Melanoma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

CHNM = cutaneous head and neck melanomas; **LM** = lentigo maligna; **MIS** = melanoma in situ; **RCM** = reflectance confocal microscopy; **SN** = sentinel node; **SNB** = sentinel-node biopsy; **SSE** = structured skin self-examination.

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Welcome to the 12th issue of Melanoma Research Review.

A number of articles in this issue have a focus on melanoma screening. A randomised clinical trial reported structured skin self-examination intervention for patients with melanoma and their partners may enhance early detection and relieve some of the burden on health services. A French nationwide survey reviewed the opinions and use of dermoscopy and reported it was a useful tool for GPs in melanoma screening. Another study reported reflectance confocal microscopy was a valid method of identifying malignant skin tumours accurately. Findings from a large-scale melanoma screening program conducted in Pennsylvania indicate increased melanoma diagnoses but little impact on skin surgeries or dermatology visits. This study had limitations and highlights the need for robust randomised controlled trials for melanoma screening.

We conclude this issue with a large study investigating racial disparities in melanoma survival. The study was conducted over 17 years and included approximately 97 000 cutaneous melanoma patients. The authors concluded that despite higher incidence of cutaneous melanoma in whites, overall survival for cutaneous melanoma in non-whites was significantly lower. This highlights the need for melanoma screening and awareness in non-white populations. This is particularly relevant in Australia given the multiple ethnicities.

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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Downstream consequences of melanoma screening in a community practice setting: First results

Authors: Weinstock MA, et al

Summary: This population-based screening program conducted in Pennsylvania aimed to quantify the potential harms associated with melanoma screening. General practitioners were trained to detect early melanoma using the INFORMED (INternet course FOR Melanoma Early Detection) program. Data from the first 8 months were analysed, showing a rise in melanoma diagnosis but no increase of skin surgeries, visits to dermatologists or distress. Limitations of this study are not being a randomised trial and the modest number of participating practitioners, as only 101 (26%) completed the training. Moreover they don't specify the duration or content of the online training.

Comment: Several studies have shown an increase of melanoma diagnosis during screening campaigns, however failed to demonstrate a reduction in melanoma mortality over the years. A pilot study in a German region in 2003-4 showed promising benefits with a decrease in mortality (Breitbart EW et al, J Am Acad Dermatol. 2012), but this was not reproduced in a national skin cancer screening program conducted for 5 years since 2008 (Katalinic A et al, Dtsch Arztebl Int. 2015). The latter being less intensive than the pilot project, which could explain this change. There is currently no high-quality evidence from randomised controlled trials on skin cancer or melanoma screening, however this study shows that at least screening is not harmful for patients.

Reference: Cancer 2016 Oct 15;122(20):3152-3156

Abstract

Early detection of new melanomas by patients with melanoma and their partners using a structured skin self-examination skills training intervention: A randomized clinical trial

Authors: Robinson JK, et al

Summary: This study evaluated the effect of a structured skin self-examination (SSE) intervention for patients with melanoma and their partners. Patients (n=494) with stage 0 to IIB melanoma and their skin-check partners were randomly assigned to receive skills training intervention or customary care. Patients in the intervention arms had significantly increased SSEs with their partners at 4, 12, and 24 months compared with the control group. Patients in the intervention arm identified new melanomas more than those in the control group and did not increase physician visits.

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Comment: About 10% of patients with melanoma will develop a second melanoma. This percentage increases to almost 20% in patients with genetic mutations for a period within 5 years after diagnosis. Therefore patients with melanoma need periodic skin-checks for life. It is known that when a melanoma is invasive, it may invade from 0.12 to 0.5 mm per month (Liu W et al, Arch Dermatol. 2006), thus between yearly physician reviews a melanoma may invade several millimetres. Some studies in melanoma patients have shown that about 1/3 of new melanomas and/or recurrences are self-detected by the patient. Therefore patients and their partners receiving training in skin check skills may enhance melanoma early detection, which may be beneficial in order to reduce physician follow-up visits in low-risk melanoma patients (stage 0 to 2B) and improve prognosis if melanomas are detected earlier. A challenge to overcome is patients often forget or are unreliable. Also if a concerning lesion is detected by the patients, they should have short-term access to a dermatology appointment. The use of total body photography, now recommended in the Australian & New Zealand guidelines for the management of melanoma in high-risk patients, adds to the "evolving" criteria of the ABCD, allowing the patients to detect a change over time in lesions that have no clinical features of melanoma.

