Dermatology RESEARCH REVIEW™

Making Education Easy

Issue 1 – 2019

In this issue:

Abbreviations used in this issue

MEK = mitogen-activated protein kinase kinase enzyme
PASI = Psoriasis Area and Severity Index

Welcome to the latest issue of Dermatology Research Review.

This issue features a range of studies concerning melanoma: reproductive factors and risk of melanoma, substandard shave biopsy outcomes, long-term overall and specific melanoma survival for primary cutaneous melanoma thicker than 2mm treated by 2cm versus 4cm surgical margin, a lack of survival advantage from lymphadenectomy in melanoma patients with positive sentinel node, and superior 5-year outcomes from dabrafenib plus trametinib for metastatic melanoma. In other areas, calcineurin inhibitor therapy brings hope to vitiligo patients, phototherapy has superior effects in psoriasis, conjunctivitis may or may not be associated with dupilumab therapy, and varicose vein laser ablation therapy improves quality of life outcomes for better perceived financial value than traditional surgical treatments.

We hope that you find these articles of academic or relevant clinical interest and welcome any feedback you may have.

Kind regards,

Dr Louise Reiche
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Reproductive factors and risk of melanoma: a population-based cohort study

Authors: Støer N et al.

Summary: This analysis of the Norwegian Women and Cancer cohort study evaluated the association between reproductive factors and risk of cutaneous melanoma. 165,712 women aged 30–75 years at inclusion were followed from 1991–2007 to December 2015. During a median follow-up of 18 years, 1347 cases of cutaneous melanoma were identified. No reproductive factors were clearly associated with cutaneous melanoma risk.

Comment: Melanoma arising in pregnancy is associated with more aggressive disease progression, raising the question of hormone influence. This Norwegian population-based cohort study examined detailed aspects of reproductive life hormonal variations (menarche age, menstrual cycle length, parity, and age at first and last birth, menopausal status, and breastfeeding duration to estimate length of ovulatory life) and cutaneous melanoma risk. No reproductive factors were clearly associated with risk in 1347 cases of cutaneous melanoma.

Reference: Br J Dermatol 2019;181(2):282-9
Abstract

The increasing use of shave biopsy for diagnosing invasive melanoma in Australia

Authors: de Menezes S et al.

Summary: This study evaluated changes over time in the choice of skin biopsy techniques for assessing invasive melanoma in Australia. Victorian Cancer Registry data were analysed for patients diagnosed with invasive melanoma in 2005, 2010, and 2015. 400 patients were randomly selected from each of the 3 years, and stratified according to final tumour thickness: thin melanoma (<1.0mm), intermediate melanoma (1.0–4.0mm) and thick melanoma (>4.0mm). 833 excisional and 337 partial diagnostic biopsies were undertaken. The proportion of partial biopsies increased from 20% of patients in 2005 to 36% in 2015, and the proportion of shave biopsies increased from 9% in 2005 to 20% in 2015. 54% of shave biopsies transected the tumour base; residual melanoma was subsequently detected in 66% of these cases using wide local excision. With base-transected shave biopsies, tumour thickness was underestimated by a mean 2.36mm for thick, 0.48mm for intermediate, and 0.07mm for thin melanomas.

Comment: Shave biopsies are quicker to perform than excision biopsies and thus are cheaper procedures. This may account for the growing use of this procedure in Victoria, Australia. However, it comes at a dangerous cost of underestimating tumour thickness and staging, and thus is NOT the recommended procedure for diagnosing invasive melanoma: excision biopsies are.

