Skin Cancer Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AI = artificial intelligence;
BRAF = v-RAF murine sarcoma viral oncogene homolog B1;
CNN = convolutional neural networks; **ctDNA** = circulating-tumour DNA;
HNM = head and neck melanoma; **ICI** = immune checkpoint inhibitor;
NRAS = neuroblastoma RAS viral oncogene homolog; **OS** = overall survival;
PFS = progression-free survival; **SLNB** = sentinel lymph node biopsy;
T-VEC = talimogene laherparepvec.

Welcome to the latest issue of Skin Cancer Research Review.

We open this issue with a small pilot study that investigated the feasibility and safety of diffusing alpha-emitter radiation therapy for recurrent or unresectable skin cancers. This study is followed by Sci Rep's study on PANoptosis, a recently identified inflammatory programmed death cell pathway. This study identified the low- and high-risk profiles of several PANoptosis-related genes. An interesting study to look out for in this issue is the nasal administration of recombinant *neospora cranium* secreting IL-15/IL-15Rα, which inhibits metastatic melanoma development in the lungs. We conclude this issue with a cohort and literature study on the association of complex lymphatic drainage in head and neck melanomas with sentinel lymph node biopsy (SLNB).

We hope that you enjoy this update in skin cancer research. We look forward to hearing your feedback.

Kind Regards,

Dr David Simpson
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Feasibility and safety of diffusing alpha-emitter radiation therapy for recurrent or unresectable skin cancers

Authors: D'Andrea MA et al.

Summary: This prospective cohort study aimed to evaluate the feasibility and safety of using diffusing alpha-emitter radiation therapy to manage recurrent or unresectable skin cancer. The researchers followed up on patients who received a 2-week to 3-week treatment course in the US during 2021 and 2022. Of the 10 participants, 6 had recurrent disease, and 4 had unresectable skin cancers. Tumours were found on the nose, chin, eyelid, scalp, trunk, neck and extremities. The median tumour volume was 2.1 cm^3. All tumours covered 85% or more; therefore, the gross tumour volume was 91%. No device-related adverse events graded three or higher were noted by this study. At 12 weeks post-treatment, there was a 100% complete response rate, 90% confirmed by CT imaging.

Comment: Current options for treating recurrent or unresectable skin cancers include radiotherapy, immunotherapy and Hedgehog inhibitor therapy, and all involve prolonged treatment courses with a high risk of adverse events. This small pilot study of 10 patients with keratinocyte cancers used an interstitial brachytherapy technique where diffuse alpha-emitting radiation sources were inserted into the tumour and left in place for two weeks. This type of radiotherapy causes minimal local adverse effects whilst being highly effective at tumour destruction and can be used in areas where external beam radiotherapy has already been used. The results showed a 100% tumour clearance rate, which will allow larger studies to proceed with the hope that the therapy can be approved.

Reference: JAMA Netw Open. 2023;6:e2312824
Abstract

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PANoptosis-related prognostic signature predicts overall survival of cutaneous melanoma and provides insights into immune infiltration landscape

Authors: Wang W et al.

Summary: This study investigated the potential regulatory role of PANoptosis and its related genes in cutaneous melanoma. The study identified three PANoptosis-related genes that could be associated with prognosis in cutaneous melanoma patients; these genes indicated that cutaneous melanoma was immune-related. They also found that prognosis-related PANoptosis genes could be associated with immune scores and infiltration of immune cells in cutaneous melanoma. Regarding drug resistance, the study found a connection between immunotherapy and drug sensitivity and prognosis-related PANoptosis genes. The study concluded that PANoptosis genes could be used for risk assessment and overall survival (OS) prediction but also reflect the immune landscape of cutaneous melanoma patients.

Comment: PANoptosis is a recently identified inflammatory programmed cell death pathway that involves the induction of apoptosis, pyroptosis and necroptosis and enhances the activation of the innate immune system. This can be beneficial in removing virally infected cells and can also improve immune reactions against cancer cells. There are several PANoptosis-related genes, and the study identified low-risk and high-risk profiles and OS. Their models appear to offer a method for identifying OS using melanoma PANoptosis gene profiling which could help identify those patients at higher risk as well as choosing appropriate therapies.

Reference: Sci Rep. 2023;13:8449
Abstract

Association of a Mediterranean diet with outcomes for patients treated with immune checkpoint blockade for advanced melanoma

Authors: Bolte LA et al.

