Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

CAM = complementary and alternative medicine;
CNS = central nervous system;
3DCRT = three-dimensional conformal radiotherapy;
IMRT = intensity-modulated radiotherapy;
MBMs = melanoma brain metastases; **SRS** = stereotactic radiosurgery.

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Welcome to the 14th issue of Melanoma Research Review

In this issue the articles address a range of topics including melanoma surveillance, early detection, diagnostic risk factors and predicting treatment outcomes. The leading article reports surveillance through a specialised clinic was a cost-effective strategy for the management of individuals at high risk of melanoma. Another study assessing patient-performed mobile teledermoscopy for the early detection of melanoma found favourable consumer acceptance.

A paper investigating prognostic impact of lymphovascular invasion in cutaneous melanoma showed lymphovascular invasion has significant prognostic impact on nodal involvement, recurrence, and overall survival in cutaneous melanoma. A small study assessing cessation of targeted therapy after a complete response in BRAF-mutant advanced melanoma reports the majority of these patients will relapse. What remains unclear is whether different treatment durations and dosages may be appropriate in these patients providing a more patient-tailored approach.

The concluding papers in this issue include an assessment of a psychoeducational intervention to reduce fear of cancer recurrence. The authors report the intervention was effective in reducing stress and increasing melanoma-related knowledge in people at high risk for another melanoma. A survey of complementary and alternative medicine in melanoma patients found nearly half of the 1089 participants used these medicines and highlighted communication on complementary and alternative medicine should become a regular topic in counselling melanoma patients.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Associate Professor Saxon D Smith

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Cost-effectiveness of skin surveillance through a specialized clinic for patients at high risk of melanoma

Authors: Watts CG, et al

Summary: This group compared the costs and benefits of specialised surveillance through a high risk clinic with standard care over a 10-year period. They found specialised surveillance was less expensive and more effective than standard care with the mean saving of A$6,828 per patient, and the mean quality-adjusted life-year gain of 0.31. The main factors contributing to this difference were detection of melanoma at an earlier stage resulting in less extensive treatment and a lower annual mean excision rate in specialised surveillance.

Comment: Australia and New Zealand continue to have the highest rates of melanoma in the world. Importantly, these rates continue to rise year on year. On the other hand, the health dollar continues to be stretched further as this finite fiscal resource is split into continuingly smaller slices leaving clinicians to do more with less. So it is important to assess the impact of surveillance programs in both terms of clinical and economic outcome. This Australian study clearly demonstrates the utility of population screening in high risk patients. It leads to earlier detection of melanoma which maximises patient survival with detection of melanoma in earlier stages. This also results in better patient outcomes not only in lives saved but also fewer invasive procedures being performed. Furthermore, there is substantial economic gain with a mean saving of $6828 per patient. Therefore, this study provides very strong evidence for surveillance programs in high risk patients.

Reference: J Clin Oncol. 2017 Jan;35(1):63-71. Epub 2016 Oct 28.

Abstract

Clinical features associated with individuals at higher risk of melanoma: A population-based study

Authors: Watts CG, et al

Summary: This team analysed the data from a New South Wales population-based observational study of 2727 patients diagnosed with an in situ or invasive primary melanoma. Thirty nine per cent of the study cohort was defined as higher risk based on a family history of melanoma, multiple primary melanomas, or many nevi. Compared with patients with melanoma who were at lower risk (ie, without any of these risk factors), the higher-risk group had a younger mean age at diagnosis (62 vs 65 years, $P < .001$). The team also noted among higher-risk patients, those with many nevi were more likely to have melanoma on the trunk (41% vs 29%, $P < .001$), those with a family history of melanoma were more likely to have melanomas on the limbs (57% vs 42%, $P < .001$), and those with a personal history were more likely to have melanoma on the head and neck (21% vs 15%, $P = .003$).