Reference: JAMA Dermatol 2016 Sep 1;152(9):979-85

Abstract

Dermoscopy, a useful tool for general practitioners in melanoma screening: A nationwide survey

Authors: Chappuis P, et al

Summary: To review the opinions and use of dermoscopy these researchers sent a questionnaire about the demographic characteristics, skin examination modalities and use and training in dermoscopy to 4057 GPs in four large regions of France. In total, 425 questionnaires were completed. Only 8% of respondents had access to a dermoscope. The researchers reported dermoscopy increased self-confidence in analysing pigmented lesions (P = 0·004), and dermoscopy users referred fewer patients to dermatologists. They also noted the number of biopsies was reduced in the dermoscopy users group (P = 0·004).

Comment: Australian guidelines recommend the use of dermoscopy with a grade A evidence, however in most European countries, such as France, it is not widely used by general practitioners. This survey carried out in France showed that less than 10% of GPs had access to a dermoscope, but the ones who used it had increased confidence in analysing pigmented lesions and reduced the number of referrals to dermatologists. The main disadvantage was the need for training, which besides online courses and lectures may require a short formal training/rotation with an expert dermoscopist to learn from real cases on a daily basis.

These findings together with several meta-analyses show that dermoscopy increases the diagnosis of melanoma by 15 times, increases sensitivity by 18% and reduces the number of lesions needed to excise compared to the naked eye evaluation. This should encourage every physician to use dermoscopy when performing a skin check (Grade A recommendation in Australian guidelines), and if dermoscopy is not available or there is a lack of training, patients should be referred to a trained physician or dermatologist. The next step now in Australia is for primary care to use dermoscopy monitoring, as there is mounting evidence that it can help detect featureless melanoma and avoid unnecessary excisions and referrals.

Reference: Br J Dermatol 2016 Oct;175(4):744-50
Abstract

Who detects melanoma? Impact of detection patterns on characteristics and prognosis of patients with melanoma

Authors: Avilés-Izquierdo JA, et al

Summary: The retrospective study of 783 primary melanomas conducted at a single institution in Madrid, Spain found that approximately half of the melanomas diagnosed were self-detected, which is consistent with previous reports. These melanomas were thicker, more frequently ulcerated and with worst prognosis than the ones detected by dermatologists, which were usually (80%) incidental findings.

Comment: As mentioned in two previous article comments, population education and skin cancer awareness campaigns may be useful, especially targeting elderly males, who consult less and later to dermatologists and have the worst prognosis. Besides education campaigns, defining the target population to implement national skin-check screening seems the logical thing to do towards improving melanoma survival. Of note, the statistics of this population are quite alarming, with a high proportion of first presentation as bleeding (17%), deep melanoma (23%) and at metastatic stage (18%).

Reference: J Am Acad Dermatol 2016 Nov;75(5):967-974
Abstract

Risk of second primary malignancies among 1537 melanoma patients and risk of second primary melanoma among 52 354 cancer patients in Northern Italy

Authors: Caini S, et al

Summary: This group evaluated the risk of developing a second primary cancer among 1537 melanoma patients, and the risk of second primary melanoma in 52 354 extracutaneous cancer patients. They reported 76 second primary cancers were diagnosed during a median follow-up of 4 years, of which 49 (64%) were during the first 2 years after melanoma diagnosis. They noted the standardised incidence ratio was increased for cancer of breast (4.10, 95% CI 2.79-6.03), thyroid (4.67, 95% CI 1.94-11.22), brain (6.13, 95% CI 2.30-16.33) and for non-Hodgkin lymphoma (3.12, 95% CI 1.30-7.50). During a median follow-up of 4 years, 127 second primary melanomas were diagnosed, with thick lesions being less frequent than for melanoma diagnosed as first cancer. The standardised incidence ratio was increased for cancer of breast (5.13, 95%CI 3.91-6.73), thyroid (16.2, 95%CI: 5.22-50.2), head and neck (5.62, 95%CI 1.41-22.50), soft tissue (8.68, 95%CI 2.17-34.70), cervix (12.5, 95% CI 3.14-50.20), kidney (3.19, 95%CI 1.52-6.68), prostate (4.36, 95%CI 2.63-7.24) and acute myeloid leukaemia (6.44, 95%CI 2.42-17.20).

