Chapter 6: Conclusions and Further Work

6.1 Introduction

This chapter discusses the conclusions drawn from the work undertaken in this thesis and attempts to place it in the context of the diagnosis of melanoma. In addition, an evaluation and criticism are presented. This is followed by suggestions for further work and potential areas of exploration that are beyond the remit of this thesis.

6.2 Conclusions

6.2.1 Summary

This thesis sought to develop predictive models using new technology, namely Spectrophotometric Intracutaneous Analysis, for the diagnosis of primary cutaneous malignant melanoma. As was discussed in chapter 2, the clinical diagnosis of melanoma is difficult and relies on the identification of visual features that are often subtle to detect. As a result, several approaches have been taken to aid the clinician in identifying sinister features of which the most commonly employed is skin surface microscopy (section 2.3). However, even this relatively simple technique requires training and expertise in its application [Binder *et al.,* 1995] and yet, the pioneers in this field demonstrated poor agreement on the most important features [Soyer *et al.,* 2001; Argenziano, 2001].

The approach taken was to identify features from the blood, collagen, total and dermal melanin SIAgraphs that could serve to indicate and disclose underlying significant histological and pathophysiological features within the lesion. Four key SIAscopy features were identified of which three indicated early primary melanoma, namely dermal melanin, blood displacement with erythematous blush and asymmetry; and another, collagen holes that indicated advanced local disease. According to the new classification system presented in this thesis, these features were resolved to the tertiary structure of the lesion at levels one and two. Furthermore, these features could be identified repeatably and reliably. Crucially, the appearance of these features could be related to underlying histological and pathophysiological phenomena. A series of clinical trials were undertaken at Addenbrooke's hospital that provided evidence that the system was indeed analysing these histological and pathophysiological features (Chapter 4).

The subsequent step was to develop predictive models for melanoma based on these features. Two main statistical approaches were used namely, logistic regression analysis and classification tree analysis and from the former a simple scoring method was derived. These models performed well in validation and predicted melanoma with very high sensitivity and

high specificity. Comparisons with other studies that employed skin surface microscopy demonstrated that these predictive models perform equally as well, if not better than this technique. In addition, these models demonstrated a significantly better performance when objectively compared to standard clinical practice. The crucial point here, however, is that the predictive models, especially the Combined Scoring method (Appendix A), uses two very simple SIAscopy features and two standard clinical features, namely age of the patient and maximum diameter of the lesion in its application whereas skin surface microscopy requires formal training [Binder *et al.,* 1995], a significant apprenticeship to apply [Morton & MacKie, 1998] and is still hampered by problems of subjectivity [Soyer *et al.*, 2001].

6.2.2 Evaluation

This thesis has achieved the stated intention of developing predictive models for the diagnosis of melanoma using Spectrophotometric Intracutaneous Analysis technology. Moreover, the models that were developed were simple and readily applicable in the clinical setting. As a result, a new field in the imaging and diagnosis of pigmented skin lesions has been established and developed. Testimony to the significance and novelty of this work were the acceptance of papers [Cotton *et al.,* 2000; Cotton *et al.,* 2001; Moncrieff *et al.,* 2000; Moncrieff *et al.,* 2001(c&d)] and invitations to speak [Moncrieff *et al.,* 2001e] at major international conferences and the acceptance of papers by international journals [Moncrieff, 2001a; Moncrieff *et al.,* 2001b] whilst undertaking this MD thesis.

The methodology used to identify SIAscopy features was heavily derived from basic medical sciences of histopathology and pathophysiology. Thus, the likely appearance of the SIAgraphs in various pathologies was predicted from their histopathological description. In addition, the SIAscopy features were deliberately kept as simple as possible, both in their description and in their classification (‘present’ or ‘absent’). This approach parallels the progress of skin surface microscopy where a few simple features were initially described. The predictive models generated by the statistical methods used in this thesis provided verification for these predictions regarding the SIAscopy features, in addition to producing a simple and powerful clinical method for appraising pigmented skin lesions.

The identification and subsequent appraisal of the SIAscopy features in this thesis give rise to numerous clinical applications in other areas of dermatology, especially oncology. In addition, these features lend themselves readily to their automatic detection and registration by bespoke image analysis systems. Furthermore, identification of these SIAscopy features could have implications in screening patients further down the chain of referral. This will be discussed further in section 6.3

