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Towards better treatment outcomes for Australians with skin keratinocyte cancers - time for the patient voice?

Abstract

Recently updated Australian national keratinocyte cancer treatment guidelines show limited advances since the previous guidelines published more than 10 years earlier. Evidence is disjointed and sometimes outdated. Emerging treatments have not been integrated into optimal care pathways. Australians have the highest incidence of keratinocyte cancers and willingly participate in clinical trials, yet we generate relatively little high-quality clinical trial evidence. Why is this and what are the ways forward? We propose increasing access to multidisciplinary teams and encouraging patient advocacy groups that can guide and collaborate with researchers and decision makers to develop better treatments and care delivery models.

Keywords: keratinocyte cancers, skin cancer, basal cell carcinoma, cutaneous squamous cell carcinoma, nonmelanoma skin cancer, Australia, patient advocacy

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Introduction

Keratinocyte cancer (also known as non-melanoma skin cancer) is Australia's 'national cancer'.[1] Keratinocyte cancers are the most common malignant tumours in Australia,[2] and Australian and New Zealand populations suffer the world's highest incidences.[3] Keratinocyte cancer includes basal cell carcinoma (BCC) and the spectrum of cutaneous squamous cell carcinoma (cSCC) from actinic keratosis through squamous cell carcinoma in situ to invasive cSCC.

Almost all keratinocyte cancers in Australia are attributable to UV radiation from the sun,[4] and minimizing UV exposure is the most effective and cost-effective prevention strategy.[2] Yet, despite our prevention campaigns, keratinocyte cancer necessitates more hospital treatments than any other cancer[5] and is probably the costliest cancer to the Australian healthcare system.[2] Patients also bear significant out-of-pocket expenses for treatment and prevention.[2,6] The Australian Institute of Health and Welfare (AIHW) estimates that the incidence of keratinocyte cancer and its associated mortality rate are rising[7] and ranks keratinocyte cancer among the top 20 killer cancers.[7]

Early detection is crucial. Treatment modalities include surgery, radiotherapy, cryotherapy, electrodesiccation and curettage, and topical and systemic chemotherapy. Emerging therapies include targeted therapy directed against the hedgehog signaling pathway, and checkpoint inhibitor immunotherapy. Optimal treatment depends on the tumour stage, anatomical site and patient-related factors.

Patients and clinicians lack decision support tools

Staging is more complex for keratinocyte cancers than many other cancer types, because the current tumour, node, metastasis (TNM) classification system for malignant tumours[8] does not consider important risk factors for local metastatic spread and factors affecting prognosis, such as tumour thickness, poor degree of differentiation, and perineural or lymphovascular invasion.[9] These factors are used by clinicians to determine optimum therapy, though there is very little data to guide this process.

When a keratinocyte cancer is amenable to multiple treatment options, patients and clinicians must consider the probability of definitive cure versus risk of recurrence, weighed against the acceptability of likely functional and aesthetic outcomes. However, in many clinical situations, the comparative risks and benefits have not been defined in high-quality trials.

Current National Health and Medical Research Council-approved Australian clinical practice guidelines[2] can offer few recommendations on patient selection factors and optimal treatment sequencing, due to limited available evidence on outcomes for each treatment modality. The guidelines make evidence-based recommendations where possible, but these do not furnish an integrated decision tree for clinicians and patients, or clearly help us identify precisely which patients should be offered which treatment. A national care pathway,[10]

published in 2016, was not intended to provide 'detailed clinical practice guidelines' and has not been updated.

Evidence gaps hamper clinical progress

Current national clinical practice guidelines, updated in 2019,[2] show few advances in treatment since the previous guidelines published in 2008,[11] which in turn reflected a lack of new evidence since the first Australian guidelines in 2002.

The 2008 national guidelines stated that 'it is fair to say that there have not been dramatic breakthroughs in either diagnosis or management since the original version was published.'[11] The working party Chair noted that 'a disappointing feature of this review is the lack of well-designed prospective randomised studies trying to answer critical questions about surgery in the treatment of these tumours' and that there had been 'virtually no new major publications since this Guide was last published' on critical areas with a lamentable 'lack of definitive answers'.

