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Review Article

An update on the management of cutaneous melanoma

皮膚黑色素瘤治療新知

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Malignant melanoma is the world's fastest growing cancer, in terms of incidence, in the Caucasian population. There is a paucity of data regarding age-related population based studies in Chinese people. There are observations to suggest that malignant melanoma is a different disease in the Chinese with a far higher proportion of lesions being acral lentiginous in nature. Controversy abounds regarding the management of malignant melanoma and good evidence to support definitive treatments is lacking. Most recently, sentinel lymph node biopsy in melanoma has been called into question as being unnecessary and of doubtful predictability. Hong Kong needs to establish a comprehensive melanoma registry and a single melanoma center to optimise epidemiological, clinical and outcome data in order to maximise improvements in patient care.

惡性黑色素瘤在白種人羣中的發病率增長極快。在中國人羣中缺乏相關的以年齡和人羣為基礎的調查研究。有觀察顯示中國人惡性黑色素瘤發生肢端雀斑痣樣病變的比例極高。有關惡性黑色素瘤的治療仍有爭論，確定性治療缺乏支持理據。最近，應用前哨淋巴結活檢術診斷黑色素瘤的必要性及其診斷價值受到質疑。香港需要建立一個綜合性的黑色素瘤登記處和唯一一個黑色素瘤治療中心，以便完善相關的流行病學資料、臨床資料和預後資料的統計，從而提升對病人的治理。

Keywords: Acral lentiginous melanoma, incidence rates, malignant melanoma, melanoma centre, melanoma registry, sentinel node biopsy

關鍵詞：肢端雀斑痣樣黑色素瘤，發病率，惡性黑色素瘤，黑色素瘤中心，黑色素瘤登記處，前哨淋巴結活檢

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Introduction

Cutaneous malignant melanoma is a very different disease in the Chinese than in the Caucasian

At the outset of this review it is important to stress the ethnocentricity of the published literature pertaining to the fascinating and challenging condition, cutaneous malignant melanoma. The overwhelming volume of the published literature

has been written by western authors and deals with Caucasian patients. A recent paper describing ethnic differences amongst patients with cutaneous melanoma was published by authors from the MD Anderson Cancer Centre in Houston, Texas.[1] On closer study, however, whilst they reported on 48,143 Caucasians, they included only 394 asian/ pacific islanders and all the patients reported in the study represented ethnic groups within the United States of America. A two part review of malignant melanoma 'in the 21st Century', published in the proceedings of the Mayo Clinic, was supported by over 500 references but in only one of these was the racial differences in incidence mentioned.[2,3] An alarming fact is that in the Caucasian population the world wide incidence rates for cutaneous melanoma have risen faster than any other malignancy over the past thirty years.[4] Amongst the Caucasian populations, there are marked differences in incidence, the highest incidence in the world being in New South Wales, Australia with a greater than seven fold rate per one hundred thousand population than Polish people in Warsaw.[5] The risk factors in these populations include: fair, freckled and moley skin, severe childhood sunburn, adult exposure to sun in individuals with unacclimatised skin (e.g. office workers) and exposure to sun bed and sun lamps. It is evident that sun and ultraviolet exposure play a major role in the development of melanoma in Caucasians. But does the same apply to the Chinese and other Asian populations? Cutaneous melanoma is rare in the Chinese population and whilst malignant melanoma is a cancer captured by the Cancer Registry (a voluntary reporting system operated by the local Hospital Authority) in Hong Kong, it is not easy to determine what proportion of the small number of cases registered reflect the actual disease burden in Hong Kong Chinese. A hospital based study from two centres extending over 18 years, identified 63 cases of cutaneous melanoma in Hong Kong ethnic Chinese.[6] It is not possible in such a study to determine incidence rates as the catchment populations were not stated and the recruitment time between the hospitals involved varied. However, the total number of patients should be considered in the context of the annual numbers of new cases of melanoma recorded in the Hong Kong Hospital Authority Statistical Returns. Figure 1 shows the absolute number of cases of melanoma over the past eight years and the absolute number of deaths each year. These data show a very alarming trend as the mortality rate from malignant melanoma has remained fairly constant at around 60% of the incidence rate. The picture in the Caucasian populations is very different and whilst incidence rates have increased dramatically, mortality rates have not risen significantly and have even fallen.[7] Part of this trend in the Caucasian populations is due to the far greater public awareness of the risks of melanoma and the presentation of lesions at a much earlier stage of the disease. Such lesions are of course associated with a much better prognosis. In Hong Kong we have some absolute figures but we do not know who is developing melanoma and who is dying from melanoma. It is obvious that a very important part of improvement in care of any medical condition must be based on good data, and that is lacking in Hong Kong, with regard to cutaneous melanoma. A detailed melanoma registry is needed. The hospital based study did indicate that 52% of melanoma cases in the Chinese population are of acral lentiginous type, this compares to less that 2% in most Caucasian