Summary: This multicentre cohort study considered the overall response rate, PFS at 12 months and immune-related adverse events for having a habitual diet and response to treatment with immune-checkpoint blockade therapy. The study included 44 Dutch and 47 British participants. The Mediterranean diet includes whole grains, fish, nuts, fruit and vegetables. It was found that there was a strong association between a Mediterranean dietary pattern and the probability of an improved overall response rate and PFS; overall response rate was 0.83, and PFS was 1.54. The study concluded that, there was a positive association between a Mediterranean diet and the response time to immune-checkpoint blockade therapy.

Comment: There have been several interesting studies showing improved efficacy with immunotherapy in both humans and mice associated with a higher-fibre diet. It seems that a diet rich in fibre and omega-3 fatty acids improve the gut microbiome, and this is associated with increased numbers of gut bacteria producing short-chain fatty acids. Patients treated with immune checkpoint inhibitors with higher levels of faecal short-chain fatty acids have been shown to have longer PFS for several solid cancers. Comparing healthy vegan, unhealthy vegan and Mediterranean-style diets – rich in whole grains, fish, nuts, fruit and legumes – there was an improved response rate and PFS for the Mediterranean diet. This appears to confirm the previous studies and adds weight to the idea that immune response is enhanced by a healthy gut microbiome produced by a varied and nutrient and fibre-rich diet.

Reference: JAMA Oncol. 2023;9:705-9
Abstract

Talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone for advanced melanoma

Authors: Chesney JA et al.

Summary: This was a 5-year final analysis from a multicentre, randomised, open-label, phase II trial. The study included eligible patients with unresectable stage IIIB-IV melanoma treated with talimogene laherparepvec (T-VEC) plus ipilimumab and randomised 198 patients into either combination or ipilimumab and found that the combination provided an improved objective response rate compared to ipilimumab alone. When comparing the two therapies, durable response rate, duration of response, PFS and OS were all increased in the combination group. The greatest difference was seen in the median PFS, with the combination being 13.5 months compared to 6.4 months with ipilimumab.

Comment: Immune checkpoint therapy has revolutionised melanoma treatment, but there are groups of patients where it might be desirable to add a second modality to address specific issues. The patients in this study had unresectable melanoma and were randomised to ipilimumab alone or combined with a lesion-directed injectable oncolytic virus (T-VEC). In patients responding to the combination therapy, there was a significantly improved duration of response and PFS, although OS at final analysis was the same. T-VEC is an interesting concept that is designed to enhance antitumor immunity, and similar therapies are likely to be used in patients with recurrent disease after immunotherapy in the future.

Reference: J Immunother Cancer. 2023;e006270
Abstract

Nasal administration of recombinant Neospora caninum secreting IL-15/IL-15Rα inhibits metastatic melanoma development in lung

Authors: Battistoni A et al.

Summary: This study aimed to evaluate the potential administration of *neospora canium* in a synergic C57BL6 mouse model of B16F10 melanoma lung metastases. The study found that the treatment of murine lung metastases with intranasal *neospora caninum* secreted human IL-15 and impaired further progression with only 0.08% of lung surface harbouring metastases versus 4.4% in wild-type treated mice, compared to 36% in untreated mice. In addition, the control of tumour development was associated with a strong increase in natural killer cells, CD8+T cells and macrophages, by up to two-, five- and six-fold, respectively. The study also found a polarisation of macrophages CD86 and CD206 towards an antitumoural M1 phenotype.

Comment: *Neospora caninum* is an obligate intracellular protozoon with no known harmful effects in humans but has been found to have a direct oncolytic activity in animal tumour models by replication within the cells and subsequent tumour cell death. This also induces an enhanced T cell and natural killer cell activation. The protozoon can be genetically altered to secrete interleukin 15 combined with the IL-15 receptor complex, further enhancing immune activation against the tumour. Using various routes of administration in a mouse lung melanoma model, it was found that *neospora caninum* had a strong anti-tumoural effect regardless of the route, but with the intranasal and intravenous routes being more efficacious than subcutaneous. Genetically modified *neospora caninum* used intranasally led to the most potent anti-tumour effect. This method of melanoma treatment offers a new treatment paradigm that can avoid problems with resistance and adverse reactions and can be manipulated to target different tumours in the future.

Reference: J Immunother Cancer. 2023;11:e006683
Abstract

Initial evidence for the efficacy of naporafenib in combination with trametinib in NRAS-mutant melanoma

Authors: de Braud F et al.