When considering the latest guidelines, published in 2019, the situation is not much changed. Few major randomised controlled trials (RCTs) have been published, and there are relatively few Australian data. While there has been an overall increase in the number of Australian keratinocyte cancer surgical or radiation treatment studies cited in Cancer Council Australia keratinocyte cancer guidelines,[12] these include very few RCTs. Most Australian intervention studies included in systematic reviews for the 2019 guidelines represented retrospective cohort studies or case series.[2]

The current guidelines identify several important evidence gaps, including the optimal roles of radiotherapy and chemotherapy in combination with other treatment modalities, and outcomes of topical treatments and cryotherapy.[2] Research priorities include new strategies for managing keratinocyte cancers in immunosuppressed patients, the role of sentinel node biopsy, and better protocols for identifying patients at risk of cSCC recurrence.[2] Few studies have compared outcomes with different follow-up regimens, so rational surveillance protocols cannot be developed[2] – unlike with other cancers.

Outcome measures are not consistent between studies,[2] so it is not possible to compare surgical with nonsurgical treatment modalities for the same patient subgroup. Current national clinical practice guidelines have called for well-designed RCTs, including Australian studies, comparing surgical and non-surgical treatments using the same well-defined endpoints and outcome measures.[2] Current US guidelines for the management of BCC[13] and cSCC[14] similarly acknowledge important evidence gaps as a barrier to the optimal management of keratinocyte cancers.

Why are there few high-quality Australian clinical trials in keratinocyte cancer?

It is not due to lack of interest in our community. Skin cancer is important to patients due to its high burden of disease and costs. There is a high demand for skin checks, as evidenced by the rise in GP-run skin clinics.[15] Australian cancer patients are well-educated and willing participants in clinical trials.

Nor is it due to lack of interest or expertise among investigators; a parliamentary inquiry report[1] noted that 'Australia has earned a global reputation for its medical research, particularly in the area of cancer research,' and emphasised that it is 'important that Australia continues to lead global research into skin cancer and work to discover new and improved treatments.'

One barrier to keratinocyte cancer research in Australia may be that it is relatively 'invisible' due to poor records. Reporting of BCC and cSCC to cancer registries is not mandated – understandably so, since reporting would be onerous (e.g. when multiple cancers are treated in a single session in an individual patient). However, this can give the impression that the government does not consider skin cancer important, despite its very high incidence and burden on the health system and the Australian public. Recognition of a disease as a national priority makes it easier for independent investigators to win funding grants. Keratinocyte cancer's non-notifiable status means it is not included in the Australia Cancer Database. AIHW relies on data from surveys and on national morbidity and mortality databases that do not differentiate between tumour types.[16] This lack of accurate incidence data hampers researchers.

Another barrier is that there have not been vocal, organised patient groups calling for better care for this form of keratinocyte cancer, unlike with other more prominent cancer types.

What is the way forward? We propose three key actions

1. Reorganise keratinocyte cancer care to ensure access to multidisciplinary teams

Multidisciplinary care is now the standard for other cancers. Cancer Australia strongly promotes this approach, but it is not yet the norm for keratinocyte cancer. Multidisciplinary care in Australia has been adopted mainly within the acute hospital setting, where co-location of providers facilitates team meetings – while skin cancers are traditionally managed in the community. This barrier might be overcome by Australians' sudden embrace of videoconferencing technology during the COVID-19 lockdown.

While most keratinocyte cancers are managed in primary care or private specialist practices, current guidelines[2] urge clinicians to consider multidisciplinary team review for patients with cSCCs with any histologic features associated with poor prognosis. For patients with locally advanced or metastatic keratinocyte cancers, access to experienced multidisciplinary teams is crucial.[2] The involvement of oncologists in the multidisciplinary team could significantly enhance keratinocyte cancer care, given the emergence of effective systemic treatments.

2. Support Australian researchers to generate locally and internationally relevant high-quality data

Given that Australia has the highest incidence of keratinocyte cancer, we should be taking responsibility for generating evidence – yet Australian studies make up an embarrassingly small proportion of world keratinocyte cancer research, despite our undeniable stake in this clinical area. Of RCTs evaluating treatments for keratinocyte cancer and published during the last 10 years in US National Libraries of Medicine-listed journals, we estimate that fewer than 10 were Australian designed and conducted, and fewer than 10 international multicentre studies included an Australian site. The Australian and New Zealand Clinical Trials Register[17] lists more than twice as many treatment trials in breast cancer and in coronary heart disease than in keratinocyte cancer.

