Skin Cancer Research Review™

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Abbreviations used in this issue:

ADL = Activities of Daily Living
AJCCv8 = American Joint Committee on Cancer version 8
BCC = basal cell carcinoma
CMMR = Central Malignant Melanoma Registry of the German Dermatological Society
CPS = cutaneous pleomorphic sarcoma
EORTC = European Organisation for Research and Treatment of Cancer
ICI = immune checkpoint inhibitor
irAEs = immune-related adverse effects
KPS = Karnofsky Performance Scale
MSS = melanoma-specific survival
OS = overall survival
PD-1 = programmed cell death 1
PFS = progression-free survival
RCM = reflectance confocal microscopy
SCC = squamous cell carcinoma
SMD = standardized mean difference

Welcome to the latest issue of Skin Cancer Research Review.

We begin this edition with a Japanese prospective study published in *The Journal for Immunotherapy of Cancer* that concludes that the development of pituitary inflammatory side effects is a strong predictor of survival outcomes in non-small cell lung carcinoma and melanoma patients treated with immune checkpoint inhibitor therapy. Like other studies showing this association, it suggests a relationship between immune-related adverse events and immunotherapy efficacy. On the topic of melanoma, we also look at results from a French real-world study that finds the combination of stereotactic radiosurgery and anti- programmed cell death 1 immunotherapy is efficacious for the treatment of melanoma brain metastases and a meta-analysis published in *The Journal of the European Academy of Dermatology and Venereology* that examines the evidence for an association between serum vitamin D levels with risk and prognosis. An interesting study recently published investigates reflectance confocal microscopy as a non-invasive diagnostic tool in suspected basal cell carcinoma but finds it cannot replace punch biopsy due to a significantly lower accuracy for diagnosis of any type and especially lower accuracy for subtyping of aggressive variants. Further on basal cell carcinoma, one-year follow-up results from a phase 3, randomised controlled trial in nodular disease could not confirm the non-inferior efficacy of curettage/imiquimod compared to the gold standard of surgical excision.

We hope you find these and the other selected studies interesting, hope they may help you improve the lives of your patients living with skin cancer and look forward to receiving any feedback you may have.

Kind Regards,

Dr David Simpson

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Pituitary dysfunction induced by immune checkpoint inhibitors is associated with better overall survival in both malignant melanoma and non-small cell lung carcinoma

Authors: Kobayashi T et al.

Summary: This prospective study published in *The Journal for Immunotherapy of Cancer* found that immune checkpoint inhibitor (ICI)-induced pituitary inflammatory side effects were predictive of improved survival in patients with non-small cell lung carcinoma or malignant melanoma. Among 174 patients treated at Nagoya University Hospital, Japan with ipilimumab, nivolumab, pembrolizumab or atezolizumab the rate of pituitary-specific immune-related adverse events (irAEs) was 9.2% (16/174). The rate was considerably higher amongst patients with melanoma than patients with non-small cell lung cancer (18.2% vs 3.7%, respectively). Pituitary dysfunction manifested as either hypophysitis with deficiency of multiple anterior pituitary hormones accompanied by pituitary enlargement or isolated adrenocorticotropic hormone deficiency without pituitary enlargement. Pituitary irAEs occurred in 24% (6/25) of patients treated with immunotherapeutics targeting the cytotoxic T-lymphocyte antigen 4 (ipilimumab) and 6% (10/167) of patients treated with anti- programmed cell death 1 (PD-1) monoclonal antibodies (nivolumab or pembrolizumab). Kaplan-Meier survival curves showed a significant mortality advantage in patients who developed pituitary-irAEs (non-small cell carcinoma, not reached vs 441 days; $p<0.05$. Melanoma, 885 vs 298 days; $p<0.05$).

Comment: Immunotherapy has been shown to have various irAEs including endocrine abnormalities. Pituitary dysfunction leading to adrenocorticotropic hormone deficiency can be hard to differentiate from general symptoms of fatigue, appetite loss and weight loss and so this study measured pituitary function during immunotherapy treatment to provide an accurate figure. Pituitary irAEs were found in 24% of patients treated with ipilimumab and 6% of patients treated with nivolumab or pembrolizumab. Patients with pituitary irAEs were found to have both improved prognosis and overall survival. The presence of thyroid irAEs did not improve melanoma prognosis but was associated with improved survival in non-small cell lung carcinoma patients. Although a specific mechanism is unknown the authors postulated that maybe melanoma and pituitary cells have shared antigens in the same way that immune-related vitiligo has been shown to be a good prognostic sign.