6.2.3 Criticisms

Criticism of this work covers three main areas that can be mostly resolved by further studies (section 6.3). First, the patients recruited to the study were from a highly selective subgroup of the population of people that possess pigmented lesions, as they had been right through the referral process from General Practitioner to Consultant Dermatologist or Plastic Surgeon and onwards to excision biopsy. It could be argued that the SIAscopy features identified are only applicable to this smaller subsample of patients and thus might not be as useful or, indeed useful at all, as a diagnostic tool in the General Practice setting. Second, the author readily acknowledges the lack of direct comparison with skin surface microscopy. As was stated before (5.3.8), it was decided not to appraise the images collected alongside the SIAgraphs given that the author had not received formal training in the technique and previous research has shown that this can lead to a reduction in performance by clinicians [Binder *et al.,* 1995]. As a result, it would have been difficult to separate a genuinely superior performance by the SIAscopy method from an underperformance of the author in diagnosing lesions using skin surface microscopy. The author would readily encourage a comparative study to redress this problem. Third, the validation experiments were too small in size to provide conclusive validation for each of the SIAgraphs produced by the SIAscope. The reason for this is that the research group was limited in time and resources to produce the appropriate-sized studies. However, the positive findings of the studies undertaken at this time and the effectiveness of the SIAscopy features as predictors of melanoma indicate that the outlay required to carry out larger trials is justified.

6.3 Further Work

6.3.1 Identifying further SIAscopy features

If Spectrophotometric Intracutaneous Analysis as a diagnostic technique for pigmented skin lesions is to mirror the progress of skin surface microscopy, then many more features will be identified; not only as useful predictors of melanoma but also as useful predictors for benign lesions too. Examples of histopathological features of melanoma that would be highly desirable to elicit include regression, fibrosis and Pagetoid spread [Mooi & Krausz, 1992a]. The latter proved difficult to reliably identify due to a limit on the lateral resolution of the SIAscope. However, computer hardware is constantly improving and at a rapid rate so that the development of a superior system in the near future could allow these smaller features to be identified.

A qualitative approach could be taken to the identification of SIAscopy features. The methodology of this thesis employed a gross quantitative approach to the SIAgraphs. For instance, dermal melanin was classified as being present or absent with no regard for the distribution pattern. It could be envisaged that subsequent analysis would investigate the

shapes that are made by the distributions of dermal melanin that would reveal the underlying histopathology such as naevus cell nests or melanophages. (An attempt was made to do this, using melanin and blood globules, but it was difficult to devise definitions that meant that they could be reliably or reproducibly identifie). In addition, the distribution of these features could be analysed with respect to the lesion. For instance, an eccentric focus of dermal melanin may indicate a focus of invasive melanoma whereas a central, uniform distribution of dermal melanin may indicate a benign compound or blue naevus. Finally, appraising the global appearance of the lesion could improve the specificity of the diagnosing clinician. This has been shown to be the case with skin surface microscopy where pattern analysis that incorporates this feature has a greater specificity than scoring methods that do not [Soyer *et al.*, 2001; Argenziano, 2001].

6.3.2 Using SIAscopy with Skin Surface Microscopy

As has been previously mentioned, a criticism of this thesis is that the two techniques have not been directly compared. Therefore a study that directly compares the two methods is very desirable. A systematic review of skin surface microscopy [Mayer, 1997] has shown that, where the diagnosis is clinically easy, the technique has little to offer. However, when the clinical diagnosis is equivocal then skin surface microscopy can improve the diagnostic performance of the clinician. It would be in this latter category of lesions where comparison of these two methods would be most useful.

More importantly, it would be useful to see whether features from skin surface microscopy could be combined with SIAscopy features. The Combined Model (Section 5.3) that used SIAscopy features with standard clinical information was shown to be superior in predicting melanoma to the model that used SIAscopy features alone. Thus, it is reasonable to assume that a method that incorporated the extra information to this model would produce a more powerful predictive model for diagnosing melanoma.

6.3.2.1 The Objective Identification of Skin Surface Microscopy Features

From the results obtained in previous studies [Soyer *et al.*, 2001; Argenziano, 2001], it is apparent that the identification of many of these features is not reliable or reproducible. Indeed, whilst Menzies (1996a) stated of blue-grey veil that, “It is the single most significant surface microscopic finding of invasive melanoma…”, this feature is less reliable or reproducible than any of the four SIAscopy features [Argenziano, 2001]. This subjectivity is a direct result of the optical properties of the skin. For instance, the perception of the colour blue may arise from any or combinations of the following: dermal melanin, deoxyhaemoglobin, haematoma, a thinning of the papillary dermis or hyperkeratosis [Cotton, 1998]. Conversely, the perception of the colour blue can be masked by organised haematoma or excessive epidermal melanin. Blue-grey veil has been described as "superficial fibrosis with melanophages and/or pigmented malignant cells in the papillary dermis" [Bahmer *et al.,*

1990]. It is possible that this prescription could be reproduced by the combination of dermal melanin and collagen SIAgraphs and this warrants further investigation.