Australian-led studies are well worth the investment; they can make a major contribution to outcomes for these cancers. Australian investigators published the first prospective study of definitive chemoradiation in patients with inoperable locally or regionally advanced cSCC, which set a new standard of care.[18]

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A 2015 report on the parliamentary Inquiry into Skin Cancer in Australia[1] called for investment in keratinocyte cancer research, acknowledging that it was critical to find new skin cancer treatments as well as trialling different combinations of existing treatments. It concluded that 'without investment in research, [keratinocyte cancer] will continue to remain Australia's most costly form of cancer to treat and will continue to be an increasing burden on the healthcare system as the Australian population ages'.[1]

While a comprehensive (all lesions) national keratinocyte cancer registry is unlikely to be feasible in Australia, registries of patients at high risk (e.g. the immunosuppressed and those with invasive or high-risk tumours) with effective clinical leadership might promote more consistent follow-up and support recruitment to clinical trials.

3. Time for patients to speak up

Patient advocacy organisations work to ensure that patients' needs and experiences are considered in decisions about cancer care. In the case of other cancers, well-organised and well-informed patient groups have achieved significant improvement in patients' experience by helping government and other stakeholders 'hear' and understand their needs. Breast Cancer Network Australia has worked with the Australian Government to increase the number of breast care nursing positions,[19] while Bowel Cancer Australia has campaigned for equitable access to colonoscopy. Cancer Voices NSW successfully advocated for on-demand consumer access to pathology reports, prompted a national survey of medical oncologists to identify service gaps, and successfully lobbied for the development of the consumer-friendly Australian Cancer Trials website.[20]

Patient advocacy groups also work with researchers to improve research quality, relevance and translation into practice. Patient groups are increasingly involved in the development of clinical pathways to help ensure people get 'the right treatment, at the right time'.[21] They also advise clinical researchers to ensure clinical questions are relevant to patients, protocols are feasible, and that patients' concerns are considered in study design.[21] Traditional cancer endpoints of recurrence and death may be less relevant to keratinocyte skin cancers, which limits our ability to translate experience from other cancers. Patients should be involved in identifying appropriate endpoints for keratinocyte cancer research.

The voice of people with keratinocyte cancer is currently barely audible to government and researchers. We encourage current and emerging support and advocacy groups to keep working to change this situation.

What happens next?

Australia's national clinical practice guidelines for keratinocyte cancer will be due for updating by 2024. Cancer Council Australia is committed to reviewing guidelines within 5 years of publication, and will update selected sections earlier if important new evidence emerges.[2] Before the guidelines are next revised, we hope to see a significant contribution of high-quality evidence from Australian researchers and greater participation of Australian patients in research. These outcomes should be considered as key performance indicators for the Australian keratinocyte cancer community.

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Statement of competing interests

Gerald Fogarty is on advisory boards for Sanofi and Merck Serono Australia, and is Chair and director of Australian Skin Cancer Foundation.

Elizabeth Paton is a former employee of Melanoma and Skin Cancer Trials Limited.

Jay Allen is a director of Australian Skin Cancer Foundation.

Julie Calvert is a director of Australian Skin Cancer Foundation.

Tamara Dawson is on an advisory board for BMS and is the Founder/Director of Melanoma and Skin Cancer Advocacy Network (MSCAN). MSCAN has received grants from BMS, MSD, Novartis and Sanofi.

Author Group of the Australian Keratinocyte Cancer Clinical Guidelines 2019: Peter Foley is on advisory boards and speaker bureaux, and has conducted clinical trials for Galderma, Sanofi and Sun Pharma, has been a consultant for GenesisCare, and is an executive member of the Australian Skin and Skin Cancer Research Centre. David Speakman has received speaker fees from Pierre Fabre for a symposium at COSA 2020. David Whiteman has received speaker fees from Pierre Fabre and is supported by an NHMRC Fellowship. Stephen Shumack is on advisory boards, provides consultancy and has conducted clinical trials for Sanofi and GenesisCare. Peter Callan, Alvin Chong, Morton Rawlin, Diona Damian, Paul Fishburn and Helena Rosengren declare no relevant disclosures.

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