Reference: J Immunother Cancer 2020;8(2):e000779

Abstract

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Prognosis of patients with stage III melanoma according to American Joint Committee on Cancer Version 8: a reassessment on the basis of 3 independent stage III melanoma cohorts

Authors: Garbe C et al., for the German Central Malignant Melanoma Registry and the European Organisation for Research and Treatment of Cancer

Summary: Lead author Claus Garbe, MD, of the Center for Dermatooncology, Eberhard Karls University, Tuebingen, Germany, reports in *The Journal of Clinical Oncology* a reassessment of American Joint Committee on Cancer version 8 (AJCCv8)- based prognosis in stage 3 melanoma. The study finds that survival rates for advanced (stage 3) melanoma published in the International Melanoma Database and Discovery Platform analysis reported in the AJCCv8 are considerably higher than that found in three large independent cohorts. The study compared survival probabilities from patients with stage 3 melanoma prospectively documented in the database of the Central Malignant Melanoma Registry (CMMR) of the German Dermatological Society between 2000 and 2012 (n=1,553) with those in the observation arm of the phase 3 European Organisation for Research and Treatment of Cancer (EORTC)-18991 trial (n=573) and the placebo arm of the phase 3 EORTC-18071 trial (n=445). Five-year melanoma-specific survival (MSS) rates from the CMMR, EORTC-18991 and EORTC-18071 cohorts were consistently lower across all risk categories of stage 3 advanced disease, with the AJCCv8 reporting a greater than 10% more favourable overall survival probability (67% vs 52.7% vs 55.5% vs 77%, respectively). The CMMR, EORTC-18991 and EORTC-18071 cohorts reported similar five-year MSS rates across all stage 3 risk categories with lower survival rates compared to AJCCv8. The difference was especially pronounced in patients with stage 3a and 3b disease (stage 3a, 80% vs 80.4% vs 72.5% vs 93%; stage 3b, 75% vs 56.2% vs 65.8% vs 83%). Comparison of ten-year MSS rates between the CMMR and AJCCv8 showed a similar pattern of more favourable survival outcomes predicted by the AJCCv8 analysis with the exception of patients with stage 3d disease (Stage 3, 56% vs 69%; stage 3a, 71% vs 88%; stage b3, 61% vs 77%; stage 3c, 44.9% vs 60%; stage 3d, 29.9% vs 24%).

Comment: Adjuvant therapy has been shown to improve the prognosis in stage 3 melanoma with improved relapse-free survival, distant metastasis-free survival and overall survival. To evaluate the benefit, we need to have accurate figures for prognosis in this group and this paper looked prospectively at three European melanoma databases. The results show a much less favourable prognosis than the AJCCv8 and also discusses an unexplained improvement in prognosis between AJCCv7 and AJCCv8. Mortality in stage 3A and 3B were particularly less favourable compared to the AJCC figures. Under reporting of melanoma-specific deaths and failure to report overall survival due to out-of-hospital deaths may have contributed. It is likely that the American figures underestimated the true melanoma-specific mortality and this information may be of value when assessing the benefit of adjuvant therapy in this group.

Reference: J Clin Oncol 2020;38(22):2543-51
Abstract

Stereotactic radiosurgery combined with anti-PD1 for the management of melanoma brain metastases: a retrospective study of safety and efficacy

Authors: Carron R et al.

Summary: This French real-world, single-center, retrospective analysis found combination stereotactic radiosurgery and anti-PD-1 therapy to be efficacious for the treatment of melanoma brain metastases. Analysis of 50 patients who received both stereotactic radiosurgery and nivolumab or pembrolizumab therapy, administered in any order, with a minimum of 12 months follow-up (median 38.89 months) showed a median overall survival (OS) of 16.62 months and a median brain-progression-free survival (PFS) of 13.2 months. Subgroup analysis of patients treated for a single brain metastasis, two to three metastases, or > three metastases found an inverse relationship between outcomes and number of metastases (OS, 60% vs 40% vs 35%, respectively. Median brain-PFS, 62.1% vs 49.7% vs 49.7%). Adverse effects included peritumoral oedema and intracranial haemorrhage. The authors commented that the toxicity rates were as expected.

