed in digital monitoring which resulted in a decrease of 9.5:1 to 3.5:1 in the baseline benign to malignant excision ratio.

Based on the above findings, the following guidelines were made:

- To assess individual melanocytic lesions of concern, the use of short-term sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma is recommended. (Grade B recommendation)
- To assess individual or multiple melanocytic lesions in routine surveillance of high-risk patients, the use of long-term sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma is recommended. (Grade B recommendation)

- Practical point: interval for short term monitoring is three months where any change leads to excision. Where lentigo maligna is included in the differential diagnosis it is recommended an additional three months of monitoring i.e. total of six months.
- Practical point: only flat or slightly raised lesions should undergo dermoscopy monitoring. Nodular lesions should not be monitored but should be biopsied.

### **Learning points:**

Routine long-term dermoscopy monitoring should be done in high-risk patients. Short-term monitoring is recommended for individual atypical lesions. Nodular lesions should be biopsied immediately instead of being monitored.