Comment: Similar to a previous meta-analysis (Caini S et al, J Dermatol Sci. 2014), this study shows that melanoma patients are at increased risk of developing a second primary malignancy. Risk of cancer was increased for brain, breast, thyroid and non-Hodgkin lymphoma. These findings may be explained by common genetic predispositions and clustering of some exposures, which are risk factors for different tumours. With the introduction of new targeted therapies and immunotherapies for metastatic melanoma, future studies will be needed to assess if these therapies modify the risk of second malignancies. The study also shows that patients with first primary non-cutaneous cancer had an increased risk of developing a melanoma (0.24% at 4 years follow up). Interestingly in these patients, when a primary melanoma was diagnosed, it was thinner (more frequent Breslow <1mm) than among melanoma diagnosed as first primary malignancy. This could be related to increased awareness of these patients and also to regular follow up with practitioners.

Reference: J Eur Acad Dermatol Venereol 2016 Sep;30(9):1491-6
Abstract

Effects of time interval between primary melanoma excision and sentinel node biopsy on positivity rate and survival

Authors: Oude Ophuis CM, et al

Summary: This retrospective observational study investigated the role of time interval between melanoma diagnosis and sentinel node biopsy (SNB) on sentinel node (SN) positivity and survival. The authors concluded no effect of time interval between melanoma diagnosis and SNB on 5-year survival or SN positivity rate was found for a time interval of up to 3 months.

Comment: Previous studies (Tejera-Vaquerizo A et al, Eur J Cancer. 2015) suggest that the interval of time between primary cutaneous melanoma excision and SNB had prognostic significance. The present study analysed 4124 patients in the database of the EORTC Melanoma Group who underwent SNB, observing that the positivity of the SN is not related to the time interval between first melanoma surgery and SNB. Moreover they found that a delay in SNB (>43 days) is not an independent prognostic factor on 5-year melanoma-specific survival. These findings are in slight disagreement with the results of Tejera-Vaquerizo A et al, who found that a delay time of ≤ 40 days between the excision of the primary melanoma and the SNB was an independent factor associated with worse melanoma-specific survival (hazard ratio 1.7 [CI, 1.2-2.5]), specifically in those with a negative SNB. A delay time of > 40 days was associated with better 5-year melanoma-specific survival (89.5% vs 82%, P=0.0002). No differences were found between the rate of false-negative SN in the two groups (21.3% vs 18.1%). It has been hypothesised that the immunosuppressive effect of the melanoma on the SN would disappear following excision of the primary tumour, allowing development of an anti-tumour immune response over the following weeks. The early excision of the SN would prevent this response, being prejudicial for patients. Further studies are needed in order to confirm if an early SNB decreases melanoma-specific survival, but taking into account all published studies, what is clear is that a delay in the SNB does not worsen the prognosis, therefore the performance of SNB shouldn't cause any time pressures and can be organised in up to 3 months since the primary excision.

Reference: Eur J Cancer 2016 Nov;67:164-173
Abstract

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Independent Commentary by Dr Helena Collgros and Associate Professor Pascale Guitera.

Dr Helena Collgros (MD) completed her Dermatology and Venereology specialisation in Barcelona in 2014. Afterwards she worked as a dermatologist in the public university hospital *Germans Trias i Pujol* in Barcelona (2014-2016). Her fields of expertise and research interests include pigmented lesions, melanoma, skin cancer and imaging techniques. She is currently working in the Sydney Melanoma Diagnostic Centre at the Royal Prince Alfred Hospital in Sydney, covering an Area of Need Position attending patients at high risk for developing melanoma and skin cancer.

