Welcome to the third Annual Evidence Update (AEU) on Skin Cancer prepared jointly by NHS Evidence - cancer and NHS Evidence - skin disorders. It includes systematic reviews and guidance published since the last Annual Evidence Update in May 2009, clinical commentaries and an overview by Dr Abby Macbeth and Professor Hywel Williams.

**Aims and intended audience**
Welcome to our third NHS Evidence Annual Evidence Update on Skin Cancer, brought to you by the combined efforts of the teams from NHS Evidence - skin disorders and NHS Evidence - cancer. The aim of the Annual Evidence Update is a simple one—to search for, filter, organise and comment on important guidelines and systematic reviews published in the field of skin cancer since the 2009 Annual Evidence Update. Our emphasis on systematic reviews rather than single randomised controlled trials is deliberate—when done well, systematic reviews offer the best potential to summarise all available evidence in an unbiased way.

Our Annual Evidence Update is primarily intended for health care professionals. Many health professionals care for people with suspected and confirmed skin cancer—including general practitioners, dermatologists, specialist nurses, surgeons (dermatologic, plastic, maxillofacial, ophthalmic and general), and clinical and medical oncologists. A range of expert colleagues with different professional backgrounds from the UK and abroad have kindly contributed insightful commentaries on important new topics included in this Annual Evidence Update. So if in some way, you deal in some with people who have skin cancer, this Annual Evidence Update is for you.

As our information is freely available in the public domain, members of the public and patients may also find some of the information useful, but we do recommended that you try the resources in our patient information section first.

**Structure of the Annual Evidence Update on Skin Cancer**
The backbone of our Annual Evidence Update is the Results, our haul of new guidelines and systematic reviews on melanoma and non-melanoma skin cancer. Last year, we split these up into melanoma, squamous cell carcinoma and basal cell carcinoma separately, but because many of the systematic reviews included this year relate to all three skin cancers (eg on ultraviolet light exposure), we have used the following overarching headings this time: (i) guidelines, (ii) causes, risks and prevention (iii) assessment and diagnosis and (iv) treatment and management. In each of those sections, we have made it clear in the subheadings which main skin cancers are covered.

Over the last year, we found two new guidelines for melanoma and squamous cell carcinoma respectively, nine new systematic reviews dealing with causes, risks and prevention, four that deal with assessment and diagnosis, and twelve that deal with treatment and disease management that include things like surgery, chemotherapy and psychological support. Although most of the evidence is related to melanoma, a lot of new material on squamous cell carcinoma has appeared in this year’s Evidence Update, which is refreshing since it has been relatively under-researched.

Trying to work your way through all 25 new systematic reviews is challenging for a busy health care professional, so in order to help you make sense of the new information, we have provided you with our selection of expert commentaries, as already mentioned. This year, we have five excellent commentaries — one from Colin Morton on topical imiquimod and fluorouracil for basal and squamous cell skin cancer, one from Irene Peat on whether or not adjuvant radiotherapy reduces local recurrences in high risk cutaneous squamous cell carcinoma, and one by Jerry Marsden on surgery for melanoma. Kevin Bradley then comments on the role of positron emission tomography in the management of malignant melanoma and finally Mark Elwood reflects on the hot topics of sunbed use, skin cancer prevention and screening behaviours.
Since not all of the new evidence is covered within these commentaries, Abby Macbeth and one of us (HW) have provided a comprehensive overview for all the new material, trying to pick out those bits of the new evidence that might change everyday clinical practice. And if your time is very short, just take a look at the summary points at the end of the overview.

Feedback and thanks
We hope that you enjoy our Annual Evidence Update on Skin Cancer and that it will become a useful reference resource that you can bookmark for current and future clinical use. It’s been a lot of work putting it together, but also great fun, and we have learned a lot about how to serve our patients more effectively – that is what it is all about after all.
You may not agree with all of the opinions expressed by our commentators, and you are welcome to send feedback to us if you think the evidence presented has been misinterpreted. If we have missed any important systematic review evidence published in the last year do also let us know, so that this can be picked up in next year’s Annual Evidence Update.
We wish to thank all our expert contributors for their stimulating commentaries, and a special thanks to Abby Macbeth, a UK Dermatology Clinical Trials Network SpR Fellow, for her work on the overview. We also thank the two teams that put this substantial knowledge resource together for you: Naila Dracup, Rupa Chandarana and Amanda Briant from the NHS Evidence - cancer team, and Douglas Grindlay from NHS Evidence - skin disorders.

2010 Annual Evidence Update on Skin Cancer - Overview by Abby Macbeth and Hywel Williams

What’s new and what may change our practice?

by Abby Macbeth, Specialist Registrar in Dermatology, Norfolk and Norwich University Hospital, and Hywel Williams, Clinical Lead, NHS Evidence - skin disorders and Professor of Dermato-Epidemiology, University of Nottingham.

This article provides the busy clinician with a quick summary of the main clinical implications from the 25 systematic reviews and two guidelines published since the 2009 Annual Evidence Update on Skin Cancer. This year, we have discussed melanoma, squamous cell carcinoma and basal cell carcinoma alongside each other rather than in separate sections since many of the systematic reviews, especially those on causes and behaviour, relate to all three skin cancer types. We also split our overview into broad themes covering (i) guidelines, (ii) causes, risks and prevention, (iii) assessment and diagnosis, and finally (iv) treatment and management, although some of the reviews clearly span more than one category.

While we comment on important methodological flaws, this article is not a detailed critical appraisal of the quality of the published material. The entire focus is on drawing out important material that may be of interest to health care practitioners, whether this be information on the nature of skin cancer or evidence that may prompt a change in treatment. Some of the material is important enough to warrant separate short commentaries by invited experts which we encourage you to read alongside this commentary for greater perspective.

As always, our summary is very much a personal interpretation—please read the systematic reviews and guidelines presented in the Results section of the Annual Evidence Update for yourself if you are interested in exploring the evidence further, and come to your own conclusions. At the end of this article, we compile a summary of our personal views on actions or inactions for clinical practice based on our reading of the new evidence.

SECTION I: NEW GUIDELINES

Melanoma

Two important guidelines for skin cancer appeared in the last year. The first is the European
consensus-based interdisciplinary guidelines for the diagnosis and treatment of melanoma (Link to PubMed abstract), which involved the European Dermatology Forum, the European Association of Dermato-oncology and the European Organisation of Research and Treatment of Cancer (EORTC). The guideline is based on an English translation of an interdisciplinary melanoma guideline of the Dermatologic Cooperative Oncology Group from Germany, which was then elaborated upon by dermatologists in Europe involved in national melanoma guideline development. Then in a second round, selected EORTC experts commented on the document. The exact methodology of the guidance development process is not clear, nor is it clear how the recommendations on treatment were arrived at and how evidence was sought to inform the guidance.

The document covered many familiar themes including excision margins, prognosis and follow-up but also discussed in greater detail the role of sentinel lymph node biopsy (SLNB) and adjuvant therapy with interferon-alpha. The evidence for the role of SLNB in risk stratification was presented and the group stated that SLNB should be routinely offered as a staging procedure in patients with tumours more than 1mm in thickness by (or less in the case of ulceration) despite there being no clear resultant survival benefit. These two statements are somewhat contradictory. Due to increasing evidence of improved disease-free survival, the expert panel described the role of interferon-alpha as adjuvant therapy for stage II-III melanoma or those greater than or equal to 1.5mm Breslow thickness. However, the decision on whether to prescribe adjuvant therapy will remain in the hands of the clinician due to potential toxicity. The positioning of the European guideline for British health care practitioners is unclear. The authors explain that the guideline should not replace existing national guidelines, but that they instead should assist health care providers of these countries in defining local policies and standards of care, and to make progress towards a European consensus on the management of melanoma. The two aims sound somewhat contradictory. An update is planned in 2012.

Squamous cell carcinoma

The second guideline is the British Association of Dermatologists (BAD) multi-professional guidance on the management of primary cutaneous squamous cell carcinoma (SCC) (Link to full text, PDF). This guideline uses a more systematic approach than the EDF guidelines with clear links to the strength of evidence supporting various treatment recommendations. The content covered risk factors for SCC and made reference to the small but concerning number of case reports of SCC arising during, or being re-activated by, biologics therapy, in particular with etanercept. These data are currently based on case reports only. The expert panel also emphasised the need for a Cancer Clinical Nurse Specialist and for members of the multi-disciplinary team to be trained in advanced communication skills in order to explain fully the diagnosis of skin cancer. It is the section on prognosis which is rather crucial for SCC since risk of metastasis, and hence initial local treatment modality, depends a lot on whether the lesion is “high risk” or not. The authors emphasise that the majority of SCCs are low risk and are amenable to many forms of treatment, but it is essential to spot those significant proportion at higher risk that need to be managed by a multi-professional team. Key factors that determine increased risk of distant spread include site (especially ears, lips, in sites of injury), size (greater than 2cm at presentation), depth (greater than 4mm thick), histological type (poorly differentiated or desmoplastic types and those with perineural involvement), those on immunosuppressive drugs, and local recurrences.