Comment: Patients with brain metastases have typically been excluded from many of the major trials of immunotherapy. This study was a retrospective analysis of real-world cases with brain metastases who received both stereotactic radiosurgery and anti-PD-1 immunotherapy. Despite many patients having multiple brain metastases there was an impressive survival rate without additional neurological adverse effects. Small trials had suggested that there might be an increase in radionecrosis with ipilimumab combined with radiotherapy but this wasn't found in this study with anti-PD-1 immunotherapy (nivolumab or pembrolizumab). As might be expected, higher volume brain disease was associated with a worse prognosis. Combination therapy with ipilimumab and nivolumab has shown promising results in brain metastases and the authors suggest that combining this biotherapy with stereotactic radiosurgery might be the next step.

Reference: Eur J Cancer 2020;135:52-61
Abstract

Biopsy outperforms reflectance confocal microscopy in diagnosing and subtyping basal cell carcinoma: results and experiences from a randomized controlled multicentre trial

Authors: Woliner-van der Weg W et al.

Summary: In a randomised multicenter trial published in *The British Journal of Dermatology* Woliner-van der Weg et al. concluded that punch biopsy for the diagnosis of clinically suspected basal cell carcinoma (BCC) cannot be replaced with non-invasive reflectance confocal microscopy (RCM). The trial randomised patients with suspected BCC to punch biopsy or RCM, with diagnosis confirmed with conventional surgical excision or follow-up. While both RCM and punch biopsy methods had high rates of sensitivity (99% vs 99%; p=1.0), the accuracy of RCM was lower for BCC diagnosis (specificity, 59.1% vs 100%; p<0.001) and had a significantly worse accuracy for the subtyping of aggressive subtypes (specificity, 33.3% vs 77.3%; p=0.003). The authors concluded that the routine clinical implementation of RCM for the diagnosis of BCC is not supported.

Comment: RCM offers a quick, non-invasive method for analysing skin lesions and avoids complications of standard skin biopsies such as pain, bleeding and scarring. Trained RCM readers were used in a real-world hospital setting to assess suspected BCCs and the results were compared with punch biopsies. Whilst patient satisfaction was higher for RCM the accuracy for identifying subtypes, particularly aggressive subtypes, was lower with RCM. Superficial BCC was detected with greater accuracy. Despite these findings RCM might be useful for mapping large lesions and assessing suspected BCCs in delicate areas such as eyelids. RCM has already been shown to be useful for mapping lentigo maligna but is not widely available here in Australia.

Reference: Br J Dermatol 2020; Jul 6 [Epub ahead of print]
Abstract

Prognostic factors, treatment, and survival in cutaneous pleomorphic sarcoma

Authors: Ibanez M et al.

Summary: This analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results database reported incidence rates and prognostic factors affecting survival in cutaneous pleomorphic sarcoma (CPS). A total of 2,423 patients diagnosed between 1972 and 2013 were included. The incidence rate of CPS was 0.152 cases/100,000 person-years. Males had a 4.5-fold higher incidence rate than females. A significant association was found between male gender, white race, age older than 40 years, primary site in the head/neck, tumour size > 15 mm, grade 3 or 4 histology and significantly shorter survival. Surgical excision improved survival but radiotherapy, either as a primary therapy or in the adjuvant setting, had no impact on mortality.

Comment: Pleomorphic sarcoma, often referred to as pleomorphic dermal sarcoma was previously known as malignant histiocytoma. It is closely related to atypical fibroxanthoma but has the potential for more severe consequences and potential metastasis and mortality. This paper assessed over 2000 patients between 1972 and 2013 with a diagnosis of CPS. Risk factors for worse prognosis were male sex, white race, age over 40 years, tumour diameter greater than 15 mm, head and neck location and more aggressive histology. Surgical excision gave an improved prognosis whilst local destruction and radiotherapy did not. Even with excision margins of 3 cm 66% of patients developed local recurrence and patients need close follow-up after treatment.

Reference: J Am Acad Dermatol 2020;83(2):388-96
Abstract

Functional status and survival in patients ≥85 years of age who have keratinocyte carcinoma

Authors: Vora N et al.

