

## Reports on Scientific Meetings

### The Chinese University of Hong Kong: Seminar on the Management of Skin Cancer

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Organisers: Dermatology Research Centre, The Chinese University of Hong Kong; Social Hygiene Service, Centre for Health Protection, Department of Health, Hong Kong

#### Genodermatoses predisposing skin cancers

Speaker: Professor Ellis KL Hon  
Associate Professor, Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong

The lecture reviewed the key features of some of the commoner genodermatoses with predisposition to skin cancers. Skin malignancy occurs in several multisystemic Mendelian disorders, such as xeroderma pigmentosum and basal cell naevus syndrome.

Nevoid basal cell carcinoma syndrome (basal cell naevus syndrome or Gorlin syndrome) is an autosomal dominant syndrome characterised by a classical triad of multiple basal cell carcinomas developing at a very early age, pits of the palms and soles, and odontogenic keratocysts of the jaw. The skin is extremely sensitive to X-radiation. The gene responsible for this syndrome, the *patched* (PTCH) gene on chromosome 9q22.3-q31, has been identified by linkage analysis.

Hereditary dysplastic naevus syndrome or familial multiple mole and melanoma syndrome (FAMMM) represents a group of heterogeneous disorders of likely polygenic aetiology characterised by a predisposition to cutaneous melanoma. A subset of patients also exhibit an inherited susceptibility to numerous atypical naevi.

Xeroderma pigmentosum is a very rare autosomal recessive disorder characterised by the early onset of multiple skin cancers. The disease is due to defective DNA repair after UV light-induced injury. Cutaneous problems of these patients are severe sunburn with short sun exposure, freckling at an early age, hyperpigmentation, excessive dryness, ageing, and cutaneous neoplasms. Other clinical features include corneal opacities, mental retardation, spasticity and deafness. The mean age of developing skin cancers is eight years old compared with sixty in the general population. The main causes of death are malignant melanomas and squamous cell carcinomas.

Epidermolysis bullosa encompasses many inherited clinically distinctive disorders that share the features of mechanical fragility of skin and blister formation. There are three major forms: epidermolysis bullosa simplex, junctional epidermolysis bullosa and dystrophic epidermolysis bullosa. One of the major complications of some sub-types of this group of diseases is the development of multiple squamous cell carcinomas from chronic non-healing wounds.

**Learning points:**

For these genodermatoses that predispose to skin cancer, clinical testing is available locally to identify the specific gene mutation in the patient or the family for the purpose of diagnosis, development of surveillance plans, genetic counseling and prenatal diagnosis. The astute physician can be the first to identify an individual with a hereditary predisposition to skin cancer.

**Mohs surgery**

Speakers: Dr. Kelvin KL Chong<sup>1</sup> and Dr. Paul CL Choi<sup>2</sup>

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Basal cell carcinoma (BCC) is the commonest skin cancer, which accounts for 90% of skin malignancy in the head & neck region. It is becoming a growing public health problem because of ageing population with exposure to increasing environmental or intentional ultraviolet (UV) irradiation early in life. It is less common in Asians than in light-skinned Caucasians, but the morbidity and mortality are higher because of late presentation and lower public and professional awareness. Non-melanoma skin cancer (NMSC) is uncommon but not rare among the Chinese population in Hong Kong. The incidence of newly diagnosed BCC from a major public dermatologic unit serving the whole territory of Hong Kong in 1990 was 16 per 10,000 new skin case attendances. Demographic data and the distribution of NMSC were comparable to those reported in Caucasians living in North America and Europe. Pigmented BCC was the commonest type of NMSC (60.1%) in the Chinese population, in contrast with rodent ulceration in Caucasians.

Dr. Frederick Mohs developed the Mohs micrographic surgery (MMS), which has helped to revolutionise the treatment of malignant skin

tumour. It is the optimal management for skin cancer in the head and neck region as it allows for total microscopic control of excision with maximal tissue preservation. Removal of successive layers of affected tissues and microscopy of the entire undersurface of each layer by the systematic use of frozen sections are used to control the excision margins. In Dr. Mohs personal series of 1986 patients, the recurrence rate for BCC (n=1773) was only 1% and the recurrence rate for SCC (n=213) was 1.9%. The overall 5-year cure rate was up to 99% as reported after MMS for primary BCC and 94% for recurrent BCC in the literature.