SIAscopy could assist in the objective identification of morphological features. Total melanin SIAgraphs could assist the clinician in the analysis of those features that are due to melanocytes such as pigment network, brown globules and black dots. However, the lateral resolution of the SIAscope at present is insufficient to assess fine networks and small dots, though a newer system is currently being developed that will address this problem. Similarly, blood SIAgraphs could help in the identification of blood lagunes that are pathognomic of capillary haemangiomas [Menzies *et al.,* 1996a] and dermal melanin SIAgraphs could help to identify blue dots that represent melanophages or melanoma cells. Further on, the automatic detection and identification of these features could be performed using computer algorithms that have been employed in other systems [http://www.molemaxii.com].

6.3.3 Automation and Computerised Image Analysis

The data provided by the SIAgraphs and the features identified thus far could be used within an automated diagnosis system. The total melanin SIAgraph provides a good means of segmenting the lesion in terms of its melanin containing regions. Once segmented, the lesion can be analysed for its border asymmetry and edge; shape asymmetry and variations in distribution of pigment. In addition, an accurate and repeatable measure of the maximum diameter of the lesion can be obtained. Earlier work has shown that analysing segmented colour images in this manner yielded useful and promising results [Hall, 1992]. Of particular interest would be the use of algorithms to objectively measure border and content asymmetry. This has proven to be a useful predictor of melanoma in clinical examination [Fitzpatrick *et al.,* 1988] and in skin surface microscopy [Stolz *et al.,* 1994; Menzies *et al.,* 1996a]. Of the four SIAscopy features, asymmetry demonstrated the least reliability and reproducibility. Objective and automated identification of asymmetry and, conversely bilateral symmetry, may serve to increase the specificity of the predictive model. Further work is currently underway to extract this information.

The SIAscopy features that were useful predictors for melanoma could be identified using automated feature extraction. Analysing dermal melanin SIAgraphs for the presence of dermal melanin is a simple enough task. However, once regions of dermal melanin have been identified, more sophisticated analysis such as shape asymmetry and roughness using wavelet functions and Fourier transformation analysis may yield further important diagnostic information [Umbaugh, 1998]. In addition, comparisons of the dermal melanin content to the total melanin content may also yield important diagnostic information that may help to distinguish an invasive melanoma from a compound naevus. This would help to increase the specificity of the system in predicting melanoma but such measurements could only be performed by using computer algorithms. Analysing collagen SIAgraphs for roughness could

be performed by either using wavelet functions and Fourier transformation [Umbaugh, 1998] or fractal analysis [Hall *et al.,* 1995]. The former two functions could be used to transform the SIAgraph. Subsequently differential analysis could be performed by filtering the resultant image into high frequency and low frequency regions. Using this technique it may be possible to extract regions of fibrosis, as well as regions of regression, from within the lesion.

6.3.4 Monitoring & Screening Patients

6.3.4.1 Monitoring of Patients

The monitoring and surveillance of patients with pigmented skin lesions is important, especially in those groups of patients with dysplastic naevus syndrome. Research has shown that detection of early melanoma can be increased in these groups by carefully comparing baseline clinical photographs with subsequent follow-up ones [MacKie *et al.,* 1993; Kelly *et al.,* 1997]. Furthermore, digital imaging systems allow the archiving and rapid retrieval of images that can be compared for the early detection of melanoma [Stolz *et al.,* 1996; Kittler *et al.,* 2000]. These systems not only utilise standard clinical photographs but also digital skin surface microscopy images that serve to enhance the diagnostic performance of the clinician. It would be useful to assess SIAscopy as a tool for monitoring these patients. Any change in the distribution of the total melanin or dermal melanin content of the lesion may indicate a change to an invasive melanoma. Furthermore, the development of displacement with blush may be associated with the onset of invasion.

Another group of patients that may benefit from monitoring with the SIAscope are those patients with lentigo maligna. Whilst the management of these patients contains areas of controversy, with most clinicians opting for aggressive treatment involving early and radical excision, there are clinical situations where more conservative management may be appropriate [Gaspar & Dawber, 1997]. SIAscopy may be able to aid the clinician in the decision process by detecting areas of dermal melanin within the lesion that would indicate the onset of invasive disease. In addition, SIAscopy may be able to detect early, localised recurrence that is a common feature of this disease.