Summary: This retrospective cohort study evaluated the prognostic value of functional status in relation to survival outcomes in elderly patients with keratinocyte carcinoma. A total of 238 patients aged ≥ 85 years treated for keratinocyte carcinoma at the Memorial Sloan Kettering Cancer Center, New York, USA between 2010 and 2015 were assessed for functional status using the Karnofsky Performance Scale (KPS) and Katz Activities of Daily Living (ADL) index. Short-term survival was predicted by high functional scores by either measure with patients with high functionality scores having half the death rate of the cohort with low functional scores (two-year OS; KPS ≤40, 37%, Katz ADL, ≤ 4 53%).

Comment: Keratinocyte cancers are a common problem in elderly populations, particularly here in Australia. Some well-meaning relatives may object to treatment due to the low mortality and indolent growth of these lesions as well as concerns regarding the patient's life expectancy. This paper showed that the very elderly who presented for management of keratinocyte cancers often had good functioning and low symptomatic comorbidities. Often elderly patients may receive sub-optimal treatment or no treatment at all due to relatives and even doctors pre-conceived ideas and yet the consequences of not treating can be disfigurement, pain, metastasis and the need for more extensive therapy. The conclusion seems to be that we should offer this group normal care and not be influenced by their age as long as their current functioning is good.

Reference: J Am Acad Dermatol 2020;83(2):463-68
Abstract

Surgery versus combined treatment with curettage and imiquimod for nodular basal cell carcinoma

Authors: Sinx K et al.

Summary: This report presents the one-year results of a phase 3, noninferiority, randomized, controlled trial assessing surgery compared to curettage/imiquimod for nodular BCC (ClinicalTrials.gov identifier NCT02242929). A total of 145 patients with primary histologically proven nodular BCC with a diameter ≥ 4mm and ≤ 20mm were enrolled and randomised to treatment at the Maastricht University Medical Center, Maastricht, The Netherlands, with either standard surgical elliptical excision including a 3 mm clinically tumour-free margin (n=72) or partial tumour debulking under local anaesthesia with a blunt curette followed by a six-week period of topical imiquimod 5% (n=73) administered five days a week. At 12 months curettage/imiquimod failed to meet the primary endpoint prespecified non-inferiority margin of -8% compared to surgery (recurrence-free rates, 86.3% vs 100%; treatment difference, -13.7%; 95% confidence interval, -21.6% to-5.8; 1-sided p=0.0004) and surgery therefore remains the gold standard for the treatment of nodular BC. The authors commented that while curettage and imiquimod cannot replace surgical excision for nodular BCC it provides a high efficacy treatment and is an option to prevent surgery overuse.

Comment: Imiquimod cream is a useful option for superficial BCC and has been shown in small studies to have a significant cure rate in thin nodular BCCs. This study compared nodular BCCs treated with combined curettage and imiquimod versus excision. Imiquimod was started one week after curettage and used for the traditional five days per week for a six-week regimen. At 12-months the combination of cream and curettage was inferior to surgery (not shown to be non-inferior). Patients and observers reported improved cosmesis particularly on the head and neck. Whilst surgery was shown to be superior for clearance at 12- months imiquimod after curettage may be a useful technique in selected cases.

Reference: J Am Acad Dermatol 2020;83(2):469-76
Abstract

The association between serum vitamin D level and risk and prognosis of melanoma

Authors: Tsai T-Y et al.

Summary: This systematic review and meta-analysis aimed to clarify the role of serum vitamin D in the risk and prognosis of melanoma. An online database search with a cut-off date of 31 Oct 2018 identified 25 studies incorporating 11,166 patients with melanoma. Vitamin D deficiency was two-fold more prevalent in melanoma patients compared to controls (odds ratio, 2.115; 95% CI, 1.151–3.885) but no significant difference in serum vitamin D levels was seen between patients with melanoma and controls (standardized mean difference [SMD], −0.185; 95% confidence interval, −0.533 to 0.162). A correlation was found between melanoma patients with lower vitamin D levels with increased Breslow thickness (≦1 vs. >1 mm: SMD, 0.243; 95% CI, 0.160–0.327) and increased risk of mortality (hazard ratio, 1.558; 95% CI, 1.258–1.931).