The recommendations state that curettage and cautery and cryotherapy must only be performed on low-risk lesions by experienced practitioners, which most probably reflects current practice across specialist centres in the UK where these techniques are used very infrequently. Radiotherapy has been reserved for those with unresectable tumours. The emerging role of sentinel lymph node biopsy was also discussed, although the overall benefit of this practice is yet to be proven.

Overall the guidance is well written and emphasises the primacy of surgical treatment as the treatment of choice in most circumstances, with 4mm margins for lower risk well-defined lesions and 6mm margins for higher risk lesions. There is also appropriate emphasis on patient education for self-examination and also on training for health care professionals involved in caring for SCC patients. The main problem with the guidance is the lack of a reliable evidence base on which to inform best practice. As the Cochrane systematic review on this topic (Link to full text) shows (discussed later), only one randomised controlled trial (RCT) has ever been published on this important form of cancer.
The lack of good evidence is a disgrace because all other observational studies are susceptible to significant biases such as a lack of a control group, selection bias, information bias and follow-up bias. Hopefully the recent Cochrane Review will stimulate a flush of new RCTs in this important area.

SECTION 2: CAUSES, RISK AND PREVENTION STUDIES

Who uses sunbeds?

A well-reported systematic review of 16 observational studies by Schneider and Kramer (Link to PubMed abstract) explored the specific social and biological characteristics of sunbed users. Worryingly one in ten young people under 18 use sunbeds, but the main users are women aged 17-30 with skin types III-IV. Sunbed users are also more likely to practice other high-risk behaviours, such as smoking, drinking and eating unhealthy foods. Having close friends or relatives who use sunbeds is also likely to encourage use. The review was perhaps limited by a relatively short search period (January 2000 to August 2008) and exclusion of any studies published in languages other than English or German.

Behaviours and attitudes towards skin cancer

Kasparian et al. (Link to PubMed abstract) were interested in the behaviours of general populations in relation to skin cancer risk who might be targeted for primary prevention or screening programmes. Their systematic review covered 91 articles published from 1980 to May 2008 with samples from the general population rather than those attending hospital. Those studies primarily addressing patients with skin cancer were excluded. They found that between 1-9% of the general population routinely use a combination of sunscreen, protective clothing, shade and timed sun avoidance. Predictors of sun protection use were sun-sensitive skin types, lower perceived barriers to sun protection, greater perceived risks of skin cancer, and female gender. Interestingly, in the general population there does not seem to be a correlation between previous skin cancer and sunscreen use. Self-monitoring appears also to be influenced by physician recommendation.

From this review it seems that sun-protection and self-monitoring practices vary considerably and these variations in data may in part be due to differing study design and recall bias. The review was a comprehensive and well-reported one, but somewhat limited since the authors only considered studies published in English, with the bulk of the data coming from Australia, New Zealand, USA and UK. Rates of sunscreen use and use of protective clothing varied considerably across studies (7-90% and 4-86% respectively) but due to the way the data were presented it is impossible to ascertain whether the variation was latitude or country dependant.

On a related theme, a well reported and interesting systematic review of 16 qualitative studies by Garside et al. (Link to PubMed abstract) explored what influences people’s decisions about skin cancer prevention. They did a very thorough search of seven databases and other sources, although they limited their search to English language studies from 1990 to 2009. They used the Health Belief Model as a conceptual framework to classify and understand the various study reports into those that dealt with perceived susceptibility of skin cancer, perceived seriousness, perceived benefits and barriers to protection behaviour, cues for action, perceived self-efficacy at detecting skin cancer. The overall quality of included studies was quite good.

Some interesting findings emerged. Children saw skin cancer as something that only applies to adults and that sunburn did not have long-term repercussions. Some adults believed that they had a low susceptibility to skin cancer because of general good health and low temperatures in the UK. Perceived severity of skin cancer was variable, and active denial was found in some sunbed users. Photoageing was perceived as being more real and taken more seriously by women. There was a mixed understanding of perceived benefits of skin cancer prevention, including a belief that a tan is protective of sun damage. Barriers to sun protection included the perception that a tan was healthy and attractive, and that adopting sun protection measures such as applying sun creams was a hassle. Cues for action included positive role models from parents and other media as well as knowing
someone who has skin cancer and media campaigns. Two studies reported participants examining themselves for signs of skin cancer although one study suggested that this might be a non-risk reduction strategy because people maintained risky behaviour as long as they monitored themselves closely enough. The authors also reported interesting differences in skin cancer prevention policies in the UK, US, Australia, New Zealand and Canada according to the narratives and “framing” of the problem depending on social, political and cultural concepts.

This was a useful systematic review for reinforcing the fact that people generally do not perceive that skin cancer is serious or that they are susceptible to it. Powerful barriers to behaviour change such as the concept of a “healthy tan” need to be countered by other positive cues such as role models, highlighting the problems of photo-ageing and tailored awareness campaigns. The review also suggests the need to tailor information to the population (and indeed in the dermatology clinic) according to age and perceived risk. Although some of the findings may seem obvious, they clearly underline that there is a long way to go in terms of using behavioural psychology to inform and educate the public about skin cancer prevention and better still, to effect a change in behaviour in those who need to change it most.

How much melanoma can be attributed to specific patient characteristics?

It is widely known that certain factors such as increased numbers of moles, fair skin and family history are associated with an increased risk of melanoma. It is less clear what overall proportion of melanoma can be attributed to people with such characteristics. Knowledge of such attributable risk (how much of melanoma is attributable to certain risk factors) as opposed to relative risk (whether a risk factor is associated with melanoma) is especially important for informing public health planning, so that efforts can be directed to that group of the population with the greatest burden of disease. Such attributable risk questions were addressed by three well reported systematic reviews conducted by the same team of Olsen et al. from Australia, published around the same time in three different journals, raising concerns about “salami” publication. The first systematic review of 49 studies (Link to PubMed abstract) estimated that around 42% of all melanomas could be attributed to people who had 25 or more common naevi, and around 25% of melanomas could be attributed to people with one or more atypical naevi. People belonging to these high risk groups might be targeted for identification, screening, and education. In a separate review on skin colour and freckling tendency (Link to PubMed abstract), the team estimated from 66 studies that around 27% of all melanomas could be attributed to those with skin types I and II, around 23% of melanoma could be attributed those with freckling, around 23% to those with blond hair colour, 10% to those with red hair colour, 18% for those with blue/blue-grey eye colour, and around 13% to those with green/grey/hazel eye colour. It is worth pointing out that these percentages will not add up to 100% since individuals frequently have more than one of the characteristics studied. In an analysis of 22 studies of familial melanoma (Link to PubMed abstract), the proportion of melanoma that could be attributed to familial risk was quite variable, ranging from 0.7% in Northern Europe to 6.4% in Australia (4% overall when all regions were combined). The authors considered the possibility of recall bias due to collection of self-reported data, and those with histological confirmation of melanoma in first-degree relatives appeared to have a higher relative risk than those that relied on recall alone, with relative risk (RR) values of 2.52 (95% confidence interval [CI] 2.31-3.00) and 1.97 (95% CI 1.61-2.42) respectively. These data may imply that we should make every effort to obtain histological confirmation of the diagnosis in first-degree relatives to accurately assess risk. This last review highlights that at a population level, familial melanoma is less of a concern than mole counts and pigmentary traits. In other words, a little bit of harm affecting a lot of people can add up to a lot more than a lot of harm affecting a few people, in population terms.

Occupational UV exposure and non-melanoma skin cancer

Ultraviolet (UV) radiation exposure is undoubtedly a key risk factor for non-melanoma skin cancers but does having an outdoor job put you at higher risk? Schmitt et al. (Link to PubMed abstract) performed a very thorough systematic review to assess whether occupational UV exposure increases the risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). The authors included 25 studies (five cohort, 17 case-control studies, and three cross-sectional), although they might have missed some articles by only searching PubMed and by excluding those that did not have an abstract.
They found that 12 out of 15 studies demonstrated a positive correlation between occupational UV exposure and SCC, and seven of these were statistically significant, with odds ratios of 1.5-4.3. The picture for BCC was less clear, with only five out of 16 demonstrating a positive correlation. Single studies postulated the increased risk of nodular BCC on the head and neck in patients with occupational UV exposure, as opposed to superficial BCCs on the trunk. Failure to adjust for recreational UV exposure and skin type was a feature of many of the included studies and the worldwide study distribution should possibly have been adjusted for proximity to the equator. The authors conclude that the link between occupational sun exposure and SCC is sufficiently strong to classify SCC as an occupational disease according to German social security law. They do not state that BCC is not an occupational disease, but simply that the evidence is less clear, mainly due to weaknesses in the studies reported to date.

What's new in melanoma genetics?