Comment: The previous Watts et al study indicated the clinical and economic benefits for surveillance of high risk melanoma patients. Therefore, it is important to independently assess what the key criteria should be to help identify and risk stratify high risk patients. This current study examined the commonly held high risk factors of: family history of melanoma, multiple primary melanomas, or many nevi. The authors demonstrated that these remain key risk factors but identified that there are differences between how we should weight these in our patient risk stratification. There is no substitution for a full skin examination in these patients. However, by knowing that patients with a personal history of melanoma are more likely to have second melanomas in the head and neck zone as compared with those with only a family history are more likely to have melanomas on limbs, doctor's can have an even higher index of clinical suspicion of early change in these sites.

Reference: JAMA Dermatol 2017 Jan 1;153(1):23-29

Abstract

Consumer acceptance of patient-performed mobile teledermoscopy for the early detection of melanoma

Authors: Horsham C, et al

Summary: Questionnaires were completed by 49 participants at high risk of melanoma (fair skin or previous skin cancer) who conducted mobile teledermoscopy; a system that allows consumers to send images of skin lesions to a teledermatologist for remote diagnosis. Participants reported that the dermatoscope was easy to use (94%) and motivated them to examine their skin more often (86%). However, 18% could not take photographs in hard-to-see areas and 35% required help to submit the photograph to the teledermatologist.

Comment: There is strong evidence that early detection leads to better patient survival outcome and economic cost-effectiveness. We have seen in the articles already discussed the utility of surveillance in high risk patients as well as understanding better the different impact of specific high risk criteria. On the other hand, it remains to be seen if the same benefits will be seen through the surveillance of the population in general. Technology continues to advance offering opportunity and risk in terms of the role of this technology in assisting in the detection of melanoma. However, even before discussing the successes and failures of computer algorithms to analyse specific lesions it is important to assess whether the population would embrace a technology solution to population screening. This study demonstrates that there is high consumer acceptance for a technology based adjuvant for the detection of melanoma. And whilst this is not a substitute to a full clinical examination by their doctor, when combined with the knowledge of risk factors as discussed above in Watts et al, this technology could play a role in assisting in earlier diagnosis.

Reference: Br J Dermatol 2016 Dec;175(6):1301-1310
Abstract

An independent validation of a gene expression signature to differentiate malignant melanoma from benign melanocytic nevi

Authors: Clarke LE, et al

Summary: A set of 1400 melanocytic lesions submitted for gene expression testing at a clinical laboratory was independently evaluated by experienced dermatopathologists. Diagnostic concordance (benign or malignant) among three dermatopathologists was required for inclusion in analyses. The researchers concluded the 23-gene expression signature differentiated benign nevi from malignant melanoma with a sensitivity of 91.5% and a specificity of 92.5%.

Comment: It has been demonstrated that around 20% of melanomas have an associated 'benign' naevi from which they have developed. This means that naevi remain a vexed issue. Recent studies have explored both retrospectively and prospectively the 'transformation risk' of different levels of dysplasia in naevi. Significant questions remain on our ability to reliably and reproducibly determine some benign melanocytic lesions from malignant especially in the grey zone between the two poles. This study by Clarke et al seeks to examine genomic expression as a way to better clarify risk in naevi by exploring the utility of this 23-gene signature to differentiate malignant and benign melanocytic lesions. The author's results do show promise but with sensitivities and specificities both in the low 90%, there remains further work to avoid the false negatives and false positives in our current systems.

Reference: Cancer 2017 Feb 15;123(4):617-628
Abstract

Histological lymphovascular invasion is associated with nodal involvement, recurrence, and survival in patients with cutaneous malignant melanoma

Authors: Tas F, et al

Summary: This group retrospectively investigated outcomes in 705 patients with cutaneous melanoma; 624 (88.5%) with lymphovascular invasion and 81 (11.5%) without. Melanoma patients with lymphovascular invasion more frequently had nodular pathology, invasion to an advanced Clark level, greater Breslow thickness, a high mitotic rate, ulceration, neurotropism, lymph node involvement, multiple lymph node involvement, recurrent disease, and metastatic disease compared to patients without lymphovascular invasion. In contrast, lymphovascular invasion was not significantly associated with age, gender, anatomic localisation, tumour-infiltrating lymphocytes, vertical growth phase, a pre-existing melanocytic nevus, or type of distant metastasis. It was also noted lymphovascular invasion was significantly associated with both recurrence-free and overall survival.