Reference: Med J Aust 2019;211(5):213-8
Abstract

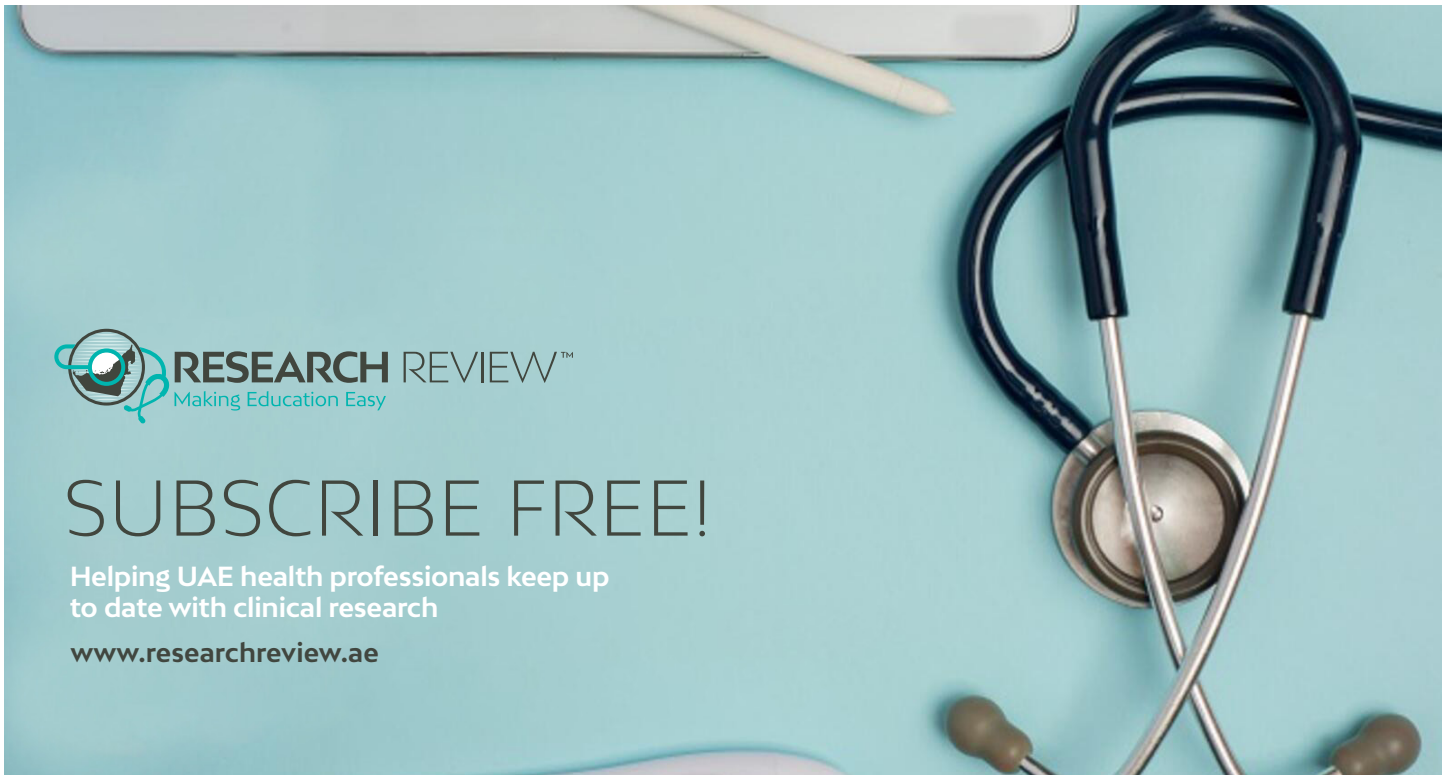
2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm

Authors: Utjés D et al.

Summary: This multicentre study compared long-term outcomes after 2cm versus 4cm surgical excision margins for thick primary cutaneous melanoma (>2mm). 936 patients aged ≤75 years from 53 hospitals in Sweden, Denmark, Estonia, and Norway with localised cutaneous melanoma >2mm and with primary site on the trunk or upper or lower extremities were randomised to treatment with either a 2cm or a 4cm excision margin. 304 deaths (49%) were reported in the 2cm group and 317 (51%) in the 4cm group during a median follow-up of 19.6 years (p=NS). 48% of deaths in the 2cm excision margin group and 52% in the 4cm excision margin group were attributed to cutaneous melanoma (p=NS).

Comment: A median follow-up of nearly 20 years in close to 1000 patients who have had thick (>2mm) melanomas excised with either a 2cm or 4cm margin is an extremely useful study for clinicians and academics alike. The finding that 42% of deaths were attributable to melanoma in this whole group, but with no significant difference between those who underwent a 2cm versus 4cm clearance provides evidence that 2cm of clearance is amply sufficient and provides a morbidity limit for patients.

Reference: Lancet 2019;394(10197):471-7
Abstract



Cost and resource implications of introducing intensive nodal surveillance for sentinel node positive melanoma in provincial New Zealand

Authors: Winstanley J et al.