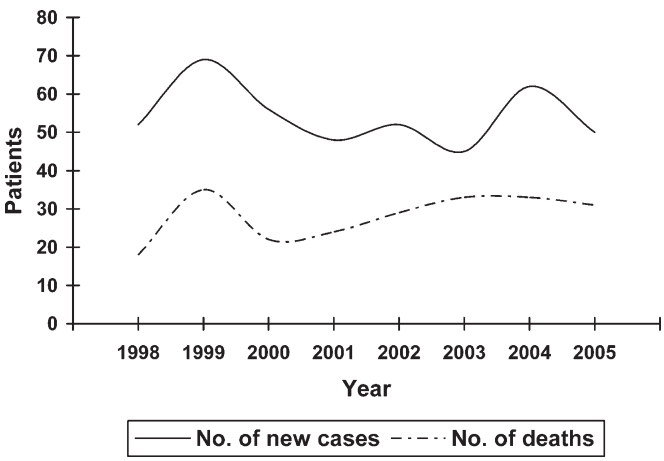

Figure 1. The absolute numbers of new cases and deaths from malignant melanoma recorded in the Hong Kong Cancer Registry 1998-2005.

studies. Twenty-one percent are superficial spreading in the Chinese compared to 60% in Caucasians. The acral lentiginous lesions are the least likely to be associated with sun exposure, so with a significantly reduced overall incidence and a significantly different pattern of morphological presentation, it would appear that cutaneous malignant melanoma is a very different disease in the Chinese than in the Caucasian.

Diagnosis of cutaneous melanoma

In Caucasian skin, the diagnosis is based primarily on the history of recent change in a long standing pigmented lesion. The changes are related to colour, size, shape, texture, sensibility and also presence of bleeding or ulceration. The best practice guidelines proposed by the British Association of Dermatologists[8] is that the patient with such a lesion should be referred immediately for a specialist review and that an excision biopsy should be performed. The situation in Hong Kong is a little different as the vast majority of skin malignancy is due to pigmented basal cell carcinomas. These do not tend to arise from pre-existing naevi and also are usually fairly slow growing. Nevertheless they can cause diagnostic confusion. In addition, the majority of melanoma is of acral lentiginous type and may be fairly well advanced by the time the patient is aware of them. Urgent referral to a specialist dermatologist may occur but there may be some reluctance to undertake an excision biopsy as this has implications both for resource utilisation and patient care logistics. The reason why excision biopsy is recommended is that definitive treatment is determined by the Breslow thickness of the lesion. For this to be accurately determined, the entire lesion needs to be assessed. There is also the theoretical risk of upstaging a lesion by implanting tumour tissue at a deeper level in the process of taking an incision biopsy. Resolving these various concerns is more a matter of organisation which will be discussed further below.

Management of cutaneous melanoma

Excision margins

With regard to local management of the primary lesion, the definitive treatment is surgical and in the absence of any relevant studies in Chinese populations, the recommendation for excision margins are as in the published best practice guidlines (Table 1).[8]

It should be noted that these recommendations are based on two randomised clinical trials[9,10] reported last century and a National Institute of Health Consensus Panel[11] reporting over fifteen years ago. More recent reviews showed no statistically significant difference between patients treated with wide or narrow excision margins with regard to overall mortality, local and regional recurrence.[12] This particular meta-analysis was performed on data derived from clinical trials of thin and intermediate lesions, and lesions >4 mm in thickness were not included. Thompson from the Sydney Melanoma Unit points out that not only is evidence lacking for thicker lesions, but also most trials have excluded patients who had melanomas in the head and neck region or distal extremities where the complexity of reconstruction

Table 1. Excision margins recommended for cutaneous melanoma[8]