Comment: When histopathology demonstrates melanoma we understand well the role of Breslow thickness and mitoses in terms of risk factor for nodal and distant spread of disease. We have also seen lymphovascular invasion as another important factor without clear guidelines as to how best to clinically stratify this risk. The authors of this study help to clearly elucidate the importance of lymphovascular invasion by the primary tumour. This should be used as a key risk indicator in patients work up for possible investigation for nodal or distant spread of disease.

Reference: Int J Dermatol 2017 Feb;56(2):166-170
Abstract

Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: A pooled analysis of individual patient data from randomised trials

Authors: Long GV, et al

Summary: This retrospective study used pooled data from randomised trials of dabrafenib plus trametinib in patients with metastatic BRAF-mutant melanoma. The analysis included 617 patients with a median follow-up of 20 months; 396 patients had progression events and 290 patients had died. The authors reported patients with normal lactate dehydrogenase concentration and fewer than three organ sites containing metastases (n=237) had the longest 1-year progression-free survival (68%) and overall survival (90%) and 2-year progression-free survival (46%) and overall survival (75%). In contrast patients with lactate dehydrogenase concentration at least two times the upper limit of normal (n=70) had the shortest 1-year progression-free survival (8%) and overall survival (40%) and 2-year progression-free survival (2%) and overall survival (7%). They also reported among the patients with disease progression (n=379), survival after progression was longest in those with progression in baseline or new non-central nervous system (CNS) lesions (n=205; median 10·0 months) and shortest in those with new CNS lesions or concurrent progression in baseline and new lesions (n=171; median 4·0 months).

Comment: We have been witness to major advances in the management of advance/metastatic melanoma. As we ride this crest of the wave in terms of treatment and outcomes, our understanding of these treatments develop further. We understand better the heterogeneity of melanoma pathophysiology, such as the importance of BRAF positivity, in treatment decision making and estimated prognosis. Long et al investigate what patient and clinical characteristics can help us potentially identify patients who will have more durable benefit when treated with dabrafenib plus trametinib. It is easy to see the importance of being able to better identify patients who will have better outcomes with a certain treatment. This article helps pave the way for more consistent expected outcomes in these BRAF mutated melanoma patients.

Reference: Lancet Oncol 2016 Dec;17(12):1743-1754
Abstract

Cessation of targeted therapy after a complete response in BRAF-mutant advanced melanoma: A case series

Authors: Carlino MS, et al

Summary: This study included 12 patients treated with BRAF/MEK inhibitors achieving complete response and ceasing treatment before progression. During the median follow-up of 16 months, 6 (50%) recurred at a median of 6.6 months after treatment cessation. The investigators concluded baseline characteristics and time to complete response and to discontinuation did not influence the rate of relapse.

Comment: As previously discussed, there have been dramatic advances in management of advance/metastatic melanoma. Whilst we continue to explore the best ways and combinations to use the new immune checkpoint and BRAF/MEK inhibitor treatments, we are seeing patients have dramatic positive responses. Obviously not all patients have such benefit to achieve a 'complete response', but for those that do the next significant question is whether you can subsequently cease treatment. Carlino et al seek to answer this very question with their small prospective cohort of complete responders. It is clear from this small study that the majority of these patients will relapse. What remains unclear is whether different treatment durations and even dosages may be appropriate in these patients allowing for a more patient-tailored approach. This is a small but important step to explore these answers.