Summary: This NZ study compared the cost and resource implications of immediate completion lymphadenectomy versus intensive nodal surveillance for patients with sentinel node positive melanoma. 294 consecutive patients with a diagnosis of primary cutaneous melanoma and melanoma in situ who presented to Northland District Health Board in 2012–2015 were included. The financial and resource burdens (including operative, outpatient and imaging interventions) of standard lymphadenectomy were calculated, as were the costs associated with intensive nodal observation for a theoretically equivalent cohort. The cost of standard lymphadenectomy treatment was $NZ7147 per patient and the theoretical cost of nodal observation was $NZ5300 per patient. Standard treatment required more operating theatre time and inpatient treatment, whereas nodal observation required more outpatient appointments and imaging.

Comment: Sentinel node biopsies on patients with melanoma help to stage their disease but do not provide survival advantage. This 3-year NZ study goes further, following patients with sentinel node positive melanoma and compares the cost and outcomes of those treated by immediate complete lymphadenectomy with those followed by intensive nodal surveillance. It found there was no long-term survival or cost benefit for surgery, and this is without cost analyses of post-lymphadenectomy morbidity. Such studies are enormously helpful in guiding evidence-based optimal clinical practice and resource allocation within limited health dollars.

Reference: NZ Med J 2019;132(1499):43-8
Abstract

Independent commentary by Dr Louise Reiche MBChB (Otago) FRACP MD FNZDSI

Dr Louise Reiche is a New Zealand physician trained vocational specialist dermatologist. Louise runs general dermatology clinics within integrated family health care: Kauri HealthCare, Palmerston North. She has additional special interests in eczema, patch testing, skin cancer surveillance and preventative dermatology health. Louise is an active executive member of the NZ Dermatological Society, Founder and Chairperson for the NZ Dermatology Research Trust, Clinical advisor for Melanoma NZ, and member of Melnet NZ, and works alongside these groups and on behalf of the NZ Dermatological Society with Cancer Society NZ and other relevant bodies in the interest of New Zealander skin health.

Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma

Authors: Robert C et al.

Summary: This study analysed data from the COMBI-d and COMBI-v trials to determine 5-year survival rates associated with first-line BRAF inhibitor + MEK inhibitor therapy in patients with metastatic melanoma. The 2 trials included previously untreated patients who were randomised to receive the BRAF inhibitor dabrafenib (150mg twice daily) plus the MEK inhibitor trametinib (2mg once daily), or placebo. A total of 563 patients received dabrafenib + trametinib. Analysis of data from the 2 trials showed that progression-free survival rates were 21% at 4 years and 19% at 5 years. Overall survival rates were 37% at 4 years and 34% at 5 years. Multivariate analysis revealed that several baseline factors (performance status, age, sex, number of organ sites with metastasis, and lactate dehydrogenase level) were associated with both progression-free survival and overall survival. 19% of patients had a complete response; these patients had an overall survival rate of 71% at 5 years.

Comment: Prevention, followed by early detection and surgical excision of melanoma remain the primary public health goals for melanoma. Permanent cure for those whose tumours are elusive or more aggressive is an area of active research and cost burden for health funders and taxpayers. Single mutation inhibitors typically generate short- term response so combining inhibitors that act in different parts of the tumour progression pathway is attractive, for synergistic and longer response rates, as shown in this study combining dabrafenib and trametinib (BRAF and MEK inhibitors). Progression-free survival rates were 21% at 4 years and 19% at 5 years. A complete response rate was seen in 19%, with an overall survival rate of 71% at 5 years in these patients. Prognosis for patients with unresectable or metastatic melanoma has changed considerably in the last 5–10 years. We look forward to yet further progress over the coming decade.

Reference: N Engl J Med 2019;381:626-36
Abstract

Treatment outcomes of topical calcineurin inhibitor therapy for patients with vitiligo

Authors: Lee J et al.

Summary: This systematic review and meta-analysis estimated treatment responses to topical calcineurin inhibitors (TCI) alone or in combination with phototherapy in patients with vitiligo. A search of MEDLINE, Embase, Web of Science and Cochrane Library databases identified 46 studies (n=1499) that were suitable for inclusion. After a median 3 months' treatment with TCI monotherapy, 55% of patients had a mild response or better, 38.5% had a moderate response or better, and 18.1% had a marked response. In subgroup analyses, face and neck lesions showed a mild response or better response to TCI in 73.1% of patients, and a marked response in 35.4% of patients. 89.5% of patients had a mild response or better to TCI plus phototherapy, and 47.5% had a marked response.

