



Editorial

Non-Melanoma Skin Cancer – An Underestimated Global Health Threat?

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Non-melanoma skin cancer (NMSC) is the most common cancer worldwide. Australia has the highest incidence of skin cancer in the world, exceeding 2000 per 100 000 person-years and it is increasing [1]. In the USA, more than 3 million individuals are diagnosed with NMSC each year [2,3]. In the UK, during 2014–2016, about 147 000 new NMSC cases were diagnosed every year, more than 400 every day [4]. Data show that between 1976 and 1984, the overall incidence of basal cell carcinoma (BCC) increased by 145% and of cutaneous squamous cell carcinoma (cSCC) by 263%. Between 2000 and 2010, women had the greatest increase in incidence rates for both types of NMSC and incidence rates were generally increasing in people younger than 40 years [5]. All available data probably represent an underestimate, as many NMSC are not reported to cancer registries. Despite the high incidence of NMSC, epidemiological data remain poor across the globe.

Fortunately, in contrast to melanoma, mortality from NMSC remains low. According to Cancer Research UK, there are about 950 NMSC deaths in the UK every year, with NMSC accounting for less than 1% of all cancer deaths (2016 data) [4]. The Canadian Cancer Society estimates the 5-year relative survival to be 100% for BCC and about 95% for SCC [6]. Given the rapidly rising incidence of NMSC and the fact that most are either preventable or curable, there is a growing interest in NMSC worldwide. The increasing incidence has already proved to be a massive burden on already stretched health care systems [7,8]. Although detailed data on current and future costs of skin cancer are limited, Vallejo-Torres *et al.* [9] estimated the expected costs of NMSC to be in the range of £889 to £1226 per case.

In contrast to other cancers, NMSC lacks robust evidence for optimal clinical management. NMSC treatment has traditionally been considered a ‘Cinderella’ service and therefore has had a significant lack of research investment. For many years, the skin cancer subspecialty has been an ‘add on’ to other specialities, especially head and neck cancers, rather than a speciality on its own. Teaching courses in skin cancer usually focus on a single treatment modality and true interdisciplinary workshops are uncommon.

For many patients, NMSC remains as a single disease entity with treatment decisions predominantly based on patient preference and clinician expertise. Most patients with early ‘low-risk’ disease are successfully treated with a non invasive or surgical modality. Patients with high risk NMSC are referred for surgery or radiotherapy which can offer similar chances of cure, but functional and cosmetic outcomes may differ. However, there is no universal staging system or agreed definition of risk grouping of tumours, often leading to discrepancies in the management of patients with NMSC. The recent eighth TNM system has also not been evaluated regarding prognostic factors and their influence on NMSC management. At the other end of the spectrum are the patients with high-risk primary, recurrent or metastatic NMSC who require multimodality treatment. Recent improvements in surgical and radiotherapy techniques and newer ablative approaches are being incorporated into clinical practice to derive a personalised treatment approach to obtain a higher chance of cure with improved functional and cosmetic outcomes. Ideally, the treatment approach for NMSC should be molecular-derived and evidence-based, taking into consideration the biological behaviour of NMSC and the overall health status, including functional and mental abilities, and preference of patients. This special issue will explore the recent developments in NMSC, appraise the current evidence and provide future directions.

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Surgical techniques have significantly changed over the past years, with further refinements in reconstructive and Mohs surgery. In their article, Kosutic *et al.* [10] illustrate how surgical reconstruction has practically lost its boundaries and the traditional aim of complete clearance in skin surgery has now been raised to a high degree of functional and aesthetic reconstruction.

Radiotherapy has been used in NMSC for over a century and remains an effective alternative to surgical excision in the definitive, adjuvant and palliative settings. As a tissue-preserving modality, compared with surgery, radiotherapy may offer better cosmetic and functional outcomes with well-tolerated side-effects, at least in a subgroup of patients. Modern skin radiotherapy can be delivered by either an external beam technique (mainly superficial or electron beams) or direct application of a radiation source (superficial or interstitial brachytherapy). Veness *et al.* [11] summarise the evidence for the use of radiotherapy for basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) with a particular emphasis on novel imaging techniques such as high frequency skin ultrasound for more accurate treatment planning and the use of radiation in elderly and frail patients. The recently published GEC-ESTRO ACROP guidelines on brachytherapy for skin NMSC shows that carefully tailored skin brachytherapy is an efficient and well-tolerated treatment offering excellent cosmetic outcomes and low toxicity [12]. It is also a good alternative, if not the treatment of choice, for those lesions that cannot be safely removed by surgery in cosmetically and functionally challenging locations (e.g. the dorsum of the hand or foot or lower leg). In addition, the variety of recommended brachytherapy schedules offers options for a shorter overall length of treatment with better patient compliance, particularly for elderly patients who represent the vast majority currently considered for brachytherapy. Hypofractionated external beam radiotherapy and brachytherapy are also clinically feasible treatment options for symptomatic NMSC in patients with poor performance status and comorbidities precluding active treatments who otherwise would have been referred for best supportive care [13,14].