Mocellin et al. (Link to PubMed abstract) systematically reviewed the evidence for associations between DNA repair gene polymorphisms and risk of cutaneous melanoma, based on the theory that incapacity to repair damaged DNA by UV irradiation and other sources may be responsible for the development of cutaneous malignancies, and that the ability to repair is encoded by a DNA repair gene. Their review consisted of 14 case-control studies of repair gene polymorphisms and melanoma risk that included 3,207 cases and 4,992 controls. Eight single-nucleotide polymorphisms (SNP) on six genes were studied. Meta-analysis showed that one SNP in particular (XPD/ERCC2) appeared to be positively associated with the development of melanoma, although the magnitude of the association was rather weak, with an odds ratio of 1.08 (95% CI 1.00-1.16). However, because the gene is quite common, the attributable risk (the proportion of all melanoma cases that may be attributable to this gene defect) is around 9.6% assuming a causal association. It is difficult to pinpoint a practical clinical application for this information at the present time, but watch this space as further larger scale studies of this complex area investigate the possible association between DNA repair gene polymorphisms and cutaneous melanoma risk.

Statins and melanoma—yet another systematic review on the same topic

A previous Cochrane systematic review [1] failed to find any clear protective effect that statins can reduce the risk of cutaneous melanoma. Our 2009 Annual Evidence Update on Skin Cancer included a systematic review that examined the same question for melanoma and other cancers [2] with similar results, i.e. the best quality studies failed to show any benefit. Yet another systematic review on the topic of statins and melanoma risk has now appeared, conducted by Bonovas and colleagues from Athens (Link to PubMed abstract). They performed a meta-analysis of data obtained from 16 randomised controlled trials on 62,568 patients of statins versus placebo in order to examine melanoma incidence, but again failed to show any protective effect. The pooled data generated a relative risk of close to one (RR = 0.92, 95% CI 0.67-1.26), although the wide confidence intervals do not exclude a modest protective or harmful effect. The neutral effect was further supported by the results of subgroup and sensitivity analyses.

We should point out that these studies were large RCTs of statins for cardiovascular disease that just happened to include cancers of all types as possible outcomes, i.e. the diagnosis of melanoma in this population was a secondary endpoint. We must also be aware of the inherent selection bias within the sample, as the individuals studied were prescribed a statin for cardiovascular risk. This implies that there may also be confounding variables, such as smoking and other high-risk behaviours, that may obscure a genuine protective or harmful effect that may be present in other populations. Perhaps it would be unfair to write-off the melanoma cell apoptosis and inhibition of proliferation and invasion demonstrated in in vitro and animal studies, on the basis of this meta-analysis. Three meta-analyses on this topic are saying the same thing, and unless some other very large RCTs on statins with good melanoma outcomes appear over the next few years, we don’t want to see any more thank you.

SECTION 3: ASSESSMENT AND DIAGNOSIS
Melanoma screening

The role of full body skin examination (FBSE) as a screening method in the general population is controversial. There is little evidence to suggest that this technique has an impact on melanoma survival and national guidelines vary in their recommendations. Valachis et al. were interested in whether the practice of FBSE was reducing over time and if guidelines impacted on frequency of examination (Link to PubMed abstract). The authors searched appropriate databases to generate a short-list of 14 included studies. Only 60% of these studies employed randomisation to select their sample of general practitioners, and data collection relied on mailed questionnaires from which the response rates were not stated. It was found that 15-82% of primary care doctors were performing FBSE for screening purposes and this appeared to be decreasing over time between 1987 and 2004 (although the trend was not statistically significant). Following sub-group analysis by geographic location, Australasian physicians appeared to be increasing the number of examinations by 2.59% annually (p=0.01, n=1,112). The presence of national guidelines did not have an impact on examination rates. Limited data were available on screening of high-risk individuals and no conclusions could be drawn, although mean rates of examination increased from 26% in the general population to 52% in this group.

This review provided an interesting glimpse of what primary care practitioners in different countries are up to in terms of skin surveillance, but the main point is whether FBSE is a useful exercise, rather than whether or not people are conducting an activity that may be a waste of time. The authors argue that despite the lack of clear evidence, the high curability of melanoma in the early stage and the non-invasive screening procedure with full body skin examination argue for the potential utility of melanoma screening. You make up your own mind. What is clear is that more data are required regarding the impact of this screening method on melanoma detection and outcome before making recommendations, as annual FBSE for the general population will have significant cost implications in both primary and secondary care. See our invited commentary by Mark Ellwood for more on this topic.

Melanoma—assessment of prognosis from tissue biomarkers

Is there a more effective way of determining prognosis after excision of a cutaneous melanoma? Rothberg et al. explored the effect of tissue biomarkers on mortality and disease-free survival figures (Link to PubMed abstract). Their very thorough review analysed 37 cohort studies of primary cutaneous melanoma and excluded acral, mucosal and ocular tumours. The studies collectively analysed the expression of 62 proteins by immunohistochemistry-based assays. In 62% of the studies, the investigators were blinded to outcome at the time of analysis and data were adjusted for Breslow thickness in most cases. Positive staining for the melanoma adhesion molecule MCAM/MUC18 (a regulator for invasion and metastasis) appeared to have the strongest value for determining prognosis, with a 16-fold increase in all-cause mortality risk (hazard ratio or HR for death = 16.34, 95% CI 3.8-70.28). However, sample sizes were small and confidence intervals were wide. Metallothionein (a DNA replication and repair effector protein) was also significantly associated with a three-fold increase in melanoma-specific mortality (HR for death = 3.08, 95% CI 2.02-4.68). The same protein was also associated with reduced disease-free survival (HR for disease recurrence = 3.77, 95% CI 2.73-5.22). Other proteins that increased melanoma–specific mortality included osteopontin, a protein that contributes to tissue invasion, with a hazard ratio of 1.55 (95% CI 1.24-1.95, n= 345) and Ki-67, a protein that is involved in limitless tissue replication, with a hazard ratio of 3.7 (95% CI 1.6-8.9, n=187).

As the majority of these studies lacked power due to small sample sizes, larger prospective studies are required to ascertain whether these markers will be useful on a daily basis to risk stratify newly diagnosed melanoma. One of the key aspects of this well conducted review is the extent to which the tissue biomarkers determine survival above conventional determinants, such as Breslow thickness. The authors point out that most studies adjust for Breslow thickness, yet in some cases this has only been done crudely in a binary fashion (i.e. thick/thin tumours), leading to residual confounding which might have obscured any further benefit of the marker. The other dilemma, not discussed by the authors, is what is the use of predicting death more accurately in melanoma patients based on tumour markers, if there is a lack of effective treatments with which to try and reduce morbidity and mortality in such high risk groups? It is possible, however, that such markers will be useful in the future when effective adjuvant treatments become available.
New imaging techniques for detection of melanoma spread

More and more departments are using sophisticated imaging techniques for assessing melanoma spread, but do they work? Jimenez-Requena et al. performed a systematic review that included a meta-analysis of 28 studies of 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) used to detect regional or distant metastases (Link to PubMed abstract). They compared the imaging results against histological confirmation of regional metastases, and other scanning techniques and histological confirmation for detection of distant metastases. The populations studied varied to include those from stage I to IV melanoma, those with known metastases at the time of scanning, and populations with recurrent disease. The results suggested that for detecting distant metastases, FDG PET has a high sensitivity and specificity. When used to detect regional metastases, the data suggest that FDG PET scanning is inferior to current histological techniques such as sentinel lymph node biopsy, as micro-metastatic deposits may not be detected. The review was a thorough one, but the main limitation as illustrated in the accompanying commentary by Kevin Bradley is that the technology has moved on a lot since 2006, the end of the search period for the review. Performance of FDG PET, which is now integrated with CT in most modern scanners, is likely to be even better nowadays. The review is also limited by the small sample sizes (n=17 to 144) of the primary studies and variations in populations studied. In summary, FDG PET scanning may have a role in the detection of distant metastases. Large scale trials to demonstrate accuracy of diagnosis of metastases and cost effectiveness of this investigation are needed.

SECTION IV: TREATMENT AND MANAGEMENT

Melanoma—surgical intervention

There is still some debate about the most appropriate excision margins to employ for primary cutaneous melanoma of different thicknesses. A Cochrane Review by Sladden et al. published in January 2010 has addressed this issue (Link to full text). Primary outcome measures of the review included time to death and/or time to recurrence, and secondary outcomes included quality of life and adverse events. Five randomised controlled trials (3,297 participants) that compared narrow margins of excision (1-2cm) to wide margins (3-5cm) for melanomas of up to 4mm Breslow thickness were identified. Randomisation and allocation techniques varied between publications and intention to treat analysis was not performed in two of the studies. Follow-up ranged from a median of 5 to 16 years. Overall survival rates favoured wider excision (HR 1.04, 95% CI 0.95-1.28) but this potential survival advantage was not statistically significant, as indicated by the 95% confidence intervals crossing 1. Recurrence-free survival also appeared to favour wider excision (HR 1.33, 95% CI 0.99-1.28, p=0.06), but again these estimates do not reach conventional levels of statistical significance. In terms of quality of life, wider excision margins were associated with poorer physical and mental function (p=0.003 and p=0.008 respectively) than narrower margins, although this difference evened out at 6 months follow-up. Wider margins were also associated with poorer scar perception, increased rate of skin grafts and increased length of stay.

