Melanoma Research Review™

Making Education Easy

Issue 9 - 2016

In this issue:

Abbreviations used in this issue:

BCC = basal cell carcinoma; **DCs** = dendritic cells; **NM** = nodular melanoma; **OS** = overall survival; **PAM** = pregnancy-associated melanoma; **SCC** =squamous cell carcinoma; **SN** = sentinel lymph node; **SNB** = sentinel node biopsy; **SSM** = superficial spreading melanoma.

Welcome to the 9th issue of Melanoma Research Review

A retrospective study of primarily early-stage melanoma, found pregnancy did not have a significant impact on tumour proliferation. The authors also noted pregnancy status was not associated with age at diagnosis, tumour site, Breslow depth, Clark level, ulceration, or overall stage. Another European study, a European-wide survey assessing the management of melanoma during pregnancy found there is a lack of consensus in Europe and highlighted the need for guidelines.

A study assessing the toxicity profile of dendritic cell vaccination in stage III and IV melanoma patients concluded vaccination is safe and tolerable and the occurrence of the immune-related side effects correlates with immunologic and clinical outcome. Data from a whole-exome sequencing suggests that mutations occur early during melanoma development, whereas somatic copy number alterations might be involved in melanoma progression.

An article evaluating clinical pathways for the diagnosis of nodular melanoma vs superficial spreading melanoma using a retrospective questionnaire from the Victorian Melanoma Service highlights the importance of addressing earlier diagnosis of nodular melanoma. An important message from this study is that monitoring is not appropriate for raised lesions and that the biopsy threshold should be very low.

A large cohort study using records from the Queensland Cancer Registry concluded patients with multiple invasive melanomas have significantly poorer survival than patients with a single invasive melanoma.

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,

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Association of non-melanoma skin cancer with second non-cutaneous malignancy in the Women's Health Initiative

Authors: Ransohoff KJ, et al

Summary: The Nurses Health Study prospective analyses found increased risk of developing breast cancer, lung cancer and melanoma in women with non-melanoma skin cancer. This team sought to replicate these findings in the large Women's Health Initiative cohort.

Comment: These results on a large cohort of > 50 year old women only confirm previous data showing that non-melanoma skin cancer is associated with increased risk for melanoma and other non-cutaneous cancer. However, cancers such as colon, endometrial, ovarian, and pancreatic cancer were not affected by baseline of non-melanoma skin cancer history in this study. On the other hand, even after adjusting for any family history of cancer, the risk was still higher for breast and lung cancers, leukemia and mostly melanoma. The authors report multiple factors associated with non-melanoma skin cancer like being older (70-79y old), less obesity, high percentage of reported family history of any cancer. Such findings can lead to a better biological pathway understanding and a better exploration of patients with high risk.

Reference: Br J Dermatol 2016 May 26
Abstract

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Independent Commentary by Associate Professor Pascale Guitera and Dr Nesrine Brahimi.

Associate Professor Guitera is currently Director of the Sydney Melanoma Diagnostic Centre (SMDC) and academic dermatologist at the Melanoma Institute Australia (MIA), with a position of Associate Professor at the University of Sydney. She undertook her dermatology fellowship in Saint Louis hospital in Paris. She was awarded the highest distinction for her PhD at the Curie Institute and SMDC on the application of instrumental techniques for the diagnosis of skin tumours. She has lived in Sydney since 2005, where she has achieved global recognition as one of the top 10 researchers of *in vivo* confocal microscopy. Dr Guitera was awarded the 2013 Wildfire Premier's award by the Cancer Institute NSW for outstanding research. She organises courses in imagery for the diagnosis of skin cancer on a yearly basis

Dr Nesrine Brahimi (MD), senior practitioner in dermatology since 2006 at Bichat Claude-Bernard university hospital in Paris, has also been working as a senior dermatology consultant since 2011 at the Gatineau-Saillant Centre, Paris. Her research interest is focused in oncodermatology, cutaneous adverse drug reactions management and teledermatology. She is currently spending a sabbatical year at the Prince Alfred Hospital and at the Melanoma Institute Australia in Sydney.