Reference: Br J Cancer 2016 Nov 22;115(11):1280-1284
Abstract

References: 1. Tafinlar (dabrafenib) Product Information. **2.** Mekinist (trametinib) Product Information. **3.** Long G et al. *Lancet* 2015; 386(9992): 444–51. **4.** Robert C et al. *N Engl J Med* 2015; 372: 30–9. **5.** Flaherty K et al. *N Engl J Med* 2012; 367–1694–1703 **6.** Long G et al. *J Clin Oncol* 2016; 34(8): 871–8. **7.** Flaherty KT et al. Oral presentation at ASCO 2016: June 3–7, Chicago, Illinois.

Adjuvant external beam radiotherapy after therapeutic groin lymphadenectomy for patients with melanoma: A dosimetric comparison of three-dimensional conformal and intensity-modulated radiotherapy techniques

Authors: Adams G, et al

Summary: Fifteen consecutively treated high-risk melanoma patients were selected; 5 treated with conformal radiotherapy (3DCRT) and 10 with intensity-modulated radiotherapy (IMRT). The group report IMRT appears to allow superior conformity of dose to the target volume while relatively sparing the adjacent the bowel and femoral head/neck.

Comment: Treatment of advanced/metastatic melanoma continues to advance rapidly in recent years. This has not only lead to advances in medications on offer but also seen a harnessing of the value of adjuvant treatments. The technology expansion in radiation oncology has seen the development of increasingly more accurate and effective systems. Furthermore, these advances have also seen a decrease in the historical adverse reactions and limitations of radiation oncology. Radiation of resected lymph node basins has been recommended previously and Adams et al report their findings on the role of external beam radiotherapy. They have essentially shown a non-inferiority of intensity-modulated radiotherapy when compared to three-dimensional conformal radiotherapy for the groin lymph node basin. They do theorise that there could be advantages in side effect profile in favour of intensity-modulated radiotherapy. This is a small case series and further research is required, especially when looking at other anatomical areas. However, it helps to highlight the advances in the setting of radiation oncology.

Reference: Melanoma Res 2017 Feb;27(1):50-56
Abstract

Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy

Authors: Ahmed KA, et al

Summary: This institutional analysis investigated outcomes of patients with melanoma brain metastases (MBMs) treated with stereotactic radiosurgery (SRS) and various systemic immunologic and targeted melanoma agents. Ninety-six patients were treated to 314 MBMs over 119 SRS treatment sessions. The authors reported twelve-month Kaplan-Meier distant MBM control rates were 38%, 21%, 20%, 8%, and 5% (P = 0.008) for SRS with anti-PD-1 therapies, anti-CTLA-4 therapy, BRAF/MEKi, BRAFi, and conventional chemotherapy, respectively. No significant differences were noted in the Kaplan-Meier local MBM control rates among treatment groups (P = 0.25). They also found treatment with anti-PD-1 therapy, anti-CTLA-4 therapy, or BRAF/MEKi significantly improved overall survival when compared with conventional chemotherapy.

Comment: This article by Ahmed et al further explores the utility of adjuvant radiotherapy in the setting of advance/metastatic melanoma. Here they retrospectively explored disease control in patients with brain metastases following stereotatic radiosurgery whilst the patient was on other various systemic agents. There were clear overall survival benefits in patients treated with newer systemic agents over traditional chemotherapy. Furthermore, there were differences in the control of distant melanoma brain metastases depending on the systemic therapy used with the stereotatic radiosurgery. Stereotatic radiosurgery will remain a key option in patients with melanoma brain metastases and understanding the best systemic therapy to be used in combination will lead to better patient outcomes in time. Further research is required, but this article acts as a guide for now.