Based on this current evidence, the potential risks associated with wider excision of 3-5cm probably out ways the benefits at present, but as Jerry Marsden picks up in his commentary, there is still considerable uncertainty surrounding this fundamental question of excision margins. Although the magnitude of the hazard ratios looks small, they are still compatible with an improved survival of up to 28% for wider excision, which is a real concern in this potentially fatal disease. Further large RCTs with a pre-specified equivalence margin, stratified by Breslow thickness, and including difficult anatomical sites are required to resolve uncertainty.

Melanoma—sentinel lymph node biopsy followed by early surgery

There is little doubt that sentinel lymph node biopsy (SLNB) can predict prognosis in melanoma more accurately than tumour thickness alone, but the key question is whether the technique can improve long term survival when accompanied by appropriate surgery if positive nodes are found. Pasquali et
al. addressed this topic through a systematic review (Link to PubMed abstract). The authors began by presenting retrospective data from the tertiary centre comparing the outcome of completion lymph node dissection after positive SLNB (CLND) and delayed therapeutic lymph node dissection after clinical detection of positive nodes (TLND). They suggested an increased median survival in the CLND group compared to TLND (119.3 months, 95% CI 65.3-172.8 vs. 62.5 months, 95% CI 30.2-94.8), but the data are highly prone to bias since it was not a randomised comparison. The TLND group appeared to be an older population (median age 53 vs. 61, p=0.03) than the CLND group. The second section of the paper described a systematic review and meta-analysis of six studies, including the above data and a total of 2,633 people with stage III melanoma. Only one of the included studies was an RCT and the remainder were retrospective in design without randomisation, which severely limits the usefulness of the review. The authors’ meta-analysis indicated that there was a significantly greater risk of death in those who had TLND versus early intervention with CLND (HR for death 1.6, 95% CI 1.28-2.00, p<0.0001). The only RCT conducted to date (MSLT-1) has failed to show any survival advantage of early CLND as opposed to TLND apart from in a post hoc subgroup [3].

We have previously commented on the lack of evidence of survival benefit for SNLB in our 2008 Skin Cancer Annual Evidence Update, and nothing much has changed since then in terms of good quality evidence. Jerry Marsden also emphasises the continuing uncertainty in his commentary but fears that the technique has already become engrained in practice. Just being able to tell some people with a new diagnosis of melanoma that they are more likely to die than others seems questionable in the absence of any survival advantage when combined with appropriate therapy. The results of the MSLT-II trial are awaited, and until more certainty about the possible benefits or disbenefits of SLNB accompanied by early treatment appears, we advocate that the technique is used only as part of well planned research studies.

Melanoma—adjuvant therapy with interferon alpha

The use of adjuvant interferon alpha for people with a melanoma at high risk of recurrence is a much debated topic and previously published data have demonstrated impact on disease-free survival but not overall survival. Mocellin et al. set about to see whether an improvement in overall survival could be shown by performing a systematic review and meta-analysis of 14 randomised controlled trials published up to and including 2008 (Link to PubMed abstract). The overall sample of 8,122 patients included 4,362 patients randomly allocated to receive interferon alpha and the majority of the overall sample were diagnosed with stage III disease (70%, n=5,693). A variety of treatment regimens and durations were used in the study designs, the effects of which were explored by a technique called meta-regression.

Following meta-analysis, a benefit in favour of the interferon alpha group was shown not only for disease–free survival (HR for disease recurrence 0.82, 95% CI 0.77-0.87, p<0.001) but also for overall survival (HR for death 0.89, 95% CI 0.83-0.96, p=0.002). The calculated number needed to treat to improve overall survival in this group was 29 (95% CI=18-81), i.e. on average, 29 patients with high risk melanoma need to be treated with interferon alpha in order to see one improved survival. Sub-group analyses did not appear to show differences in disease-free survival according to differing interferon regimen, including higher doses, length of follow-up or study design. TNM classification appeared unrelated to disease-free survival, although those studies that exclusively enrolled patients with stage III disease did not show a significant improvement in overall survival. This review confirms a small but significant improvement in disease-free survival and overall survival with interferon alpha adjuvant therapy for stage II-III melanoma, but further studies are required to determine optimal dosing regimens and duration. A Cochrane Review addressing this same topic is currently in preparation.

Melanoma—isolated limb perfusion

Most clinicians will be familiar with isolated limb perfusion (ILP) as a potential treatment for melanoma situated on the limbs. The potential benefits of this localised form of chemotherapy in terms of complete response and survival was studied by Moreno-Ramirez et al. (Link to PubMed abstract) in a systematic review of studies that included people with unresectable locally advanced melanoma of the limbs (Stage IIIB and IIIC). The team identified 22 eligible reports that included 2,018 patients.
Only two of these studies were RCTs, the remainder being observational studies, many without a control group. The median reported combined response rate to isolated limb perfusion in this group was 90.35%, with complete response in 58.20% (median, range=25.0-89.0%). An improvement in complete response rate (CR) was seen when melphalan was combined with tumour necrosis factor (TNF), in comparison with melphalan alone, when all study data were combined, but this was not statistically significant (CR 68.90%, range 26.0-89.0%, and CR 46.50%, range 25.0-76.0%). The first of the two RCTs was published in 1999 [4] and randomised 64 patients to either TNF alpha plus melphalan or the same two drugs with the addition of interferon gamma. Complete response was not significantly different (59% versus 78% in the two and three drug arms respectively). The second RCT in 2006 [5] randomised 133 patients to hyperthermic limb perfusion with either melphalan alone or melphalan plus TNF alpha. Complete responses at 3 months were very similar in the two groups (25% in melphalan alone versus 26% with melphalan plus TNF alpha, P=0.890) and other treatment responses, such as partial response and mortality, were similar. Serious adverse events were commoner in the melphalan plus TNF alpha group (16% versus 4% in the melphalan alone group, P=0.46).

The main weakness of this systematic review was lack of ability to compare survival rates with other methods of treatment and lack of included RCTs, although we appreciate that recruitment for RCTs at this stage of tumour progression may be difficult. In summary, ILP may be helpful in improving survival and reducing need for amputation in unresectable stage IIIB-C limb melanoma, but as a previous systematic review has concluded [6], the technique cannot be recommended until better trial evidence becomes available.

Squamous cell carcinoma—treatments in general

A new Cochrane systematic review investigates the effects of interventions for non-metastatic SCC ([Link to full text](#)). Only RCTs were included and studies of in situ and pre-malignant lesions were excluded. Primary outcomes included time to recurrence and quality of life. After reviewing almost 3,000 studies, only one RCT met the criteria for inclusion. The RCT included 65 participants from a tertiary cancer centre and studied the effect of adjuvant 13-cis-retinoic acid in combination with interferon alpha following surgery with or without radiotherapy for primary SCC. The study participants had aggressive, high-risk tumours. There was no difference in time to recurrence between the treatment and control groups (HR=1.08, 95% CI 0.43-2.72), but the study was fairly inconclusive given the wide 95% confidence intervals. No quality of life data were available. This Cochrane Review has highlighted a shocking lack of reliable evidence for informing the treatment of cutaneous SCC. As the SCC guidelines discussed earlier in this review showed ([Link to full text, PDF](#)), most current treatment modalities are based on evidence from case series only. The Cochrane Review authors are currently performing a review of the lower levels of evidence pertaining to this subject, but it is important to emphasise the need for prospective randomised controlled trials in order to make fair comparisons.

Squamous cell carcinoma—adjuvant radiotherapy

Adjuvant radiotherapy (ART) after surgical excision of squamous cell carcinoma with perineural invasion is not recommended in the updated BAD SCC guidelines. So, what exactly is the evidence for this intervention and is this a treatment we should recommend? Jambusharia-Pahlajani et al. ([Link to PubMed abstract](#)) performed a systematic review of this topic including completely excised, high-risk, primary, non-anogenital SCC without nodal or distant metastases. Only 14 of the 49 included studies actually examined the effect of ART, and these were composed of a single cohort study and various case series. No randomised-controlled trials were found on this subject. Data were not controlled for tumour stage, which severely limits the ability to make even indirect comparisons.

The population of 91 patients that received adjuvant radiotherapy included in the review were diverse and comprised of those who had received Mohs surgery, standard excision, and those with absent and present perineural invasion. The authors noted that cases treated with ART demonstrated statistically significant higher rates of regional and distant metastases but stated that local recurrence and disease specific mortality were equivalent in the two groups. Because clear surgical margins were documented in only a small fraction of those given surgery plus adjuvant radiotherapy (8%,
7/91), many such cases may have had positive or uncertain surgical margins. Outcomes were similar for those patients with perineural invasion given surgery plus adjuvant radiotherapy versus those given surgery alone. Despite the brave attempt of the authors to look at various subgroups, very little can be said about the value of adjuvant radiotherapy for high risk SCC in the absence of randomised comparative studies. In her commentary, Irene Peat suggests that the skin cancer multi disciplinary teams are the appropriate correct forum for discussing the potential management of such uncertainty until better evidence becomes available.