Comment: Vitiligo (cutaneous depigmentation) causes significant morbidity in visible anatomic sites in darker pigmented skins. In many cultures it is associated with stigma and alienating taboos. It may be associated with other autoimmune diseases, have a familial predisposition or be triggered by drug therapy, particularly melanoma immunotherapies. Prognosis is variable and poorer in those with acral involvement and more extensive disease. Prolonged treatment courses are often required with attendant short- and long-term adverse effects. This systematic review and meta-analysis shows encouraging benefit from the use of TCI: at least mild response in 55%, moderate in 39% and marked in 20%. Combined with phototherapy, even better results are achieved: at least mild response in 90% and marked response in 48% of patients. Prolonged TCI use is not associated with cutaneous atrophy, a risk seen with lengthy use of corticosteroids in vitiligo. In addition to eczema, vitiligo is another disease for which improved access to TCIs is desirable in NZ, where they are currently not funded.

Reference: JAMA Dermatol 2019; published online May 29
Abstract

Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent)

Authors: Reich K et al.

Summary: The multicentre phase 3 IMMvent study compared the efficacy and safety of risankizumab and adalimumab in patients with moderate to severe plaque psoriasis. 605 patients aged ≥18 years were randomised to receive risankizumab or adalimumab in a double-blind design. For weeks 0–16 (part A), subcutaneous risankizumab 150mg was administered at weeks 0 and 4, or subcutaneous adalimumab was administered as an 80mg dose at week 0, a 40mg dose at week 1, then a 40mg dose every 2 weeks. For weeks 16–44 (part B), adalimumab intermediate responders were re-randomised to continue with open-label adalimumab 40mg or switch to risankizumab 150mg. At week 16, a 90% improvement from baseline PASI (PASI 90) was achieved in 72% of risankizumab recipients and 47% of adalimumab recipients ($p<0.0001$), and static Physician's Global Assessment scores of 0 or 1 were achieved in 84% and 60% of patients in the respective groups ($p<0.0001$). In part B, PASI 90 was achieved at week 44 in 66% of patients who switched to risankizumab and 21% of patients who continued with adalimumab ($p<0.0001$). Adverse events were reported in 56% of risankizumab recipients and 57% of adalimumab recipients in part A, and in 75% and 66% of patients in the respective groups in part B.

Comment: Most psoriasis sufferers desire normal skin and treatment that will work promptly, with minimal adverse effects. Physicians would love to help them fulfil this dream but hitherto would be cautious about promising such outcomes, particularly for patients with more severe disease with a track record of therapy recalcitrance. Achieving PASI 90 in 72% is progressing towards that dream. Having ongoing new, alternative agents available keeps hope alive for patients and doctors. In this study, risankizumab outperforms adalimumab in degree, speed and duration of response but at the cost of more reported adverse events. Time will judge whether patients deem that balance acceptable.

Reference: Lancet 2019;394(10198):576-86
Abstract

Patient-reported outcomes of adalimumab, phototherapy, and placebo in the Vascular Inflammation in Psoriasis trial

Authors: Noe M et al.

Summary: The multicentre VIP trial compared the effects of adalimumab and phototherapy on health-related quality of life in patients with psoriasis. 97 patients (mean age 43.5 years, median PASI score 16.7) were randomised to receive subcutaneous adalimumab (80mg at week 0, 40mg at week 1, then 40mg every 2 weeks), narrowband ultraviolet B phototherapy 3 times per week, or placebo injection for 12 weeks. Health-related quality of life was assessed every 4 weeks using the Dermatology Life Quality Index and EQ-5D-3L Index score. At week 12, patients being treated with adalimumab or phototherapy were more likely to achieve the minimal clinically important difference in the Dermatology Life Quality Index compared with placebo (odds ratio [OR], 2.88 and 8.83, respectively). Patients treated with phototherapy were more likely to achieve the minimal clinically important difference in EQ-5D-3L Index score compared with placebo (OR, 9.78) and adalimumab (OR, 4.07).