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

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.

The use of Mohs micrographic surgery (MMS) for melanoma in situ (MIS) of the trunk and proximal extremities

Authors: Stigall LE, et al

Summary: This single-institution, retrospective study sought to evaluate Mohs micrographic surgery for MIS of the trunk and proximal extremities, and determine adequate excision margins for MIS when total margin evaluation is not used. Of the 882 cases one local recurrence occurred (0.1%). Only 83% of MIS were excised with a 6 mm margin. Margins of 9 mm were needed to excise 97% of MIS.

Comment: This study doesn't aim to use Mohs surgery to treat MIS, but to use this technique to evaluate which are the adequate excision margins for MIS. The study highlights what others (Kunishige JH et al, J Am Acad Dermatol. 2012) have already suggested: margins of 9 mm are needed to excise 97-99% of in situ melanomas, while the 6 mm margins only achieve clear margins in 83-86% of them. Both studies, including a sum of 2002 MIS (882 + 1120), concluded that a 5 mm margin for MIS is inadequate, however they don't take into account that usually excision of the primary melanoma is performed with a 2 mm margin and afterwards a wide excision of 5 mm is conducted (the total sum of both excisions result in a 7 mm margin approx.), which may increase the percentage of clear margins identified as 6mm. Moreover, in Kunishige's study 53% of MIS were located on the face, and therefore lentigo maligna (LM) subtype were likely to account for a notorious percentage of melanomas. LM is well known to have a wider extension beyond pigment seen using dermoscopy and usually margins > 5 mm are needed. The current study only analysed MIS located on non-chronic sun-exposed areas, so although the subtype of melanoma is not revealed in the study, we shouldn't expect a high percentage of LM. In 2011, based on these and other studies, the American Academy of Dermatology guidelines changed their recommendation from 5 mm to 5-10 mm margin. The Australian guidelines still include a 5 mm wide excision for MIS with a grade-C recommendation - of note this is clinical margins, not pathological. In light of the recent studies maybe we should consider to extend the margin recommendation to 5-10 mm, however further randomised trials or meta-analysis are needed to provide sufficient evidence at this respect.

Reference: J Am Acad Dermatol 2016 Nov;75(5):1015-1021
Abstract

A meta-analysis of reflectance confocal microscopy for the diagnosis of malignant skin tumours

Authors: Xiong YD, et al

Summary: This meta-analysis assessing the accuracy of reflectance confocal microscopy (RCM) for the diagnosis of malignant skin tumours included a total of 21 studies involving 3108 patients with a total of 3602 lesions. The pooled results for sensitivity and specificity were 93.6% (95% CI: 0.92-0.95) and 82.7% (95% CI: 0.81-0.84) respectively. Positive likelihood ratio and negative likelihood ratio were 5.84 (95% CI: 4.27-7.98) and 0.08 (95% CI: 0.07-0.10) respectively. Subgroup analysis showed that RCM had a sensitivity of 92.7% (95% CI: 0.90-0.95) and a specificity of 78.3% (95% CI: 0.76-0.81) for detecting melanoma and for detecting basal cell carcinoma were 91.7% (95% CI: 0.87-0.95) and 91.3% (95% CI: 0.94-0.96) respectively.

Comment: Routine diagnosis of skin tumours includes clinical and dermoscopic evaluation and it is confirmed by histopathologic examination. However there is an increased demand of non-invasive techniques to avoid biopsies, especially for lesions located in cosmetic sensitive areas. In the last years, several techniques that enable non-invasive and real-time diagnosis have been developed, such as RCM and optical coherence tomography. RCM is already widely used for pigmented lesions, melanoma and non-melanoma skin cancer, not only for diagnostic purposes, but also to monitor treatment response and to delineate lesions' margins avoiding repeated excisions because of positive margins. This meta-analysis complements the previous published one, which included only melanoma detection in clinical equivocal lesions. 21 studies were selected, involving 3602 lesions. The accuracy of RCM varied for each diagnosis, but overall sensitivity and specificity were very high. RCM diagnostic features are reproducible and diagnostic algorithms are used, however proper training is needed, as it has been reported that the observers' experience may influence in their diagnostic accuracy (Rao BK et al, J Am Acad Dermatol. 2013). Although RCM increases sensitivity and specificity of dermoscopy, RCM is not meant to be used as a screening technique for all skin cancers; it is directed to a lesion of concern with no clear diagnosis under dermoscopy. When both techniques are combined in clinical practice, the number needed to treat to detect a melanoma decreases.