**Topical treatments for various non-melanoma skin cancers**

Topical imiquimod and fluorouracil are currently used regularly, but what is the evidence for use in BCC, SCC and Bowen’s disease? There is a rather worrying lack of evidence, according to the systematic review by Love et al. (Link to PubMed abstract). This team reviewed 30 studies, only six of which were RCTs, the remainder being retrospective reviews and case-studies. Treatment regimens varied considerably, follow-up was relatively short and sample sizes were small. Most of the included trials excluded high-risk and large (>2cm²) lesions, and 75% of the included papers had some degree of funding from pharmaceutical companies. No meta-analysis was possible. In low-risk superficial BCCs, topical 5% imiquimod produces histological clearance at 6-12 weeks in 80% of patients in randomised controlled trials (433/544). A total of 98 patients were treated across five trials of imiquimod for Bowen’s disease, with a maximum response rate of 88%. Very little evidence was available for the use of fluorouracil in this review, with only 31 patients with superficial BCC treated, with a 90% clearance rate at 3 weeks. The authors concluded that the evidence was lacking for any clear indication, with the exception of both agents for superficial BCC, and fluorouracil for Bowen’s disease. No comment can be made about the success of treatment of invasive SCC, and the treatment of nodular BCC was associated with unacceptably low histological clearance rates. Success rates of these therapies may be overestimated due to the likelihood of publication bias in case series. In an accompanying commentary, Colin Morton draws our attention to significant local adverse effects for both topical imiquimod and topical 5-fluorouracil and the better response of lesions to photodynamic therapy in the few studies that included such a comparison. Large-scale RCTs with standardised treatment regimens are required to back up the current treatment indications. An RCT study of 500 patients comparing topical imiquimod versus surgical excision for superficial BCC and low risk nodular BCC has been underway [7] and the 3-year comparison of clinical recurrence rates is due to be reported in early 2011.

**Basal cell carcinoma around the eye—to Mohs or not to Mohs?**

Periocular BCC can be difficult to treat due to factors relating to nearby eye, eyelid and tear duct function and disfigurement caused by wide excisions. Mohs micrographic surgery (MMS) may help to preserve normal tissue whilst ensuring a complete excision, but is there evidence to support the use of this time-consuming and potentially costly treatment modality? Narayanan et al. carried out a Cochrane Review addressing these objectives with primary outcomes of time to recurrence, cost difference and complications of standard excision versus MMS for periocular BCCs (Link to full text). Sadly, not a single randomised controlled trial was found which meant that they could not make any reliable conclusions. The authors commented briefly on non-randomised, retrospective studies and highlighted one large RCT that included tumours on various facial locations. That study showed slightly lower recurrence rates in the MMS group after 30 months follow-up, although these data did not achieve statistical significance (3% vs. 2% for standard treatment). An Australian MMS database prospectively recorded data on high-risk periocular BCCs and included 1,295 patients, and the authors reported a 0% and 7.8% recurrence rate for primary and recurrent BCC respectively, although there was no comparator. Smaller studies noted recurrence rates of 1-5% after periocular MMS. We agree with the bottom line of the Cochrane Review authors—no reliable conclusions can be drawn until the comparison of MMS versus excisional surgery for periocular BCC is addressed in a large high quality RCT that stratifies tumours according to recurrence risk.

**Psychosocial care and quality of life for people with skin cancers**

Cornish et al. (Link to PubMed abstract) sought to determine the impact of melanoma on quality of life
Although the overall population was highly selected because it was composed of those treated in tertiary centres, some interesting themes emerged in their systematic review. Typical QoL impairments evident at diagnosis included insomnia and impaired emotional functioning, and were predominantly associated with poor health status and larger excision margins. Those with excision margins of 3cm were more likely to report impaired quality of life in comparison with those with 1cm margins. However, as in the systematic review by Sladden et al. discussed earlier (Link to full text), these physical factors reduced over time and were replaced by anxiety regarding potential recurrence. Comparisons were also made between those receiving treatment with surgery alone versus those receiving interferon therapy. Interferon was independently associated with impaired quality of life. A short study follow-up period was noted in most of the included studies, with only two out of thirteen being studied for 2 years or more after diagnosis and some having follow-up of only 4 months post-diagnosis. Also, these results may not be transferable to all populations due to language bias, the range of treatments received (surgery alone to interferon), and the highly selected populations studied. Psychological assessment and support may need to become a more integral part of melanoma follow-up, particularly in those with poor health status, lack of social network and metastatic disease.

These findings were echoed in the systematic review by Kasparian et al. that aimed to study psychological distress among those with, or at high risk of, melanoma (Link to PubMed abstract). Approximately 30% of those with melanoma experience psychological distress in need of clinical intervention—rates which are comparable to people with breast and colon cancer. Patients with melanoma experienced levels of anxiety greater than levels of depression, with rates of 23% (range 18-44%) and 11% (6-28%) respectively. The authors suggest that the effects of a diagnosis of melanoma should be considered as a variant of post-traumatic stress disorder. Stress responses appeared to increase with increasing tumour grading and thickness. Other correlates of psychological distress were female gender, young age, lower levels of education, unemployment, advanced disease, ill-health and tumours located on visible sites. Family history of melanoma and presence of CDKN2A gene mutation did not appear to increase levels of anxiety in the limited data available. In terms of coping strategies, active, problem-focused styles lead to improved adjustment in comparison to those who use passive or avoidant techniques. Active styles may be linked to increased social support and religious belief and may be associated with better overall outcome. This review supports the development of a brief screening tool to be used in the outpatient department and the need for detection of psychosocial distress, particularly in the high-risk groups listed above. The authors also suggest that patients should have access to cognitive behavioural therapy to adjust coping strategies in accordance with the evidence.

Quantification of such psychological consequences of melanoma diagnosis was studied further in a German systematic review by Beutel et al. of 31 studies (Link to PubMed abstract). Quality of included studies was fairly poor due to factors such as small study size, cross-sectional design, unclear response rates and a lack of similar methods for reporting such psychological consequences. After allowing for disease stage, psychological factors such as coping with disease and social support seemed to be critical for determining quality of life for all melanoma patients, including those undergoing therapy for metastatic melanoma. The role of psychotherapy for melanoma patients at all disease stages needs to be assessed.

WILL OUR PRACTICE CHANGE?

NEW GUIDELINES

• In the absence of any survival advantage, we are not convinced of the value of routinely offering sentinel lymph node biopsy as a staging procedure for all melanomas greater than 1mm thick as recommended by a European consensus guideline.
• The most crucial point for us to emerge from the British Association of Dermatologists guidelines on the management of primary cutaneous squamous cell carcinoma (SCC) is to identify tumours at high risk of distant spread according to site, size, depth, histology, immune status and local recurrences.
• The SCC guidelines have also heightened our awareness of the need to look out for skin cancer developing in or being reactivated by biological therapies.
• The SCC guidelines illustrate a shocking lack of high quality evidence to inform treatment decisions for people with SCC. We will therefore seek to encourage patients to participate in randomised controlled questions that address important treatment dilemmas in order to progress knowledge.

CAUSES, RISKS AND PREVENTION
• We will perform more targeted counselling on discouraging sunbed use in high-risk individuals, such as women aged 17 to 30 years with skin types II and IV who also have other unhealthy behaviours such as smoking, and also take the opportunity to discourage sunbed use in accompanying friends and relatives. We will also be more aware of possible sunbed use in our paediatric clinics, given that one in ten people less than 18 years also use sunbeds.
• We will continue to encourage sun protection, avoidance and self-monitoring in the general population.
• Despite decades of public education campaigns, there is still compelling evidence that the public do not perceive that skin cancer is serious and that it applies to them. The concept of a “health tan” remains as a significant barrier to skin cancer prevention. We will explore such beliefs more directly in the clinic in future.
• We will be more aware of the fact that although individual patients seen in clinic who have a family history of melanoma may be at high risk of developing a melanoma themselves, other factors such as high mole counts, atypical naevi, fair skin and freckles are far more important in contributing to the total burden of melanoma at a population level.
• We will make more effort to obtain histological confirmation of the diagnosis of melanoma in first-degree relatives to more accurately assess patient risk of melanoma.
• We will ask our patients with SCC more about their occupational exposure to sunlight and encourage reporting of SCC and possibly basal cell carcinoma (BCC) as an occupational disease.
• Some DNA repair genes like XPD/ERCC2 might represent a low-penetrance melanoma susceptibility gene, but research in this area is still at too early a stage to be clinically useful.
• We will not tell our patients that being on statins may reduce melanoma risk as some in vitro studies have suggested.
• We do not advocate full body skin examination of all patients by general practitioners to identify early melanoma until there is better evidence that it is worthwhile.

ASSESSMENT AND DIAGNOSIS
• A range of tissue biomarkers can predict all cause and melanoma-specific death even when adjusted for Breslow thickness, but the robustness and utility of such data is unclear at present. We will not be asking our histopathologists to run such marker studies unless we are clearer about what we can do with the information.
• Fluorodeoxyglucose positron emission tomography (FDG PET) combined with CT scanning may be useful for detecting distant melanoma metastases, but not for detecting regional spread.