Comment: Over time, accepted research methodologies and ethical standards change. In the early days of phototherapy, quality of life assessments were not done. To adequately assess outcomes of traditional therapies compared to current and evolving therapies, it is useful to reassess these using modern and current methodologies as was undertaken in this randomised, controlled study of patient-reported outcomes of adalimumab, phototherapy and placebo in patients with a PASI score over 16. Phototherapy achieved better health-related quality of life improvements than adalimumab. This has practical implications for clinical practice, particularly in a resource-constrained environment.

Reference: J Am Acad Dermatol 2019;81(4):923-30
Abstract

Conjunctivitis in dupilumab clinical trials

Authors: Akinlade B et al.

Summary: Dupilumab blocks the shared receptor component for interleukin (IL)-4 and IL-13, and is approved in the US for patients aged ≥12 years with moderate to severe atopic dermatitis not controlled topically. This analysis of placebo-controlled trials of dupilumab in atopic dermatitis (n=2629), asthma (n=2876), chronic rhinosinusitis with nasal polyps (CRSwNP; n=60) and eosinophilic oesophagitis (EoE; n=47) investigated the incidence of conjunctivitis in patients taking dupilumab. In most atopic dermatitis trials, the incidence of conjunctivitis was higher in dupilumab recipients than placebo controls, and was higher in patients with more severe atopic dermatitis and those with a previous history of conjunctivitis. Most cases recovered or resolved during the treatment period; two patients permanently discontinued dupilumab due to conjunctivitis or keratitis. In asthma and CRSwNP trials, the incidence of conjunctivitis in dupilumab recipients was lower than that seen in atopic dermatitis trials; dupilumab did not increase the incidence compared with placebo. There were no reports of conjunctivitis in the EoE trial.

Comment: Conjunctivitis can be a troubling side effect from dupilumab, jeopardising therapy longevity for atopic dermatitis. What this study reveals is that atopic dermatitis, particularly severe disease, predisposes to conjunctivitis and patients who respond well to dupilumab achieve a reduced incidence of conjunctivitis. Preceding conjunctivitis therefore does not contraindicate the use of dupilumab. Future research will hopefully elucidate the pathogenesis of and optimal therapies for independent and treatment-induced conjunctivitis in atopic dermatitis.

Reference: Br J Dermatol 2019;181(3):459-73
Abstract

Five-year outcomes of a randomized trial of treatments for varicose veins

Authors: Brittenden J et al.

Summary: This study compared the long-term effectiveness of endovenous laser ablation, ultrasound-guided foam sclerotherapy, and surgery in patients with primary varicose veins. 798 patients at 11 centres in the UK were randomised to receive laser ablation, foam sclerotherapy, or surgery. Primary outcomes at 5 years were disease-specific quality of life and generic quality of life, as well as cost-effectiveness based on models of expected costs and quality-adjusted life-years (QALYs) gained. 75% of participants completed quality of life questionnaires. After adjustment for baseline scores and other covariates, scores on the Aberdeen Varicose Vein Questionnaire were significantly better among patients who underwent laser ablation or surgery than among those who underwent foam sclerotherapy. Generic quality of life measures did not differ between treatment groups. At a threshold willingness-to-pay ratio of £20,000 per QALY, 77.2% of the cost-effectiveness model iterations favoured laser ablation. In a two-way comparison between foam sclerotherapy and surgery, 54.5% of the model iterations favoured surgery.

Comment: Varicose veins per se have little impact on patient long-term survival. However, they adversely impact on quality of life for sufferers, and additional disfigurement (due to progressive sequelae from dependent hyperpigmentation and morbidity from eczema, lipodermatosclerosis, predisposition to allergy sensitisation, cellulitis, ulceration and skin cancers) certainly does. Weight loss, surgically correcting perforating vessels, and long-term compression hosiery are the mainstay therapies in these scenarios and, if undertaken early in the disease process, prevent the sequelae. Treatments to reduce primary varicose veins regrettably do not replace these (so are seldom funded publically) but do help improve quality of life regarding the unappealing appearance of varicose veins and are typically self-funded. This study reveals that the disease-specific quality of life 5 years after treatment was better after laser ablation or surgery than after foam sclerotherapy. Laser ablation proved to be the most attractive to willing payers.

Reference: N Engl J Med 2019;381:912-22
Abstract