Reference: Ann Oncol 2016 Dec;27(12):2288-2294
Abstract

Psychoeducational intervention to reduce fear of cancer recurrence in people at high risk of developing another primary melanoma: Results of a randomized controlled trial

Authors: Dieng M, et al

Summary: Participants were randomly assigned to intervention (n = 80), comprising of a psychoeducational resource and telephone-based psychotherapeutic sessions, or usual care (n = 84). Assessments were completed at baseline, 1 month and 6 months. At 6 months, the intervention group reported lower fear of cancer recurrence severity, trigger, and distress scores than the control group in the baseline-adjusted models. The decrease in fear of cancer recurrence severity (but not triggers or distress) remained statistically significant after adjustment for other covariates. At 6 months, the intervention group also reported lower stress and improved melanoma-related knowledge compared with the control group.

Comment: When we treat melanoma we do not just treat the disease but also the patient suffering from it. All too often when I talk to my patients who have had melanoma they talk about it being this constant 'knot' in the back of their mind which they cannot shake. Some become understandably paranoid about every potentially changed or new lesion. Others I think just hide it better than some. The diagnosis of cancer has dramatic biopsychosocial impacts on the patient and their loved ones. This is no truer than in melanoma which behaves like no other form of cancer. Dieng et al help show us the importance of psychoeducational interventions to help our patients with melanoma reduce stress and fear of cancer recurrence through imparting melanoma-related knowledge. In the clinical setting this will not happen as a single event, but rather by small increments over time with each interaction with their multidisciplinary team. We all have a key role to play in this to support our patients.

Reference: J Clin Oncol 2016 Dec 20;34(36):4405-4414
Abstract

Use of complementary and alternative medicine: A multicenter cross-sectional study in 1089 melanoma patients

Authors: Loquai C, et al

Summary: This article evaluated the prevalence and predictors for the use of complementary and alternative medicine (CAM) in melanoma patients.Participants (n=1089) attending at one of 7 skin cancer centres in Germany completed a survey using a structured questionnaire on CAM. Forty one per cent of participants used CAM and half of those using CAM (56.8%) marked that this made them feel better. Predictors of CAM use were education, psychological support, interest in CAM and previous CAM use.

Comment: It is not surprising in this day and age that patients with any significant medical condition will seek any means by which to help or cure their situation. I, like many others in different specialties, see this in many conditions that I treat, for example as a dermatologist it tends to be eczema, psoriasis and acne. This is certainly truer for cancer patients. However, this is not something that has been well explored in the setting of melanoma patients. Although, I have met a patient who was trying to cure their choroidal melanoma by drinking copious amounts of tomato juice. This study by Loquai et al demonstrates that it is important for us to be open and willing to discuss CAM with our patients who will likely seek it one way or another. By being open and willing to discuss CAM in a non-judgmental way supports patients in their time of need as a patient is more than just the disease we treat. This will help prevent unnecessary harms and delay in treatment, such as my patient and his tomato juice, but will also help identify potential adverse medication interactions between conventional medicine we prescribe and the CAM the patient seeks out.

Reference: Eur J Cancer 2017 Jan;71:70-79
Abstract

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Independent Commentary by Clinical Associate Professor Saxon D Smith

Clinical Associate Professor Saxon D Smith is a consultant dermatologist in private practice in Gosford, Australia, a staff specialist at Royal North Shore Hospital, St Leonards, Australia and a clinical associate professor at the University of Sydney, Australia. He runs public clinics at Royal North Shore Hospital in surgical cutaneous oncology; immune-oncology management and surveillance in advance melanoma; multi-disciplinary team with plastic surgery on the management of hidradenitis suppurativa; multi-disciplinary team with neurology on skin diseases in neurology including management of adverse reactions of treatment; and dermatology in renal transplant patients. His current active areas of interest in research include: adult and paediatric psoriasis and its comorbidities; adult and paediatric atopic dermatitis; skin cancer awareness and sun protection behaviours; melanoma and non-melanoma skin cancer management in advance disease; medical education; and the medico-legal interface in dermatology. He is also currently involved in several pharmaceutical trials from phase II to phase IV.