**Learning points:**

MMS, by its unique horizontally oriented frozen sections, achieves the highest cure rates and maximum tissue conservation in the management of specific primary and recurrent skin cancers. The Mohs micrographic surgeon adds a valuable skill in the treatment of advanced and complicated skin cancers; with interdisciplinary cooperation, the contribution is exceedingly beneficial to patients.

**Genetics of skin cancers**

Speaker: Professor Ka-Fai To

Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Hong Kong

Non-melanoma skin cancer is one of the commonest cancers worldwide even though the mortality is low. Although many environmental and genetic factors contribute to the development of skin cancers, the most important is chronic exposure to UV radiation from sunlight. Like all other cancers, non-melanoma skin cancer arises from an accumulation of genetic abnormalities that result in severe cellular dysfunction. A number of genes have been proposed in the development of non-melanoma skin cancer, including p53,

CDKN2A, Bcl-2 and the Ras family of genes, which are typically associated with proliferative and differentiation processes. Also, a number of genetic disorders that predispose individuals to non-melanoma skin cancer have also been identified. Genetic abnormalities in these genes may be the result of somatic mutations that may be promoted by environmental carcinogens, especially UV radiation. UV radiation acts as a carcinogen to induce "UV signature" DNA mutations. UVB causes direct damage and UVA causes indirect damage by inducing oxidative stress. In addition to mutations of genes that directly result in carcinogenesis, polymorphic variants of genes may also play a role in the susceptibility to NMSC. These susceptibility genes may have immunogenic, detoxifying or transcriptional roles that could be involved in increased mutagenesis or activation of cancer-causing genes.

Cutaneous malignant melanoma is one of the most feared cancers because of the aggressive behaviour it displays at a very early stage. Its incidence is increasing fast, possibly because of increasing recreational exposure to sunlight. Many studies conducted over several decades on benign and malignant melanocytic lesions as well as melanoma cell lines have implicated numerous genes in melanoma development and progression. To date, two high-risk melanoma susceptibility genes CDKN2A and CDK4 have been identified. Causal mutations in both genes cosegregate with melanoma and are inherited in a dominant pattern. The CDKN2A gene, located on chromosome 9p21, is the major known high-risk melanoma susceptibility gene. CDKN2A, a tumour suppressor gene, encodes two distinct proteins translated, in alternate reading frames (ARF), from alternatively spliced transcripts. The  $\alpha$  transcript, comprising exons 1 $\alpha$ , 2, and 3, encodes a low molecular weight protein, p16. The p16 protein regulates G1-phase exit by inhibiting the CDK4-mediated phosphorylation of the retinoblastoma protein. The smaller  $\beta$  transcript, comprising exons 1 $\beta$ , 2, and 3, specifies the alternative product p14ARF. p14ARF acts via the p53 pathway to induce cell cycle arrest or

apoptosis. For ease of presentation, we use CDKN2A to represent mutations in the  $\alpha$  transcript; thus, all CDKN2A mutations involve the p16 protein. For mutations of exon 1s and large deletions that involve the p14ARF protein, we use ARF. In contrast to CDKN2A, few families with cosegregating CDK4 germ-line mutations have been identified. To date, all cosegregating CDK4 germ-line mutations have been identified in exon 2, which codes for the p16 binding site.

### **Learning points:**

The clinical implications of the genetics of skin cancer are far-reaching and likely to soon impact the diagnosis, treatment, and prevention of a variety of benign and malignant skin conditions.

## **Epidemiology and clinical features of skin cancers in Hong Kong**

Speaker: Dr. Shiu-Kee Hui

Medical and Health Officer, Social Hygiene Service, Centre for Health Protection, Department of Health, Hong Kong

Skin cancer is one of the commonest cancers in human. Generally, there is an increasing trend of skin cancers in most Western countries. In Hong Kong, the number of new cases of skin cancer increased from 244 to 619 per year (60%) in 22 years (1983-2005). The number of deaths also increased from 24 to 49 per year (51%) during this period.