Breslow thickness	Excision margins	Grade of evidence
In situ	2-5 mm	Level B, Grade III
<1 mm	1 cm	Level A, Grade I
1-2 mm	1-2 cm	
2.1-4 mm	2-3 cm	
>4 mm	2-3 cm	Level B, Grade III

was related more directly to the margin of excision.[13] Another very authoritative review in the New England Journal of Medicine displayed a comprehensive algorithm for the management of cutaneous melanoma and for lesions with a Breslow thickness of ≧2.01 mm, an excision margin of ≧2 cm was suggested.[14] It would be inappropriate to leave this discussion without observing that the majority of melanomas in the local population are acral lentiginous and that these tumours do not figure highly in any trial of excision margins. Also there are controversies regarding the acral lentiginous lesion particularly regarding diagnosis, clinical criteria and prognosis.[15,16]

Regional lymph nodes

Another very controversial area in management of cutaneous melanoma is the management of regional lymph nodes. Melanoma is the skin cancer with the greatest metastatic potential, spreading locally, via lymphatics to regional nodes, and by the blood stream to distant organs. Over the last quarter of a century there have been some major changes, as well as controversies, over the surgical management of the regional nodes. Traditionally, elective lymph node dissection was considered for patients without evidence of nodal disease. This however did result in increased morbidity and a growing awareness that it imparted no survival benefit. Thus, alternative methods of staging the disease were sought.[17] The practice of sentinel lymph node biopsy has now become fashionable. The sentinel lymph node is defined as the first drainage lymph node from the primary tumour site and the first site of any nodal metastases. Sentinel localisation is based on blue staining and radiolocalisation using TC-99m sulphur colloid.[18] Sentinel nodes are excised and sent for immunohistochemical staining or more sophisticated analysis using RT-PCR detecting mRNA for tyrosinase. The role of sentinel lymph node biopsy is not, however, without controversy. Sentinel-node negative patients still develop local and regional recurrences,[19] sentinel nodes may appear as 'in transit' nodes outside regional node basins leaving a dilemma as to how to manage the regional nodes[20] and melanoma patients with positive sentinel nodes who do not undergo a completion lymphadenectomy do not have a statistically different prognosis from patients undergoing completion lymphadenectomy.[21] The prognostic false-positivity of the sentinel node in melanoma is the topic of review in a recent paper which cogently argued against sentinel node biopsy and suggested that ultrasonography was the best way to image regional node-basins.[22] This review underlined the significance of the findings of the multicentre selective lymphadenectomy trial reported by Morten.[23] As in so many aspects of cutaneous melanoma, the evidence is not available upon which clinical practice can confidently be based. More studies are needed.

Systemic therapies

The same applies for the advanced melanoma. The search for effective adjuvant therapy to prevent local and regional recurrence has focused on the marked immunogenicity of melanoma. Immunotherapy approaches have included trials of interferon, interleukin-2 and melanoma vaccines.[24] A review looking at the treatment of metastatic melanoma focused on the standard treatment with dacarbazine but concluded that whilst this generally produced poor outcomes, adding other therapies did not show any significant improvement.[25] The most recent review to look specifically at vaccines reveals an interesting twist. The paper from Morton's group described the basic vaccine strategies and methods of enhancing vaccine efficacy. They concluded by acknowledging that the efficacy of therapeutic cancer vaccines was dependent upon tumour burden and so the optimal setting for therapeutic immunisation was after resection of all clinically apparent tumour.[26] The 'twist' is that over fifty years ago intrepid pioneers were undertaking some very interesting clinical 'experiments'. Patients with resected advanced malignant disease were having small amounts of tumour being re-implanted after it had been lethally irradiated. Dramatic remission of disease was noted in some, but not all, patients. This was anecdotal medicine but was relayed by the surgeon responsible and he rose to great heights in the field. The point being that there are

potential solutions but they need to be more predictable, safe and specific.

Conclusion and the way ahead

Cutaneous melanoma continues to be a most challenging tumour. It is the tumour with the fastest growing incidence in the Caucasian population but appears to be a different disease in the Chinese population. When considering advances in treatment, it is first essential to define the problem. What Hong Kong needs as a matter of urgency is a melanoma registry. There are good examples of these around the world and it would not be an onerous task to establish such a registry. The challenge then arises in ensuring that the appropriate data is collected and submitted. With the relatively small number of patients involved, this should be possible. The question then arises as to whether the medical community in Hong Kong has reached sufficient maturity to take the next step. From the patients' perspective, which is an enlightened view of medical practice, what Hong Kong needs is a single, multi-disciplinary, multi-specialty melanoma centre established on the foundation of the data, co-ordinated by dedicated nurses and supported by all medical professionals in Hong Kong by appropriate referral of patients. Figure 2 depicts a