The occurrence of non-melanoma malignant skin lesions and non-cutaneous squamous-cell carcinoma among metastatic melanoma patients: An observational cohort study in Denmark

Authors: Li H, et al

Summary: This historical cohort study evaluated the background rates of new-onset non-melanoma skin lesions and non-cutaneous squamous cell carcinoma (SCC) among 2,814 metastatic malignant melanoma patients. The authors reported the median age at metastatic melanoma diagnosis was 64 years. Over 40% of patients died within one year of metastatic diagnosis and approximately 70% died within 5 years. The percentages of patients with prior history or prevalent disease at metastatic melanoma diagnosis included: 8.6% with cutaneous SCC or basal cell carcinoma (BCC), 3.9% with actinic keratosis, and 0.7% with Bowen's disease. No patients had past or current non-cutaneous SCC per study exclusion criterion. The incidence of non-melanoma skin lesions during the 6 months post-metastatic melanoma diagnosis was: BCC 1.8%; actinic keratosis 0.8%; cutaneous SCC 0.1%; Bowen's disease 0.04%; and keratoacanthoma 0%. Non-cutaneous SCC was observed in 3 patients (0.1%).

Comment: With the new generation therapies for melanoma, other cutaneous malignancies may evolve such as SCC (especially with BRAF inhibitors). In this Danish study, the findings proved that non-melanoma malignant skin lesions and non-cutaneous SCCs are rare among patients with metastatic melanoma. In fact, less than 8.6% of the patients developed a SCC or a BCC. But the study did not report any medication history or other risk factors. It provides a background rate in a population-based study with no control group and may not be directly generalised to a different country or ethnic group (in particular heavily sun damaged Australian population).

Reference: BMC Cancer 2016 May 3;16(1):295
Abstract

Members of the Melanoma Group of the EORTC. Pregnancy and melanoma: A European-wide survey to assess current management and a critical literature overview

Authors: Ribero S, et al

Summary: A total of 290 questionnaires were completed. The team found a large heterogeneity for the answers given in the different clinical scenarios with 50% of the answers showing discordance. They also found discordant answers for the counselling of women about a potential delay in getting pregnant after a high-risk melanoma; 35% for a 2 year wait minimum vs. 57% no waiting needed. In contrast, for thin melanomas there was more concordance with 70% of the physicians recommending no delay.

Comment: Melanoma is one of the most common malignancies to occur during pregnancy, with an estimated incidence of 2.8 to 5.0 cases per 100,000 pregnancies. We need to emphasise that all the criteria for removing suspicious lesions should be the same during pregnancy or not.

There is no consensus in the management of future pregnancy & melanoma accruing in pregnant women. This survey shows quite a lot of discordance in the issue of sentinel node biopsy (SNB) and advise regarding future pregnancy both in thin and thick melanomas. These findings highlight the disparity of physicians most likely because the data are scarce but it seems that SNB is a safe procedure during pregnancy and foetal transmission of melanoma is so rare that abortion should not be recommended. More guidelines to make decisions about treating women of child-bearing age are awaited.

Reference: J Eur Acad Dermatol Venereol 2016 May 27
Abstract

A comparative study of proliferative activity and tumor stage of pregnancy-associated melanoma (PAM) and non-PAM in gestational age women

Authors: Merkel EA, et al

Summary: This group examined tumour proliferation rates and reviewed medical records and pathology reports from women given a diagnosis of melanoma between 2006 and 2015. They reported in 50 PAM and 122 non-PAM cases, a diagnosis of melanoma in situ was associated with PAM. Among invasive melanomas, there was no difference in proliferative activity between groups. They also noted pregnancy status was not associated with age at diagnosis, tumour site, Breslow depth, Clark level, ulceration, or overall stage.

Comment: This retrospective study reviewed some of the data available to answer the previous survey. The authors did not observe any difference in proliferative activity between PAM and melanoma in non-pregnant women of reproductive age as well as no association between pregnancy status and age at diagnosis, tumour site, Breslow thickness, or overall stage. These findings are reassuring but other recent studies describe worse outcomes for women with a pregnancy-associated melanoma and it is still important while the field is controversial to follow closely these pregnant women and those at age of procreation. Of note also only 8 cases of PAM had mitotic activity therefore the sample may be too small to be sure there is no concern with proliferation activity.

Reference: J Am Acad Dermatol 2016 Jan;74(1):88-93
Abstract

Immune-related adverse events of dendritic cell vaccination correlate with immunologic and clinical outcome in stage III and IV melanoma patients

Authors: Boudewijns S, et al

Summary: This retrospective study investigated toxicity profiles in melanoma patients, vaccinated with monocyte-derived or naturally circulating autologous dendritic cells (DCs) loaded with tumour-associated antigens gp100 and tyrosinase. Median follow-up time was 54.3 months in stage III patients (n=82) and 12.9 months in stage IV patients (n=137). The team showed treatment-related adverse events occurred in 84% of patients with grade 3 toxicity in 3% of patients. They noted the most common adverse events were flu-like symptoms (67%) and injection site reactions (50%), and both correlated with the presence of tetramer-positive CD8 T cells.