The increase in the number of new cases and deaths of skin cancers can be largely attributed to the ageing community. As individuals are gaining longevity, a further increase in the number of new cases and deaths is anticipated. Avoidance of overexposure to ultraviolet radiation and early recognition and management of skin cancer is of paramount importance in altering this trend. Health care providers should be familiar with the presentations and clinical features of different skin

cancers in order to achieve the goal of early detection and treatment.

Melanoma has four clinical subtypes: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma. Superficial spreading melanoma is the commonest type of melanoma found in Caucasians which is characterised by brown or black macules with colour variegation and irregular borders. Common sites of involvement are the back in males and lower extremities in females. Nodular melanoma usually presents as a blue, black, red or flesh coloured nodule that may ulcerate or bleed. Lentigo maligna melanoma is the least common form that usually occurs on the face of older individuals. Acral lentiginous melanoma is the commonest form in Asian and African ethnicities. In Chinese, the commonest site is the feet. The ABCD rule and the Glasgow seven-point check list may be used as a guide for early detection of melanoma.

Basal cell carcinomas commonly develop on the face and have a characteristic pearly glistening appearance. Squamous cell carcinomas are mainly found in sun-exposed areas and ultraviolet radiation is the major risk factor. They have a variety of appearances and frequently need a biopsy to make the diagnosis. Cutaneous squamous cell carcinoma in situ includes specific entities such as Bowen's disease and erythroplasia of Queyrat. Other cutaneous malignancies include cutaneous T-cell lymphomas, angiosarcomas, extra-mammary Paget's disease and Kaposi's sarcomas.

### **Learning points:**

The number of new cases and deaths of skin cancer are increasing in Hong Kong. Fighting this trend includes avoiding over-exposure to ultraviolet radiation and early recognition and management of skin cancers.

## **Management of cutaneous melanoma extremities**

Speaker: Dr. Kwok-Chuen Wong

Department of Orthopaedics and Traumatology, Alice Ho Miu Ling Nethersole Hospital, Hong Kong

The prevalence of cutaneous melanoma in Chinese is not as common as that in Caucasians but there is a higher incidence of acral melanoma in Chinese. A thorough examination is required in patients with melanoma in extremities. The focus of examination should be put on the skin with all nodal basins and subcutaneous tissues. For those confirmed to have invasive melanoma, investigations should include a chest X-ray, blood tests such as liver function testing and lactate dehydrogenase. Computed tomography (CT) or positron emission tomography (PET) are not recommended as a routine evaluation as the yield is low in absence of symptoms or abnormal physical findings.

In 2002, the American Joint Committee on Cancer (AJCC) published a revised staging system for cutaneous melanoma. It included new strata for primary tumour thickness by incorporation of primary tumour ulceration in both the tumour (T) and node (N) classification.

In patients with localised melanoma, wide excision of the tumour allows curative treatment. However, there are some controversies in managing patients with clinically negative lymph nodes. Elective lymph node dissection (ELND) and sentinel lymph node biopsy (SLNB) may prolong survival in these patients. In patients with clinically palpable regional lymph nodes, therapeutic lymph node dissection (TLND) is an effective palliative or sometimes curative treatment. The treatment options for metastatic melanoma are limited and experimental treatments include chemotherapy, biological therapies and biochemotherapy, but no single treatment has been proven to prolong survival.

**Learning points:**

A thorough examination of the skin, all nodal basins and subcutaneous tissues are required in patients with melanoma involving the extremities. For those confirmed to have invasive melanoma, investigations should include a chest X-ray and blood tests like liver function test and lactate dehydrogenase. Computed tomography (CT) or positron emission tomography (PET) are not recommended as routine evaluation due to their low yield in those without symptoms.

**Management of skin cancer with radiotherapy**

Speaker: Dr. Wai-Man Sze

Private Clinical Oncologist, Hong Kong

Skin cancer represents a wide spectrum of malignant disease. Different types of tumours can arise from various structures in the skin. The diversity of histogenesis has contributed significantly to the variation in natural behaviour and radiosensitivity of different skin tumours. In general, surgery remains the mainstream treatment for most types of skin cancer. The use of radiotherapy in treatment of skin cancer depends on the extent and radio-sensitivity of the individual case and is useful when surgery is not feasible or resection is incomplete. Radiotherapy also plays an important role in the palliation of the less radiosensitive types or disseminated skin cancer.