Comment: Melanoma is known to be associated with a history of sunburn, brief intense sun exposure and recreational sun exposure rather than chronic occupational exposure. The role of vitamin D has been of interest since higher levels were shown to be associated with improved prognosis in many cancers including colorectal, bladder and prostate cancer. This study pooled data from multiple studies to explore the relationship between vitamin D levels and both melanoma risk and melanoma prognosis. Overall, there was no association between vitamin D levels and risk but one particular study was at odds with the others and when removed from analysis there appeared to be a significantly increased risk with vitamin D deficiency. Higher vitamin D levels were shown to be associated with thinner tumours with a lower Breslow thickness and improved prognosis. The mechanism may be due to the antineoplastic effect of adequate vitamin D levels and its ability to induce differentiation and inhibit angiogenesis and invasion of melanoma cells.

Reference: J Eur Acad Dermatol Venereol 2020;34(8):1722-29
Abstract

Patient-centered management of actinic keratosis. Results of a multi-center clinical consensus analysing non-melanoma skin cancer patient profiles and field-treatment strategies

Authors: Philipp-Dormston W et al.

Summary: The SPEAK (Supporting Professional Expertise in Actinic Keratosis) program was developed by a European collaboration between 22 dermato-oncologists to assist healthcare physicians in optimising treatment and communication with patients with actinic keratosis. The program establishes six psychosocial-defined patient profiles with associated management and treatment approaches and aims to increase treatment adherence by fostering patient-doctor relationships and communication.

Comment: Patients with multiple actinic keratoses are a daily presentation in our clinics and can be a challenge to treat due to poor compliance, adverse reactions from therapy and problems meeting patient's expectations. This paper presents the consensus opinion of a panel of experienced dermatologists and aims to tailor treatment to patient sub-groups. Factors such as lack of patient engagement, cosmetic concerns and patient anxiety are explored. The conclusions give some guidance but for many of us we will have already formulated our own treatment "menu" which we apply to our patient population. Interesting points are using practitioner-directed treatments in patients who lack engagement which eliminates poor compliance and also choosing to excise lesions in very anxious patients in order to remove the lesions and obtain histopathology. Cryotherapy was advised against in this study because the patient profiles were for field therapy and it was felt it would miss sub-clinical disease, lead to more scarring and require multiple rounds of treatment.

Reference: J Dermatolog Treat 2020;31(6):576-82
Abstract

Independent commentary by Dr David Simpson

Dr David Simpson is a skin cancer doctor on the Sunshine Coast in Queensland. He has a masters degree in Skin Cancer Medicine from the University of Queensland and is a teaching assistant on the MMed program.

Intralesional methotrexate for the treatment of advanced keratinocytic tumours

Authors: Gualdi G et al.

Summary: This multi-center retrospective study assessed targeted intralesional chemotherapy with methotrexate for the treatment of non-melanoma skin cancers. Analysis included a total of 35 patients with squamous cell carcinoma (SCC; n=21), keratoacanthoma (n=12) or BCC (n=2) treated with varying doses and protocols of methotrexate injection. Patients with BCC did not respond to methotrexate therapy. Patients with keratoacanthoma had superior responses compared to patients with SCC, with all patients responding to treatment and 92% achieving a complete resolution of tumours. Less than half of patients with SCC responded to methotrexate (47.6%; defined as an improvement of > 50%) and 38% did not respond at all. The authors determined the most effective dose and protocol to be a four to six-week treatment of 25 mg/ml/week methotrexate. Mild anaemia was the most common adverse effect and affected one third of patients.

Comment: Elderly patients presenting with larger tumours in difficult anatomical locations require evaluation of the expected morbidity and mortality of the tumour versus the benefit and harms of treatment. Methotrexate arrests cell division by blocking the production of thymidylic acid, preventing DNA synthesis and arresting cell replication, and so might be useful in rapidly growing tumours. In this study of 35 patients with an average age of 80 whose tumours were considered unsuitable for either surgery or radiotherapy, methotrexate was administered via subcutaneous injections into four quadrants of the tumours. 92% of the keratoacanthomas resolved whilst 47% of cutaneous squamous cell carcinomas responded and 14.8% had a partial response. Only two BCCs were included and neither responded. Five of the 35 patients developed anaemia with one requiring a blood transfusion. The authors speculated that BCC is less likely to respond due to its slower growth and cell division. Whilst the response rate in keratoacanthomas is impressive this tumour is expected to spontaneously resolve within six weeks even if untreated and so the benefits of methotrexate seem unproven.

Reference: Dermatol Ther (Heidelb) 2020;10(4):769-77
Abstract

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