Comment: It is a time of revolution in the treatment of stage III and IV melanoma because of immunotherapy. This article studied vaccination with monocyte-derived or naturally circulating autologous DCs. The authors main points are first that adverse effects were not highly toxic (with only 3% of patients having a grade 3 toxicity) and second that there was a significant correlation between adverse effects and clinical outcomes.

This second fact has been also reported for other immunotherapy like anti-PD1. Of note, the median overall survival is less impressive than anti-PD1 which also have an excellent safety record (in monotherapy) and are less expensive. Nevertheless, these type of treatments maybe a powerful and well tolerated alternative when others have failed.

Reference: J Immunother 2016 Jul-Aug;39(6):241-8
Abstract

Sentinel lymph node biopsy in thin cutaneous melanoma: A systematic review and meta-analysis

Authors: Cordeiro E, et al

Summary: These researchers assessed 60 studies (10,928 patients) with the aim of quantifying the proportion of sentinel lymph node (SN) metastases in patients with thin melanoma. They found the pooled proportion of SN metastases in thin melanoma was 4.5% and concluded thickness ≥0.75mm, Clark level IV/V, mitoses, and microsatellites significantly increased the odds of SN positivity.

Comment: The role of sentinel lymph node biopsy for staging is not discussed but still remains very controversial for survival benefit. The role of SNB for melanoma <1mm is controversial with <4.5% of metastasis found. This meta-analysis of 60 studies including 10,928 patients reviewed the proportion of SN metastasis for < 1mm Breslow patient. Pooled analysis demonstrated an 8.8% SN positivity rate for melanoma >0.75mm, 7.3% for Clark level IV/V, 8.8% for mitoses >1/mm2, and 26.6% for presence of microsatellites. The authors suggest that all patients with melanomas >0.75 mm treated in a high-volume centre should be offered SNB. The SNB would be a worthwhile procedure particularly for patients who could be candidates for an adjuvant trial.

Reference: Ann Surg Oncol 2016 Mar 1
Abstract

Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): A multicentre, randomised, phase 3 trial

Authors: Leiter U, et al

Summary: The group screened 5,547 patients with SNB and 1,269 (23%) patients were positive for micrometastasis. Of these, 241 patients were randomly assigned to the observation group and 242 to the complete lymph node dissection group. They found 311 (66%) patients (158 in the observation group and 153 in the dissection group) had sentinel lymph node metastases of 1mm or less. Median follow-up was 35 months. Distant metastasis-free survival at 3 years was 77·0% (90% CI 71·9-82·1; 55 events) in the observation group and 74·9% (69·5-80·3; 54 events) in the complete lymph node dissection group. The group note the required number of events was not achieved, leading to the trial being underpowered. In the complete lymph node dissection group, grade 3 and 4 events occurred in 15 patients (6%) and 19 patients (8%), respectively. Adverse events included lymph oedema, lymph fistula, seroma, infection and delayed wound healing.

Comment: Their results showed no difference in survival in patients treated with complete lymph node dissection compared with observation only. Consequently, they suggest complete lymph node dissection should not be recommended in patients with melanoma with lymph node micro metastasis of at least a diameter of 1mm or smaller.

This study has several limitations in particular being underpowered with around 1 in 3 patients randomised. The main problem is the short term follow up when we know from trials like MLST1 and cohort studies that lymph node metastasis can appear after 5 or even 10-15 years for minimal disease.

Interesting data is the high level of adverse events in the surgical arm. These data are at least convincing for elderly patients who should definitively be monitored. The results of MSTL2 should be more reliable and available next year.

Reference: Lancet Oncol 2016 May 5. pii: S1470-2045(16)00141-8
Abstract

Thin and thick primary cutaneous melanomas reveal distinct patterns of somatic copy number alterations

Authors: Montagnani V, et al

Summary: Melanoma thickness is a well-established prognostic indicator in melanoma. This study compared clinical and pathological characteristics of 5 thin (<1 mm Breslow thickness) and 5 thick (>4 mm Breslow thickness) in primary cutaneous melanomas. The authors found that the number of point mutations in thin and thick melanomas is similar suggesting they occur early during tumour development. On the contrary, the high frequency of somatic copy losses and gains in thick melanomas but not in thin melanomas suggests an association between somatic copy number alterations and tumour progression.