Reference: J Eur Acad Dermatol Venereol 2016 Aug;30(8):1295-302
Abstract

Cutaneous head and neck melanoma (CHNM): A population-based study of the prognostic impact of tumor location

Authors: Helsing P, et al

Summary: These researchers studied 1074 cutaneous head and neck melanomas (CHNM) from 8120 cases of cutaneous melanomas. They reported CHNM were more frequently found in men, more often nodular and LM cutaneous melanomas, and diagnosed at higher T stage compared with cutaneous trunk and extremity melanoma. CHNM located on posterior sites were diagnosed at significantly higher T stage, and were more often diagnosed with ulceration and at more advanced stage compared with CHNM located on anterior sites.

Comment: When we think about melanoma located on the head and neck we mainly think about LM, but actually 1/3 of the melanomas in these locations are nodular and 1/3 superficial spreading melanomas. This study with data from a national cancer registry in Norway, including over 1000 invasive CHNM shows similar results to other larger US studies (Tseng WH et al, J Surg Res. 2011). Because melanomas located on the hairy scalp and posterior sites are difficult to see, the diagnosis tends to be done late when they become raised (invasive) or bleed (ulcerated); therefore they have a worse prognosis. When diagnosed, the clinical stage was local in 91.7% of cases, regional in 6% and metastatic in 2.3%. Five years after diagnosis, the estimated risk of dying due to the melanoma was 12.5%. However, T stage and clinical stage were the only significant prognostic factors, whereas tumour location showed no significant effect. Posterior site location was associated with higher T stage, but >70% of the lethal CHNM were located on anterior sites and >60% were nodular. Therefore we can speculate that these melanomas grow and metastasise faster, thus should be managed promptly. As mentioned in a previous research review, melanoma detection campaigns addressed to hairdressers could aid the detection of these lesions at earlier stages.

Reference: J Am Acad Dermatol 2016 Nov;75(5):975-982.e2
Abstract

Racial disparities in melanoma survival

Authors: Dawes SM, et al

Summary: This large study over the span of 17 years included a 97 000 cutaneous melanoma patients, finding that overall survival in non-whites was significantly lower, despite the incidence being greater in whites (45.8/100.000), followed by Hispanics (6.8), Asians (5.72) and blacks (1.35). Melanomas in non-whites occurred at higher frequencies in regions not sun-exposed (trunk, lower legs) and atypical locations (palms, soles, nail and mucosa). Melanomas in non-whites were diagnosed in later stages (76% of white patients diagnosed at stage I vs 53% of black patients), mostly because a lack of awareness by the patients themselves but also by the physicians attending them.

Comment: The results of this study should put us on alert to screen and inform these patients, also as we'd expect to find more of these cases in the future, given the multiple ethnicities in Australia/NZ. Interestingly, overall survival stratified by stage showed a significant difference between white and black patients diagnosed at stages I and III, and also between whites and non-whites at stages I-II. Stages IV displayed no significant differences. There are multiple explanations for these findings. It may indicate that melanomas in non-whites are more aggressive or that there is a difference in secondary prevention (less screening or diagnosis difficulty because different presentations) or follow up of early stages melanomas, between white/non-white patients. Maybe white patients are more aware of melanoma and therefore seek earlier medical consultation, while non-whites have a misconceived notion that they are not at risk for melanoma. Also socioeconomic and insurance status could influence the access to medical care.

Reference: J Am Acad Dermatol 2016 Nov;75(5):983-991
Abstract