Common selection criteria for radiotherapy include age, surgical risk, and tumour size. Elderly patients with high surgical risk or with head and neck lesions which require extensive reconstruction after resection are candidates for radiotherapy. A typical radiotherapy treatment course consists of 5-10 fractions that lasts for 1-2 weeks. A small lesion can be treated with a single fraction while

large and extensive tumours may require a treatment course of up to 6-7 weeks.

**Learning points:**

The use of radiotherapy in treatment of skin cancer depends on the extent and radiosensitivity of the tumour and it is useful when the tumour is unresectable or disseminated. Age, surgical risk, and tumour size are the main determinants of selection for radiotherapy.

**The sun, skin cancers and sunscreen**

Speaker: Dr. William YM Tang

Dermatology Research Centre, The Chinese University of Hong Kong

There is cumulative evidence to support a causal association between skin cancer and ultraviolet rays (UVR). The wavelength spectrum of UVRs extends from 100 nm to 400 nm and is divided into UVA (320-400 nm), UVB (290-320 nm) and UVC (100-290 nm). UVC is mostly absorbed by the ozone layer. UVB and UVA pass through the atmosphere and reach the surface of the earth. The solar UVRs at the earth surface consist of about 95-98% of UVA and 2-5% of UVB.

UVRs produce different biological effects on human skin. Immunosuppression and photocarcinogenesis are closely linked to the causation of skin cancer. Both UVA and UVB are important in the causation of skin cancer, in particular the non-melanoma skin cancer e.g. basal cell carcinoma and squamous cell carcinoma. There is a possible role of UVA in the pathogenesis of melanoma but strong evidence to support this causation is still lacking.

UVA penetrates deep into the dermis of the skin, causing the release of reactive oxygen species leading to DNA damage. On the other hand, UVB penetrates only to superficial skin, causing direct

DNA damage by formation of cyclobutane pyrimidine dimer and pyrimidine pyrimidone. In the pathogenesis of skin cancer, p53 tumour suppressor gene plays an important regulatory role. Mutations in the p53 gene are early events in the development of UV-induced skin cancers and are frequently found in pre-malignant actinic keratosis.

Most sunscreens focus on 'sun protection factor' (SPF), which refers to the ratio of time for minimal erythema development after applying a sunscreen product on the skin compared to when a sunscreen is not used. The protection grade of UVA (PA) system based on persistent pigment darkening (PPD) is also widely adopted. An ideal sunscreen should give an effective, long lasting protection against both UVB and UVA, and should be free from adverse effects. Future development of sunscreen will aim to provide an effective and equal protection against both UVB and UVA.

**Learning points:**

UVRs plays an important role in causation of skin cancer. Both UVA and UVB protection are important.

**Histopathology of skin cancers**

Speaker: Dr. Paul CL Choi

Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Hong Kong

Among all skin cancers, malignant melanoma has one of the worst prognoses. Melanoma can be divided into 5 histological subtypes, which include superficial spreading, nodular, lentigo maligna melanoma, acral lentiginous and mucosal lentiginous types. Acral lentiginous melanoma is the commonest subtype in Chinese. The histological features include an increase in the number of single, spindle shaped melanocytes in lentiginous growth pattern, acanthotic epidermis with elongated rete ridges, presence of Pagetoid cells and dyscohesion of nests. The dermal features include the spindle shaped cells coursing in fascicles, presence of cytologic atypia with hyperchromasia and pleomorphism, increased mitotic activity, lack of maturation and the tendency for extension down to adnexal structures.

Low power microscopic evaluation of melanocytic lesions is inadequate for avoiding the potential pitfalls of misdiagnosing lesions such as nevoid melanoma. Examination of several high power fields for cytological atypia and mitotic activity is prudent.

Additional histological features which may provide prognostic information include Breslow thickness, presence of ulceration, satellitosis, host lymphocytic infiltrate, mitotic activity and numbers of involved lymph node.

**Learning points:**

Histology provides important diagnostic and prognostic information in management of skin cancers.