There are numerous alternative local treatments in NMSC. O'Donoghue *et al.* [15] discuss the use of electrochemotherapy and other ablative treatments and provide evidence for their effectiveness in selected patients with various types of NMSC, stressing the importance of the 'right treatment to the right lesion' and patient preference.

Metastatic and locally advanced inoperable cSCC is not infrequent, especially in the aging population. A recent Public Health England study of a cohort of patients with cSCC and metastatic cSCC in England from 2013 to 2015 indicated a cumulative incidence of metastatic cSCC of 1.1% in women and 2.4% in men with a primary cSCC [16]. This unique population-based study identified significant increases in the risk of metastasis in patients who were aged 80 years and above, male, immunosuppressed, in higher deprivation quintiles and with primary cSCC located on the ear and lip.

Although chemotherapy may be considered in metastatic or locally advanced NMSC, there is no established standard of care. cSCC is usually treated similarly to head and neck cancers, with a combination of platinum and 5-fluorouracil; but response to treatment is very disappointing and often worse than in mucosal SCC of the head and neck. Toxicities of the platinum–5-fluorouracil combination can be significant. Despite a rapidly rising incidence and complexity of NMSC treatments, phrases such as 'paradigm shift' or 'breakthrough discovery' are rarely heard of in the context of NMSC. Nevertheless, there are some notable successes in systemic therapies using hedgehog inhibitors, PD-1 inhibitors and other emerging novel agents [17]. It is remarkable to see the transformation in care for patients with metastatic cSCC, from best supportive approaches to novel treatments that not only improve quality of life but also possibly improve survival. Currently, these novel systemic treatments are indicated only in patients with metastatic or locally advanced NMSC not suitable for surgery or radiotherapy and their role in the adjuvant setting needs further evaluation.

The term NMSC has traditionally been used to refer to all skin cancers except melanoma. Due to the overwhelming incidence of BCC and SCC compared with other types of NMSC, the term 'keratinocyte carcinoma' has recently been proposed due to their common origin from epidermal keratinocytes. Craig [18] provides an excellent dermatopathological review of uncommon cutaneous malignancies, including adnexal tumours and cutaneous sarcomas. This article is a much-needed guide for non-specialists to navigate among complex classifications and pathological diagnosis in NMSC. This spectrum of tumours, although rare, is becoming more commonly discussed at multidisciplinary team meetings and presents a real challenge in diagnosis and treatment.

Immunocompromised patients have a higher risk of developing NMSC compared with the general population. NMSC in transplant patients also tends to be more aggressive, leading to higher morbidity and mortality. The article by Collins *et al.* [19] dedicated to immunocompromised patients reviews the aetiology and prevention together with management and treatment strategies for NMSC and field cancerisation.

Merkel cell carcinoma (MCC) is a rare neuroendocrine skin cancer, traditionally included under the term of NMSC, although its origin and aetiology remain unclear. Merkel cells share both epidermal and neuroendocrine features. There is some evidence indicating immunosuppression, ultraviolet light exposure and polyoma virus infection as possible aetiological factors. The incidence of MCC is also rising at a rate higher than that of other skin neoplasms. Due to the relatively low incidence previously, the existing evidence for the management of MCC is based mainly on case series and single-arm institutional studies. Steven *et al.* [20] have reviewed the current diagnostic approach and management of MCC in primary and metastatic disease, with emphasis on evolving systemic treatment options.

Primary cutaneous lymphomas (PCL) remain a challenging diagnosis. These are non-Hodgkin lymphomas that

present in the skin with no evidence of extra-cutaneous disease at diagnosis. PCL must be distinguished from nodal or systemic malignant lymphomas secondarily involving the skin. The World Health Organization classification encompasses over 100 distinct lymphoid neoplasms. Specht and Skov [21] review the current understanding and the range of local and systemic treatment options for PCL.

This special issue of *Clinical Oncology* on NMSC therefore gives an insight into the evolving concepts in diagnosis and novel treatment options and their potential clinical applications. We hope the issue will be a valuable reference for daily clinical practice and will inspire the readers in designing future clinical studies. Finally, it is now time for more collaborative interdisciplinary effort to derive a robust evidence-based approach for the optimal management of NMSC before it becomes a real global health threat. We would like to dedicate this Special Issue to Dr Tony Woo, an Australian Radiation Oncologist, who made an immense positive difference to the lives of many patients, including those suffering from skin cancer.

Conflict of Interest

The authors declare no conflict of interest.

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