TREATMENT AND MANAGEMENT
• Only five studies have compared narrow versus wider excision margins for primary cutaneous melanoma, and although narrower margins do not appear to confer a worse prognosis, there is still some uncertainty around the estimates, suggesting that more very large RCTs are needed, especially for intermediate thickness tumours.
• A clear survival benefit of sentinel lymph node biopsy plus early lymph node removal for positive nodes in melanoma has not been shown. We will only advocate the use of the technique as part of well-planned research studies or when clear clinical survival or relapse-free benefits are shown.
• Adjuvant therapy with interferon alpha has been shown to improve disease-free and overall survival in melanoma patients at high risk of recurrence, and we will consider the use of such treatment where possible.
• A systematic review has suggested that isolated limb perfusion of people with advanced melanoma of the limb may be associated with useful complete responses. The evidence is weak, however, since it is mainly composed of uncontrolled observational studies. The place of isolated limb perfusion remains controversial until better trial evidence becomes available.
• Although adjuvant radiotherapy following surgery has been shown to reduce local recurrence in tumours such as breast cancer, there is no reliable evidence to suggest that such a technique is
useful for high risk SCC. It is our view that the technique should only be used as part of a research study.

- The evidence base for using topical imiquimod and topical 5-fluouracil for SCC, BCC and Bowen’s disease is limited despite their widespread use. We will continue to use surgery as our first choice for non-melanoma skin cancer, but we will also consider using topical 5% imiquimod for superficial BCCs where surgery is not possible and topical 5-fluouracil for Bowen’s disease where surgery is difficult.
- In the absence of randomised controlled trials, it is unclear whether Mohs micrographic surgery offers any benefit over excisional surgery for periocular BCC.
- Around one in five patients with newly diagnosed melanoma experience clinically important anxiety and around one in ten experience depression that may be amenable to treatment. We will endeavour to elicit such factors more actively with future melanoma patients, and to offer suitable support which may include cognitive behavioural therapy and psychotherapy if available.
- It is important to explore quality of life issues in melanoma, even in patients with very early disease with long survival prospects.

Additional references
   Link to full text
   Link to PubMed abstract
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The largest body of evidence reviewed relates to the use of topical 5% imiquimod for low risk, superficial BCC. Reflecting data from three double-blind randomized controlled studies, 81% of patients were histologically free of disease at 6 or 12 weeks where treatment was applied at least daily for at least 5 days/week, for a period of 6-12 weeks. Reduced efficacy was associated with less frequent dosing regimens and larger tumours. Clearance rates overall are inferior when using imiquimod for nodular and infiltrative BCC. Although one study of small, low risk nodular BCC achieved 76% histologic clearance 6 weeks after applying imiquimod once daily for 12 weeks, the rate was only 42% in the group receiving six applications/week for 6 weeks.

Data on response are more limited for topical imiquimod use in SCC in situ (Bowen’s disease) and invasive SCC. Once daily applications for 12-16 weeks to patients with SCC in situ achieved clearance rates of 73-88% (by histologic confirmation at 6-12 weeks or clinical follow-up for 6-19 months). Only seven patients with invasive SCC have been reported, all in one study, with five (71%) achieving clearance on clinical exam and by punch biopsy 4 weeks post-treatment. Coincident with preparing this review, a case report describes amputation due to bone invasion by progression of SCC in situ of the finger following treatment with imiquimod 5% cream [2]. Such a cautionary note emphasizes the obligation for closer follow-up of patients following non-surgical therapies to pick up persistent/recurrent disease.

Turning to topical fluorouracil (i.e. topical 5-fluorouracil), intensive topical therapy with 5% fluorouracil cream, applied twice daily for an average of 11 weeks, cleared 90% (histologic confirmation) in one study of 31 superficial BCC cases. More data pertain to topical fluorouracil in treating SCC in situ. Two studies applying fluorouracil once daily for 1 week, then twice daily for 3 weeks, achieved 56% and 48% clinical clearance rates respectively at 12 months. These were comparison studies with topical photodynamic therapy (PDT). The authors of the systematic review fail to mention that in the study directly comparing these modalities, 82% of lesions cleared and remained clear over 12 months following PDT, compared with 48% after fluorouracil. Moreover, severe eczematous reactions occurred in over 20% of patients receiving fluorouracil and ulceration in 10%, with no such reactions following PDT [3]. Use of fluorouracil cream for longer may improve efficacy—in another study twice daily applications for 8 weeks cleared 85% lesions.

Before rushing to implement these protocols, the high frequency of adverse events with certain protocols requires consideration. Inflammatory reactions are common with imiquimod, with more intense reactions associated with more intensive use (although achieving higher clearance rates). Erythema, pain, dermatitis and pruritus are commonly reported following topical fluorouracil use. I certainly find patient tolerance an issue when pursuing the recommended protocols in my sun-damaged Celtic population.

Despite systematic reviews and national/international therapy guidelines, I remain intrigued by variations in practice between countries for the same disease indications. The authors of this review, based in the US, fail to mention PDT, although not currently FDA approved beyond actinic keratoses, and include a favourable cost comparison with Mohs surgery. Current BAD therapy guidelines recommend topical imiquimod (A,1) as a fair choice along with curettage, cryotherapy or PDT, for small and large low risk superficial BCC, with PDT as treatment of choice for large lesions [4]. The guidelines on Bowen’s disease or SCC in situ recommend imiquimod (B,1) and fluorouracil (BII-i) as a fair choice, but with cryotherapy or curettage ranked higher for small lesions in good healing sites, and PDT superior for lesions in poor healing sites [5]. Updated guidelines for treating squamous cell carcinoma advise surgical excision over topical imiquimod (C,IV) or fluorouracil (C,IV) [6].

In conclusion, the evidence contained in this systematic review led me to add the ‘?’ in the title to this commentary—not to mislead skim readers! Yes, the review supports the FDA approval of imiquimod for superficial BCC <2cm on non-face/scalp sites, applied once daily, 5 days/week for 6-12 weeks. Yes, if you can persuade your patient with BCC to use topical fluorouracil twice daily for 11 weeks, there is a 90% expectation of clearance. Yes, topical fluorouracil for SCC in situ can clear around 85% of lesions, if tolerated, when used twice daily for 8 weeks. No, limited data and superiority of alternative therapies leads me to agree with the review authors in not recommending these agents for nodular/infiltrative BCC or invasive SCC, nor imiquimod for SCC in situ. Will this review change my practice? Probably not, although I may consider more intensive use of these agents in certain patients where alternative therapy options are relatively contra-indicated. Maintaining a wide choice of therapies, surgical and topical, hospital and home based, also helps us aspire to high quality
individualized care.

References


2010 Annual Evidence Update on Skin Cancer - Commentary by Irene Peat

Does adjuvant radiotherapy reduce local recurrence in high risk cutaneous squamous cell carcinoma?

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Approximately 95% of cutaneous squamous cell carcinomas presenting in clinical practice are cured by surgical excision if the margins are clear. There remains, however, a group of patients at high risk of recurrence despite apparently adequate surgery. Current treatment guidelines [1, 2] detail these risk factors, which particularly relate to size of tumour, histological features and anatomical site. Adjuvant radiotherapy is very successful in reducing local recurrence after surgical clearance in other situations, notably breast cancer. Does it have a role here?

Jambusaria-Pahlajani et al. [3] attempt to answer this question in an overview of the English language literature published between 1980 and 2006, using a MEDLINE search for the identified high risk factors. They found 1,888 possible papers, but only 49 had outcome data which could be accurately correlated with treatment given, and of 2,449 patients, only 91 were confidently assigned to an adjuvant radiotherapy group. Even here details of tumour characteristics, surgical and radiotherapy techniques and outcome were missing more often than not, and a number of patients had prophylactic nodal rather than tumour bed irradiation. This is disappointing given the estimate of 3 million new cases of cutaneous squamous cell carcinoma diagnosed worldwide each year, but not really surprising, as there were no randomised controlled studies available comparing surgery to surgery with radiotherapy, and the retrospective literature cannot be expected to answer a question not posed at the time. The authors reasonably conclude that the evidence available is not sufficient to decide the question.

Do the guidelines help? The BAD [1], having surveyed much the same literature, is silent. In their guidelines the NCCN [2] include a review published more recently [4], and recommend that adjuvant
Radiotherapy should be offered if there is extensive perineural or large nerve involvement. Clinical Oncologists might wish to argue that there is little to be lost by offering a course of prophylactic irradiation to the tumour bed. The field size can be generous, and with careful technique acute effects are predictable and usually well tolerated, and treating a well healed scar or skin graft does not usually impair the late cosmesis significantly. Radiotherapy is only absolutely contraindicated in a few genetic conditions. However, should the patient be required to attend for a treatment which might prove unnecessary or unsuccessful?

Nowadays, the Skin Cancer MDT (Multidisciplinary team) is the forum for these discussions. The surgeon knows the patient and how well they tolerated the first procedure, and understands the consequences of recurrence, particularly with regard to further surgery. The pathologist adds an assessment of how many and how serious the risk factors are. The radiotherapist takes into account both the clinical situation and the level of anxiety round the table, and carries this forward into the consultation with the patient. Through Skin Cancer Networks, there is opportunity to initiate and contribute to randomised trials, but there is a good deal which could be done immediately and routinely. If each MDT were to record ‘high risk’ cases prospectively and then audit and publish the results of their standard treatment, there would be a large national resource of clinical experience available within the next five years. Even if it were only possible to identify a group of patients where radiotherapy failed to prevent recurrence, then at the very least, some patients could be spared a futile intervention.