6.3.4.2 Screening Patients

It would be useful to evaluate the SIAscope in the setting of general practice where the possibility exists to screen patients before being referred to the Dermatologist at the local hospital. One study that assessed the referral patterns to a pigmented skin lesion clinic by GP's found that after a dramatic increase in the referral rate this then plateaued at 13 per 100000 patients with a 'strike rate' of 1 in 33 lesions being confirmed as melanoma [Melia *et al.,* 1995b]. A further study has also shown an increase in diagnostic skill with simple education but a wide variation in skill between the GP's was still observed [Bedlow *et al.,* 2000]. These studies would perhaps indicate that there is a wide variation in skill and referral

patterns that may be in part due to the low prevalence of melanoma in this clinical scenario coupled with the desire not to miss a potentially fatal disease at a curable stage. Analysis of individual SIAscopy features showed that the presence of dermal melanin had a very high sensitivity (and consequently a very low false-negative rate) for melanoma. It would be possible to produce a small device that simply detected the presence of dermal melanin alone that could be used in this setting. Whilst there remains the potential to miss not only the very small proportion of melanomas that do not display dermal melanin but also the amelanotic melanoma, the system could prove a useful tool in reducing the number of 'unnecessary' referrals to the local hospital.

In addition to screening in the general practice setting, there also remains the possibility of screening patients by using telemedicine techniques at the local hospital. A study demonstrated the potential of this method by assessing images that were sent to a Consultant

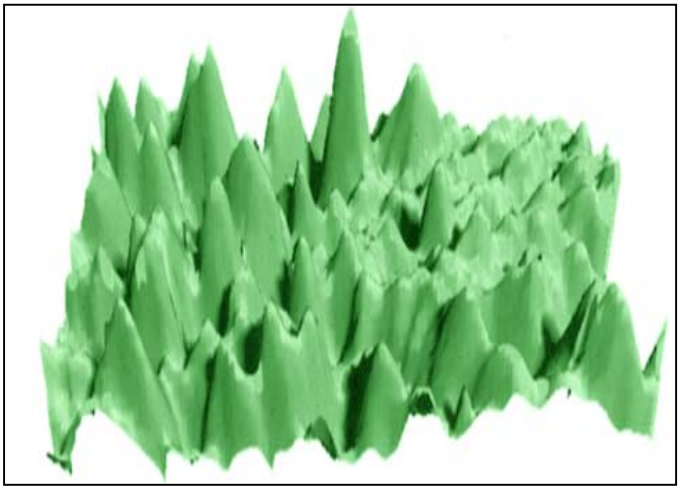

Figure 6.1
3-D topographical map generated from collagen SIAgraph of a BCC. The right side of the image demonstrates flattening of the contour of the dermoepidermal junction at the margin of the invasive tumour

Dermatologist by a junior colleague from a peripheral hospital [Lewis *et al.,* 1999]. One problem with the technique in this study was the loss of visual information produced by photographing and digitising the image. As SIAgraphs are graphical representations of digital information, this would not be an issue in this situation.

6.3.5 Application of the SIAscope in Other Cutaneous Diseases

This thesis has demonstrated that the SIAscope is a powerful and useful tool in the diagnosis of pigmented skin lesions. It is not unreasonable to suggest that the role of the SIAscope could be extended to the diagnosis and management of non-melanoma skin cancers and vascular anomalies.

6.3.5.1 Basal Cell Carcinoma

In the management of basal cell carcinoma, the main problem is not usually one of diagnosis but of adequate treatment. Often the peripheral margin of the tumour extends beyond the region that can be seen by the naked eye meaning that the surgeon needs to take a

substantial rim of normal skin to be sure of adequate clearance [Stal & Spira, 1997]. Furthermore, tumours may extend deeper that may be clinically apparent at time of excision. In cosmetically sensitive areas, treatment may include Moh's micrographic surgery that can take many hours to complete [Ashinoff, 1997]. By producing three-dimensional topographical maps of the collagen SIAgraph, it may be possible to detect areas of local destruction or change in the contour of the dermoepidermal junction caused by invasive tumour (figure 6.1). These maps may help to demarcate the lateral margin of the tumour. Similarly, advanced invasive disease may be indicated by collagen holes that may aid the surgeon in the pre-operative planning of excision margins of the tumour.

6.3.5.2 Port Wine Stains

Port wine stains are congenital vascular malformations that formed from an abnormal dilatation of the vessels in the papillary dermal plexus. Treatment usually involves lasers that selectively ablate vessels according to the absorption spectra of deoxyhaemoglobin and oxyhaemoglobin [van Gemert *et al.,* 1997]. The power produced by the lasers is proportional to the amount of heating of the dermis that is produced and also the depth of penetration of the light beam into the skin. Therefore there is a cut-off point that occurs at which treatments of larger and deeper vessels are at the risk of significant and permanent scarring. Standard treatment involves calibrating the laser by observing the results of a test-patch in a less visible region of the body. It is possible for the SIAscope to return information regarding the depth and concentration of the vessels within the lesion by direct measurement of these parameters as well as by visual analysis of the distribution of haemoglobin in the blood SIAgraph. As a result, it would be useful to investigate the use of the SIAscope not only as a system for calibrating the laser but also for screening of patients and advising them as to the likelihood of scarring as a result of the treatment.