Journal of Plastic, Reconstructive & Aesthetic Surgery (2014) 67, 1322–1332

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

A model for lentigo maligna recurrence using melanocyte count as a predictive marker based upon logistic regression analysis of a blinded retrospective review☆

Mark Gorman [a,*], Muhammad A.A. Khan [b], Paul C.D. Johnson [c], Andrew Hart [a], Bipin Mathew [d]

[a] *Canniesburn Plastic Surgery Unit, Glasgow, UK*
[b] *Castle Hill Plastic Surgery Department, Hull, UK*
[c] *Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK*
[d] *Hull Royal Infirmary Pathology Department, Hull, UK*

Received 7 November 2013; accepted 27 May 2014

KEYWORDS
Lentigo maligna;
Lentigo maligna melanoma;
Surgical excision;
Diagnosis;
Recurrence;
Predictive model

Summary *Background:* The pre-malignant skin lesion lentigo maligna (LM) presents a particular challenge. Pathologists demonstrate poor diagnostic concordance and often struggle to assess whether excision margins are truly negative. This can lead to equivocal histology reports and a lack of clear guidance with which surgeons may rationalise their surgical management plans. Based upon the biological principle that tumour burden increases the chance of recurrence, we propose a shift in diagnostic paradigm, using melanocyte count (MC) at an excision margin to predict LM recurrence.
Methods: This retrospective study reviewed all cases of LM from a regional UK melanoma centre (1996–2011), to include 167 excisions, from 99 patients. Pathology slides were assessed for MC (blinded) at the most affected margin. Seven secondary markers of neoplasia were additionally evaluated. Logistic regression analysis was used to model the relationship between MC and recurrence.
Results: MC is a strong predictor of LM recurrence ($p < 0.0001$). A regression curve predicts risk for individual MCs, which may also be divided into three risk strata; low (0–11% [MC 0–20]), intermediate (15–89% [MC 21–30]), and high risk (92–100% [MC $\geq$ 31]). MC misclassified

☆ Preliminary study results presented at the Douglas Murray Plastic Surgery Prize Meeting, in Birmingham, UK, 22 September 2012; interim results presented at the Annual Scottish Plastic Surgery Meeting, in Dunkeld, UK, 25–26 October 2012; Awarded the ASiT-PLASTA prize at the Annual ASiT International Surgical Conference, in Manchester, UK, 5–7 April 2013.

* Corresponding author. Canniesburn Plastic Surgery Unit, Jubilee Building, Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK. Tel.: +44 1412115600; fax: +44 1412115652.
E-mail address: drgorman@me.com (M. Gorman).

http://dx.doi.org/10.1016/j.bjps.2014.05.058

0.6% of cases in the low and high risk groups compared with 21% for pathologists, who were also equivocal for 18% of excisions. MC's inter-rater concordance was high (>0.9). The secondary factors were all independently associated with recurrence, but failed to improve predictive ability supplementary to MC.
Conclusions: MC confidently predicts LM recurrence and is more accurate and reliable, whilst also reducing the uncertainty of current pathology assessment. Risk estimates for any given MC can be easily charted using the regression curve graph, where confidence interval and risk group boundaries demonstrate the degree of certainty associated with any given prediction. This change in approach is congruent with tumour behaviour. A recurrence 'tipping point' corresponds to the sharp risk increase across the intermediate group's narrow band of MC.

Introduction

Lentigo maligna (LM) is a pre-malignant lesion, with progression to invasive melanoma (LMM) estimated at 5—15%.[1] Managed by surgical excision, lesions occur most commonly on the head and neck in cosmetically sensitive areas.[2] When assessing excision margins LM presents a challenge for pathologists'.[3] Its histological criteria are difficult to distinguish from benign changes that also occur secondary to sun exposure.[4,5] Diagnostic uncertainty makes it more difficult to provide definitive guidance regarding surgical management.[6] To improve pathological accuracy this study investigated an alternative approach to LM diagnosis based upon the degree of 'tumour burden' at an excision margin.

LM occurs only as a foci over severely sun-damaged dermis and is histologically characterised by an increased number of atypical melanocytes at the dermoepidermal junction (Figure 1).[7] Atypical melanocytes may exhibit pagetoid spread (upward migration in the epidermis), extend down adnexal structures, and be contiguous, singular or form nests. A challenge for pathologists is that these criteria overlap with benign changes also seen with long-term sun exposure.[5] As all sun-exposed areas have an increased number of melanocytes,[8] it can be difficult to determine between LM and solar-induced melanocytic hyperplasia (SIMH).[5] Diagnosis is further challenged when LM tapers off at a margin's edge (a potential skip lesion, see Figure 1). Melanocytes can appear cytologically atypical; when they are in fact temporarily 'activated' (photoactivated melanocytes deposit melanin dendritically to surrounding keratinocytes, again see Figure 1).[9] These uncertainties have led to a lack of agreement between pathologists when interpreting excision margins.[10—12] The most comprehensive study to date, investigating diagnostic accuracy, found only moderate inter- and intra-observer concordance (*K* values 0.4—0.6 [0 indicating agreement expected by chance, and 1 indicating perfect agreement]).[13] The authors state that assessment was further confounded by failures to uniformly apply the criteria of published guidelines.[14,15] Mentorial influence and consideration of less evidenced secondary factors (proxies for neoplasia) also lead to varying thresholds of what is considered a positive margin.[11,13]

Seeking a more reliable method to margin assessment our approach was modelled on tumour behaviour.[16] The biological principle that tumour burden increases the chance of recurrence (or tumour invasion) has been used to rationalise oncological grading, as with Breslow thickness in malignant melanoma.[17,18] We postulated that as the number of melanocytes (melanocyte count: MC) increased at an excision margin so would the chance of recurrence, and thus investigated MC's ability to predict LM recurrence.

As tumour burden increases, a biological tipping point may be identified, which should approximate to the point the risk of recurrence starts and significantly increases.[19]

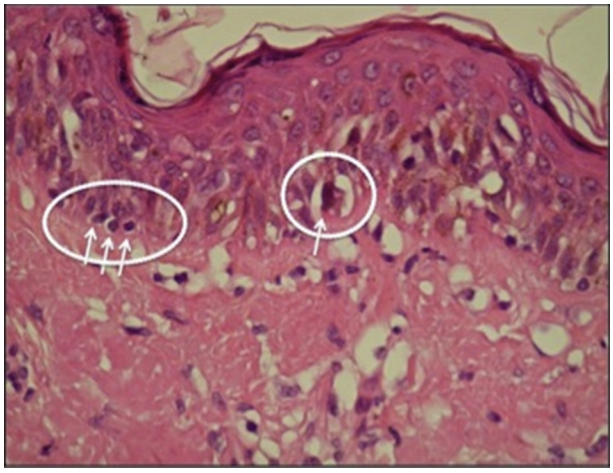

Figure 1 Pathology slide illustrating the challenges associated with LM margin assessment. Three contiguous atypical melanocytes (characteristic white halos) are identified to the left of the picture, straddled by keratinocytes, running along the basal layer of the epidermis. Just right of centre there appears to be a more obvious, much larger atypical melanocyte. However, it may actually represent a non-neoplastic 'activated' melanocyte (occurring secondary to UV light initiation, when melanocytes deposit melanin dendritically to surrounding keratinocytes). Therefore atypical looking melanocytes may indicate solar-induced melanocytic hyperplasia as opposed to the presence of LM. In this instance, where LM appears to 'peter out', there is difficulty in judging whether the excision margins are clear.