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2010 Annual Evidence Update on Skin Cancer - Commentary by Jerry Marsden

Surgery and melanoma – what next?

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Surgery is the only curative treatment for melanoma, and yet there are still real uncertainties about what comprise the standards of care. There are two key issues: what is the margin of normal skin that should be excised around a primary melanoma to minimize metastatic risk, and what is the benefit that might accrue from early treatment of regional lymph nodes? Two recently published systematic reviews attempt to answer these questions [1, 2].

‘Wide’ margins—5 cm—were unchallenged for primary melanoma until the late 1970s. The realization that metastatic risk was low in melanoma < 0.75 mm Breslow thickness coincided with evidence that the mutilating radical mastectomy conferred no advantage over conservative breast cancer surgery. The surgical oncology pendulum swung from radical to conservative treatment—but, for melanoma, with no hard evidence. Since then, there have been five randomised controlled trials of surgical margins in primary melanoma, involving 3,297 patients. However, only one is adequately powered to answer the key question—does surgical margin affect survival? The number of patients required to answer this question is large, since about 80% of melanoma patients are cured by primary surgery,
and most of the 20% or so who relapse will have had micro-metastatic disease at the time of
diagnosis. In only a small minority, therefore, will the extent of local treatment—the surgical margin—
affect outcome. Despite this, assertions that narrow margins are as good as wide margins are
commonplace, though the evidence does not support such confidence.

The Cochrane systematic review by Sladden et al. [1] is a thorough exploration of this issue of
excision margins, and is a welcome addition to our knowledge. The methodology is robust and the
conclusion is unsurprising: the data are consistent with a 5% relative reduction in overall mortality in
favour of narrower margins, and a 15% relative reduction in overall mortality in favour of wider
excision. The conclusion is clear: we need better data. For us to be uncertain in 2010 about such a
crucial issue as the adequacy or otherwise of curative treatment is unconscionable. Although
melanoma is uncommon, the 1,800 or so patients required to confidently demonstrate equivalence
between margins in 2-4 mm thick melanoma is clearly achievable in a multi-national trial. But first we
need to accept that we don't already know the answer. Sladden et al. take us closer to that
realisation.

Sentinel lymph node biopsy (SLNB) is a technique designed in the early 1990s to help answer the
second big question in the surgical treatment of melanoma—does early treatment of regional lymph
nodes improve outcome? It now seems unlikely that this is the case as the Multicentre Selective
Lymphadenectomy Trial 1 (MSLT-1) has so far not shown significantly improved survival in those with
a positive SLNB treated by elective completion lymphadenectomy (CLND) [3]. But the trial suffers
from the same problem as those investigating excision margins—that only 20% of patients
randomised to the SLNB procedure are positive, and so 80% cannot benefit from the
intervention which is being tested, CLND. This is likely to be an underpowered study; the final results
are awaited.

In another paper included in this year's Annual Evidence Update, Pasquali et al. carried out a
retrospective analysis of their own patients treated with early SLNB guided lymphadenectomy
compared with delayed lymphadenectomy [2]. They found no difference in survival. However, they
then conducted a meta-analysis of five studies plus their own data (n=2,633), and their results
suggest that patients having early, SLNB-guided lymphadenectomy do have improved survival (HR
1.6, 90% CI 1.28-2.00, P<.0001). Although only one of the five studies was randomized, and the
biases of retrospective studies are well known, the results are difficult to ignore. In this context, the
negative results of MSLT-1 are surprising; they do require confirmation.

It was realized in the early 1990s that SLNB provided improved staging information, and the
procedure rapidly acquired a life of its own outside, but in parallel with, MSLT-1. This then led to a
difficulty—what to do with patients with a positive SLNB outside a clinical trial? Most proceeded to
CLND on the assumption that this was safer than no treatment, though only another 20% have further
nodal involvement in the dissected basin. The follow-on study MSLT-2 compares outcomes in
patients with a positive SLNB treated with nodal observation or CLND. If CLND has a survival
advantage, this will prompt review of the findings of MSLT-1, since it will suggest that more surgery,
earlier, is better. The real problem is that SLNB and CLND have now become entrenched as routine
practice in the surgery of primary melanoma, leading to the paradox that we are possibly
undertreating primary melanoma because of inadequate evidence, and probably overtreating
secondary melanoma for the same reason. Hardly a rational position.

The possible survival differences between these surgical interventions may seem small to us, but for
patients are important. We need to mobilise surgical opinion: if the effort underpinning the vast
literature on SLNB had been chanelled into clinical trials these questions would have been answered
long ago. The first step is to re-examine our own received wisdoms about the surgery of melanoma.

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PET/CT (positron emission tomography/computed tomography) using the glucose analogue 18FDG (18-fluorodeoxyglucose) has an established role in the staging and management of many malignancies such as lung and oesophageal cancer and high grade lymphomas. Within the UK, most cancer networks have adopted guidelines that 18FDG PET/CT is indicated in all patients with malignant melanoma relapse suitable for radical therapy (estimated at 30 patients per million population). It is recognised that the indications for 18FDG PET/CT will expand as evidence of its utility becomes available. Two meta-analyses have attempted to provide such evidence in cutaneous malignant melanoma.

The most recent meta-analysis, by Jimenez-Requena et al. [1], is included in this year's Annual Evidence Update. Using rigorous inclusion criteria for studies between 2000 and 2006, this paper extended and included a previous meta-analysis [2] by one of the authors spanning the period 1980–1999. Within the later period, only 17 of 431 studies met the inclusion criteria, making a total of 24 studies available for quantitative meta-analysis with histopathology of regional nodes and/or metastases or at least six months follow up with clinical or imaging progression of metastatic disease. It was concluded that 18FDG PET was:

- not useful in the evaluation of regional metastases as it did not detect microscopic disease, although specificity was high at 0.99 (95% CI 0.97–0.99);

- useful in the detection of distant metastases, specificity 0.86 (95% CI 0.77–0.92) and a diagnostic-odds-ratio (DOR) of 37.89 (95% CI 15.8–90.86); sensitivity was too heterogeneous for summative calculation.

The variable that most influenced the DOR of different studies and caused the most heterogeneity was the year of publication. This is most likely due to the evolution of PET technology with consequent improvement of sensitivity/specificity. Indeed, this is the major criticism of this meta-analysis since all of the studies included were performed on PET only scanners and (although it is not stated) many were without attenuation correction. Since 2003 all new, clinical systems in the UK are integrated PET/CT scanners. This immediately led to a major improvement in specificity since the addition of anatomical imaging can correctly diagnose small 18FDG avid foci that are due to benign pathology such as rib fractures. The incorporated diagnostic quality CT also means that small, potentially PET negative, pulmonary nodules may be detected which can be the first sign of metastatic disease. Therefore, most PET based publications from the pre-PET/CT era underestimate sensitivity and especially specificity.

The other meta-analysis, by Krug et al. [3], which was included in last year's Annual Evidence Update, confined itself to the role of 18FDG PET in the initial staging of cutaneous malignant melanoma from 547 publications up to April 2007, judging 28 studies involving 2,905 patients as meeting inclusion criteria (including histopathological or clinical/radiological follow up). This study included more technical information regarding scan quality; 11/28 studies had no attenuation correction but four of the more recent studies involved PET/CT scanners—fortunately these were larger and somewhat better performed studies involving a total of 809 patients. The pooled estimates of 18FDG PET for the detection of metastasis in the initial staging of cutaneous malignant melanoma was sensitivity 83% (95% CI 81–84%), specificity 85% (95% CI 83–87%), and DOR 19.8 (95% CI 10.8–36.4). Results from eight studies suggested that 18FDG PET was associated with a 33% management change (range 15–64%). They felt that this provided good preliminary evidence
that 18FDG PET and particularly PET/CT was useful for the initial staging of patients at risk of soft
tissue, lymph node and visceral metastases.

Overall, the major disappointment is that despite the hundreds of publications and probably millions of
patients who have undergone PET scanning in melanoma, that so few studies have been published
that can provide us with robust answers to clinical utility.

It is clear that PET/CT has no role in early disease since it will always lack the sensitivity required to
detect early disease in a regional, sentinel node. However, 18FDG PET/CT is sensitive and specific
for the detection of distant metastatic disease (with the exception of cerebral metastases due to
obligate high background uptake of 18FDG). Prospective trials are required to clarify the additional
benefits of 18FDG PET/CT either following or replacing more widely available imaging modalities in
appropriate, at risk groups.

In the UK, it may be that the major impetus to increased use of 18FDG PET/CT in melanoma, both for
improved staging and disease response assessment, will be the advent of new chemotherapy agents.

References

performance of 18F-FDG PET in cutaneous melanoma. European Journal of Nuclear Medicine
and Molecular Imaging 2010;37:284-300.