Comment: Previous genomic studies in melanoma have focused on advanced primary or metastatic melanomas. This may be the first genomic study that could detect interesting data for early stages of the disease and in particular thin melanomas but the small sample impairs solid conclusions. Further large studies are also required to establish whether higher frequencies of somatic copy number alterations in thick tumours are a result or a driver of progression.

Reference: Oncotarget 2016 Apr 15
Abstract

An assessment of clinical pathways and missed opportunities for the diagnosis of nodular melanoma versus superficial spreading melanoma

Authors: Cicchiello M, et al

Summary: Pathways to diagnosis were assessed using a retrospective questionnaire of 120 patients from the Victorian Melanoma Service. The study cohort consisted of 60 nodular melanoma (NM) patients, age and sex matched to 60 superficial spreading melanoma (SSM) patients. The authors found significant differences in opportunities missed to make a diagnosis of NM compared to SSM, with 43% of NM biopsied at a first encounter compared to 70% of SSM. All SSM were diagnosed within three reviews, whereas 33% of NM required at least three and up six reviews until biopsy. Patients with NM were more likely than those with SSM to be reassured that their lesions were benign. They concluded there were no significant differences in terms of time delay to diagnosis between NM and SSM.

Comment: The authors report that NM accounts for 14% of all melanomas diagnosed in Victoria and contributes 43% of melanoma-related deaths because of its high vertical growth. Therefore, NM needs to be recognised and treated quicker than the superficial spreading types.

Although in this study the overall delay to diagnosis was comparable for both NM and SSM, it seems that the patient needed to convince their doctors to biopsy (not the other way around) with multiple visits necessary in a majority of cases and 50% of doctor reassuring wrongly the patient at the first visit.

The big message is that monitoring is not appropriate for raised lesions and that the biopsy threshold should be very low. Of note, 56 out of 60 NM randomly identified from the Victorian Melanoma Service database were amelanotic. It is also a major message that amelanotic melanomas are more difficult to assess and a low threshold to biopsy is definitely applicable. Physicians must be aware of these killing-types of melanoma that are not displaying the classic abc features.

Reference: Australas J Dermatol 2016 May;57(2):97-101
Abstract

Ten-year survival after multiple invasive melanomas is worse than after a single melanoma: A population-based study

Authors: Youlden DR, et al

Summary: Of 32,238 melanoma patients included in the study, 29,908 (93%) had a single invasive melanoma, 2,075 (6%) had two, and 255 (1%) had three. The team reported 10-year cause-specific survival for these three groups was 89%, 83%, and 67%, respectively. The hazard ratio of death within 10 years from melanoma was two times higher for those with two melanomas (hazard ratio = 2.01, 95% CI = 1.57-2.59; P < 0.001) and nearly three times higher when three melanomas were diagnosed (hazard ratio = 2.91, 95% CI = 1.64-5.18; P < 0.001) compared with people with a single melanoma, after adjustment for key prognostic factors. The team noted melanoma-specific mortality remained elevated after adjusting for maximum thickness or ulceration of any melanoma regardless of the index tumour.

Comment: Patients with a history of melanoma are most likely to develop a second primary melanoma during the 3 months following the diagnosis of the first one. This large cohort study identified cases from the Queensland Cancer Registry of invasive melanoma diagnosed between 1995 and 2008 and confirms poorer prognosis in patients with multiple melanomas compared to those with a single melanoma. These findings must influence management of patients with a history of melanoma and even more for those with multiple melanomas. The American Joint Committee on Cancer has adopted a pragmatic approach regarding prognostic criteria for patients with more than one melanoma, with their guidelines focusing solely on the most “severe” tumour but this study shows that the number of melanomas diagnosed also needs to be considered. This study is one of the first demonstrating clear adverse outcomes (maybe because of statistical method and high number of events). Of course cancer registry does not allow all risk factors to be recorded (family history…) nor death association with the diagnosis to be totally accurate but these findings may influence the prognosis of 7% of the melanoma patients in Australia and needs to be disseminated. It is common knowledge that high-risk patients need to have more regular follow up but the number and type of imageries is debated. Moreover, the possibilities of new adjuvant therapies make these data even more relevant.

Reference: J Invest Dermatol 2016 Mar 24
Abstract

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