Summary: This study includes the results from the expansion arm of a phase Ib, open-label study on the safety, tolerability and preliminary antitumoural activity of naporafenib. This study included 46 and 30 patients enrolled in escalation and expansion groups, respectively. In the escalation group, six patients had grade ≥3 dose-limiting toxicities, these included dermatitis acneiform, maculopapular rash, increased lipase, and Stevens-Johnson syndrome. In the expansion group, the recommended doses were naporafenib 200mg twice-daily plus trametinib 1mg once-daily and naporafenib 400mg twice-daily plus trametinib 0.5mg once-daily. Common treatment-related adverse events experienced by all patients during expansion were rash, an increase in blood creatine phosphokinase diarrhoea and nausea. The objective response rate, the median duration of response and median PFS during expansion was 46.7%, 3.75 and 5.52 months, respectively, in patients treated with naporafenib 200mg twice-daily, plus trametinib 1mg once-daily.

Comment: NRAS was the first described oncogene in melanoma and was discovered in the 1980s. Up to 20% of melanomas have activating NRAS mutations – part of the MAP kinase pathway responsible for cell proliferation, differentiation and cell death. Targeted therapy is available for the more common BRAFV600 mutations, but there are no approved medications inhibiting NRAS mutations. Combination therapy is used to avoid resistance to treatments, and this small study used a new NRAS-targeted drug - naporafenib – with a MEK inhibitor – trametinib – in patients with NRAS mutations. The most common adverse reactions were skin-related, but there was one death from haemorrhage secondary to thrombocytopenia and 2 cases of Stevens-Johnson syndrome requiring steroids and drug cessation. Overall, 30% of patients experienced a partial response, and the PFS was 5-6 months.

Reference: J Clin Oncol. 2023;41:2651-60
Abstract

Circulating tumour DNA-based molecular residual disease detection for treatment monitoring in advanced melanoma patients

Authors: Eroglu Z et al.

Summary: This retrospective analysis included a personalised tumour-informed circulating DNA (ctDNA) analysis on prospectively collected plasma samples. Cohort A included patients with stage III disease receiving adjuvant immune-checkpoint inhibitor (ICI) therapy and observation. This cohort had molecular residual disease positivity associated with significantly shorted distant metastasis-free survival. Cohort B included unresectable stage III/IV patients who received ICI therapy and had a shorter PFS than cohort A. Cohort C focussed on patients with stage III/IV disease on surveillance after the planned completion of ICI therapy. All patients in cohort C remained PFS for a median of 14.67 months for ctDNA-negative patients, and ctDNA-positive patients all experienced disease progression.

Comment: Currently, patients with advanced melanoma are followed up clinically and radiologically whilst receiving immune checkpoint inhibitor (ICI) treatment or monitored following diagnosis or completion of therapy. ctDNA can be tailored to the individual patient's mutations and was found to be useful for predicting disease recurrence, response to treatment and prognosis. Patients who had been ctDNA-negative but had become positive developed recurrent disease three months prior to radiologically evident disease, and a negative ctDNA predicted a good response to ICI and PFS. A rising ctDNA or a high initial ctDNA predicted a poor prognosis. Combining this with tumour mutational burden appears to offer a useful prognostic indicator for ICI-treated patients (with a higher mutational burden indicating a better response to ICI treatment).

Reference: Cancer. 2023;129:1723-34
Abstract

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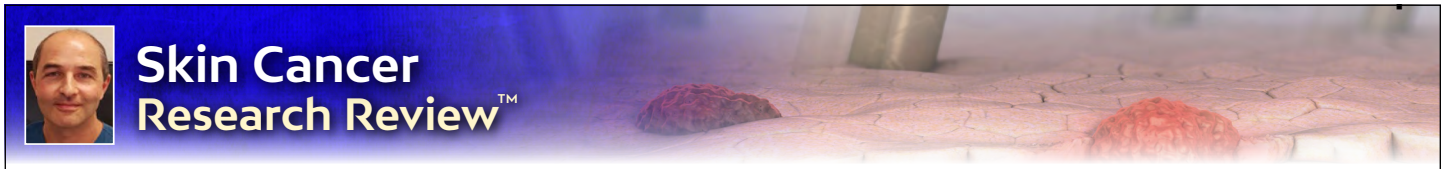
Observational study investigating the level of support from a convolutional neural network in face and scalp lesions deemed diagnostically 'unclear' by dermatologists

Authors: Kommoss KS et al.