Link to PubMed abstract


Link to PubMed abstract


Link to PubMed abstract

2010 Annual Evidence Update on Skin Cancer - Commentary by Mark Elwood

Sunbed use, skin cancer prevention and screening behaviours

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The main environmental cause of melanoma and other skin cancers is ultraviolet radiation, either from
the sun or from artificial sources such as sunbeds. For melanoma, the mechanism likely involves both
the initiation of melanocytic nevi and their transformation into melanoma, and also the development of
melanoma without a clear nevus stage. Analyses of the melanoma relationship to artificial tanning
show an estimated risk of about 1.7 for regular or frequent exposure, which is not dissimilar from the
association with high levels of intermittent sun exposure [1]; however, both associations will be
underestimates because of measurement errors, and for both, the risks are higher in those with
greater skin sensitivity.

Legislation to control sunbed use exists in Scotland and many other countries. The Sunbeds
(Regulation) Bill in Westminster concentrates on restricting the use of sunbeds by those under age 18
and, for all users, ensuring staffing and accurate health information. The emphasis on young users
relates to the duty of protection, not a limitation of the hazard to this particular age group. Solar
ultraviolet (UV) exposure and sunburns throughout life, and not just in childhood and adolescence,
are linked to melanoma, as is sunbed use [2].

Statements about restricting sunbeds are often linked to comments that melanoma incidence is
increasing rapidly, but they have only a small influence on this. Incidence is rising in young adults,
and more in women than men at ages under age 35, but the maximum increase is in those over age 60 (http://info.cancerresearchuk.org/cancerstats/types/skin/). In men up to age 45 and in women up to 64, melanoma mortality has been reasonably stable since early 1990s, although it is increasing at older ages. These trends relate to cohort effects and solar ultraviolet exposure patterns in the past, as well as to increasing public and clinical awareness and earlier diagnosis.

A recent systematic review by Schneider & Kramer [3] includes 16 surveys in six countries (nine in the US, two in the UK). The results are unsurprising—sunbeds users are typically aged 17 to 30, are more often women than men, and they are more likely to have made other hazardous choices, in cigarettes, alcohol and diet. They are likely to know (or admit to knowing) relatively little about the health risks, to feel that tanning makes them feel better and more relaxed, to be enthusiastic about the cosmetic advantages of a tan, and to have friends and family members who use sunbeds.

A systematic review of prevention and screening behaviours related to skin cancer by Kasparian et al. [4] includes 91 papers (not all listed), of which 32, chosen because they used a multivariate analysis, are tabulated in detail; these include 15 from the US, seven from Australia, five from Europe, but none from the UK. This is a selective review, as these studies cover many issues. The authors conclude that women, as compared to men, are more likely to use protective measures such as sunscreen, skin self-examination and doctor skin examination, and these behaviours are influenced by a greater perceived risk of skin cancer and by a doctor’s recommendation for screening. That some characteristics, such as the female predominance, apply to both a hazard, the use of sunbeds, and also to sun protection measures, is not a contradiction but a relevant clue; it suggests that many people accept the message that artificial tanning is safe, and consider sunbeds a protective strategy.

One thing lacking in these reviews, and indeed in the approaches to regulation, is any comparison between sunbed use and solar ultraviolet exposure, and information on how people use sunbeds, whether as a substitute for solar exposure or as an adjunct to it. There is good evidence that sunscreens are often used to increase tolerance to solar exposure, resulting in a higher carcinogenic dose and higher melanoma rates [5]. Sunbeds may be used in the same way, resulting in higher exposures to both artificial and natural UV radiation. The default position of dermatologists may be to warn young patients against sunbeds, but they should apply this to all ages and match it by reinforcement of the message to avoid unnecessary or excessive solar exposure. Encouragement of alternatives such as spray-on tans to achieve the same cosmetic effect seems a little-explored option.

In both these systematic reviews the authors accept that screening for skin cancer is a beneficial behaviour. Yet no randomised trial has been done, as noted in another new review of skin screening in primary care by Valachis et al. [6]. The one randomised trial which was piloted in Australia [7] was not completed due to lack of funding. As one of the investigators, I would comment that the research budgets were approved after much peer review, but funding for the screening itself from health service funds was not obtained, perhaps because of background views (contrary to the evidence) that a trial was unnecessary either because screening was of obvious value (mainly clinicians) or that it was clearly not cost-effective (administrators). So at present, the best we have is two case-control studies, supporting the value of self-screening [8] and whole-body screening by a doctor [9], and lots of lower level evidence. The review by Valachis et al. [6] applies meta-regression analysis to 15 surveys to suggest that over time, fewer primary care physicians are doing skin screening in the US, with little change in Europe, and a small increase in Australia. But the data validity does not justify the sophisticated analysis: the surveys use different questions and methods, and ask if a doctor performs whole-body skin examinations, with no data about how often or on which patients, or whether the purpose is clearly screening and not investigation of worried, symptomatic or high risk patients.

References

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2010 Annual Evidence Update on Skin Cancer - Patient information resources

Skin Cancer AEU Patient info 2010

Skin cancer general
Skin cancer Macmillan Cancer Support - [view]
Sunsmart campaign: Cancer Research UK - [view]
Skin cancer: British Association of Dermatologists - [view]
Embarrassing Bodies mole examination video Channel 4 - [view]
Improving outcomes for people with skin tumours including melanoma: Information for the public : National Institute for Health and Clinical Excellence - [view]
The Karen Clifford Skin Cancer Charity (SKCIN) - [view]
Sun damaged skin slideshow: Web MD and Boots.com - [view]
Skin Cancer (malignant melanoma): NHS Choices - [view]
Marcos Line Telephone help and advice - a resource and advice centre for Skin cancer patients and their families, funded by the Wessex Cancer Trust (01722) 415071.
Melanoma

Malignant melanoma information centre: Cancerbackup - [view]

Melanoma skin cancer: CancerHelp UK - [view]

What's new in melanoma? Melanoma Research: CancerHelp UK - [view]

Skin Cancer (malignant melanoma): NHS Choices - [view]

Melanoma: British Association of Dermatologists - [view]

All about skin cancer – melanoma: American Cancer Society - [view]

What's new in melanoma research? American Cancer Society - [view]

Basal cell carcinoma

Skin cancer (Non melanoma): NHS Choices - [view]

Skin cancer – not melanoma: CancerHelp UK - [view]

Basal cell carcinoma: British Association of Dermatologists - [view]

Squamous cell carcinoma: British Association of Dermatologists - [view]

Basal cell carcinoma: SKCIN - [view]

Basal cell carcinoma: The Skin Cancer Foundation - [view]

All about skin cancer – basal and squamous cell: American Cancer Society - [view]

What's New in Research and Treatment of Squamous and Basal Cell Skin Cancer? American Cancer Society - [view]

Imiquimod: Boots Web MD - [view]

Topical fluorouracil: Medicine.net - [view]

PET-CT scan CancerHelp UK - [view]

2010 Annual Evidence Update on Skin Cancer - Uncertainties about the effects of treatments for skin cancer

Identifying Uncertainties in Cancer and Skin Disorders

NHS Evidence - cancer and NHS Evidence - skin disorders are collaborating in a project being led by the James Lind Alliance to identify uncertainties about the effects of treatments. We will be working with various partners and contributors to identify uncertainties relating to treatments in skin cancer.

UK Database of Uncertainties about the Effects of Treatments (DUETs)

Uncertainties are being added to UK DUETs which has been established to publish uncertainties that cannot currently be answered reliably by referring to up-to-date systematic reviews of existing research evidence.

Raising the profile of uncertainties in this way will help to stimulate and direct future research where it is most needed.

UK DUETs draws on three main sources to identify uncertainties about the effects of treatments:
• Patients’, carers’ and clinicians’ questions about the effects of treatments
• Research recommendations in reports of systematic reviews and clinical guidelines
• Ongoing research, both systematic reviews in preparation and new ‘primary’ studies

For this year’s Annual Evidence Update we have sought to identify uncertainties about the effects of treatments for skin cancer in the new systematic reviews that we have found, and have now added them to DUETs.

View uncertainties in skin cancer here

View uncertainties in cancer here
Currently there are only a few uncertainties on the Cancer module but this is work in progress and we will be adding to these over time.

View uncertainties in skin disorders here

2010 Annual Evidence Update on Colorectal cancer - Patient Resources

General

1. Beating Bowel Cancer [view]
Information and support for anyone affected by bowel cancer.

2. Bowel Cancer UK - [view]
Information and support for anyone affected by bowel cancer

3. CancerHelp UK: Bowel Cancer (Colorectal cancer) section - [view]
Information about causes and symptoms of bowel cancer, tests and treatment, living with bowel cancer, and current research

4. Lynn's Bowel Cancer Campaign - [view]

5. Macmillan Cancer support/Cancerbackup: Cancer of the large bowel information centre - [view]
Information on colon cancer, including how it is diagnosed, treatments you might have, possible side effects and how to get further support.

6. NHS Choices - Bowel cancer [view]

7. National Institute for Health and Clinical Evidence (NICE) - Information for the public on bowel cancer [view]

8. American Cancer Society: What’s new in colorectal cancer research and treatment? [view]

9. Healthtalk online [view]
Patient experiences of bowel cancer screening

10. NHS Bowel Cancer Screening Programme: NHS Cancer Screening Programme [view]