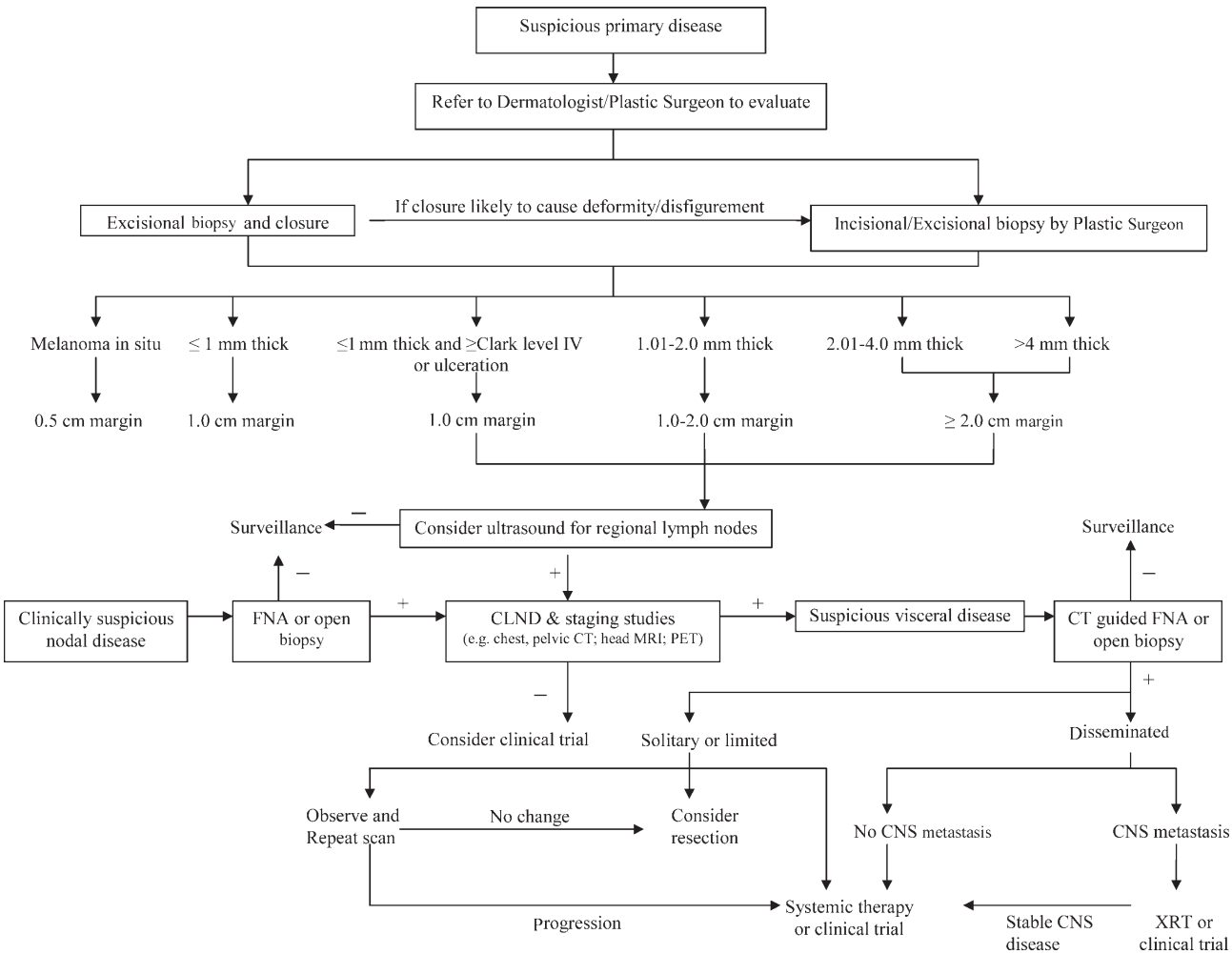

Figure 2. Algorithm for the management of cutaneous melanoma (based on reference 14).
Abbreviations: FNA, fine needle aspiration; CLND, completion lymph node dissection; CT, computed tomography; MRI: magnetic resonance imaging; PET, position-emission tomography; CNS, central nervous system; XRT, external radiation therapy; minus sign: no evidence of disease; plus sign: evidence of metastasis.

management algorithm based on the key point that non-specialist practitioners will refer suspicious lesions. This requires both professional and public education. Thereafter the ideal situation is to have a single multidisciplinary team treating patients in accordance with internationally accepted best practice standards and accumulating detailed local outcome data upon which future developments in care will be based.

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