Summary: This web-based classification task study included a convenience sample of 100 face and scalp lesions that were benign, malignant or unclear. After reviewing one dermoscopic image per case, 8.8% were unclear, and management was incorrect in 58.8% of the truly malignant case and 43.9% of truly benign cases. The management decisions were incorrect in 32.8% of truly malignant cases and 76.4% of truly benign cases. The researchers suggested that this false management could be reduced by accepting convolutional neural networks and artificial intelligence (AI) by 6.9% in truly malignant and 38.2% in truly benign cases. After dermatologists received full case information, 3.7% of diagnoses remained unclear to dermatologists, which triggered more excisions than follow-up examinations.

Comment: Facial lesions can be difficult to diagnose due to the overlap of dermatological and clinical features with benign lesions. Previous studies have demonstrated the high accuracy of convolutional neural networks (CNN) versus expert dermatologists, but this study sought to assess the benefit of using AI as a second opinion in difficult cases. The accuracy of diagnosis was found to be improved when added extra close-up images and clinical information such as age, sex and anatomical site were sent to the dermatologists. With the addition of CNN AI, the accuracy of diagnosis and subsequent management was greatly improved, reducing unnecessary excisions and avoiding inappropriate observation/non-treatment, and this is likely to be the most widely adopted method for using it in routine clinical practice. Other studies have also found a difference in the accuracy of AI for diagnosing melanoma compared to expert dermatologists when clinical features are included as opposed to only analysing dermatoscopic images, and it is likely that the real-world diagnosis of skin cancers relies on more than just image analysis.

Reference: Eur J Cancer. 2023;185:53-60
Abstract



Independent commentary by Dr David Simpson

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Surgical outcomes of lymph node dissections for stage III melanoma after neoadjuvant systemic therapy are not inferior to upfront surgery

Authors: Zijlker LP et al.

Summary: This retrospective cohort study included 120 high-risk stage III melanoma patients, 44 received neoadjuvant systemic therapy, and 76 underwent upfront surgery. The study found no significant difference in the overall rate of postoperative complications and postoperative morbidity between the two groups in terms of seroma and lymphedema. The researchers found a non-significant difference towards a slightly longer duration of surgery after neoadjuvant immunotherapy or textbook outcomes. They concluded that there are comparable results between lymph node dissection after neoadjuvant systemic immunotherapy and upfront lymph node dissection for stage III melanoma.

Comment: A potential problem with neoadjuvant therapy might be a delay before lymphadenectomy and increased difficulty in performing surgery due to fibrosis and scarring, but previous studies reported that surgery after targeted therapy was, in fact, easier than without. This study using neoadjuvant immune checkpoint therapy appears to show no significant problems regarding surgical complications; however, the risk of infection in the first month was greater with ICI but greater in the second month with upfront surgery, whilst overall not significantly different. Steroid use with ICI therapy did not appear to explain this. More patients in the neoadjuvant group had sentinel lymph node biopsies which might be a factor in their earlier higher infection rate, but overall, the conclusion was that neoadjuvant therapy does not lead to worse outcomes with subsequent lymph node dissections.

Reference: Eur J Cancer. 2023;185:131-8
Abstract

Association of complex lymphatic drainage in head and neck cutaneous melanoma with sentinel lymph node biopsy outcomes

Authors: Pasha T et al.

Summary: This cohort study and literature review compared the accuracy, prognostic value and long-term outcomes of SLNB in head and neck melanoma (HNM). They compared the false-negative and omission rates for SLNB in HNM, limb and trunk. HNM melanoma had a higher median age at diagnosis and had the highest false-negative rate (34.5%) when compared with the trunk (14.8%) and limb (10.4%). Between HNM and the other two regions, the melanoma-specific survival and recurrence-free survival rates were no different and lower for HNM, respectively. On lymphoscintigraphy, patients with HNM had the highest promotion of multiple hotspots. The study also found that head and neck location was an independent risk factor for recurrence-free survival.

Comment: SLNB has become the most important staging investigation for predicting melanoma prognosis, but the site can influence the difficulty in performing the test and interpreting the results. HNM has complex lymphatic drainage, and when compared to SLNB in trunk and limb sites, HNM has the most variable drainage, followed by the trunk, and then the limbs. In this study, the false negative rate for SLNB in HNM was high, and the rate of multiple lymph node hotspots was the greatest of the three regions. Multiple lymph node hotspots and lymph node groups detected on SLNB are associated with lower melanoma-specific survival and higher recurrence rates. Patients with HMN would benefit from increased surveillance to detect recurrent disease and access to early advanced therapy.

Reference: JAMA Otolaryngol Head Neck Surg. 2023;149:416-423
Abstract

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