Re: Draft Wiki guidelines for KC

Thank you for inviting feedback on the draft Wiki guidelines for managing keratinocyte carcinoma (KC).

Our team have had a chance to review the documents. Those that have reviewed the draft are:
- Associate Professor Howard K. Steinman. Dermatologist. Mohs Surgeon. Dallas, USA
- Professor Christopher Zachary. Chair Department of Dermatology. University of Ca Irvine, USA
- Professor Anthony Dixon. AOCD and ACCO. Docklands, Victoria
- Dr. Stuart Anderson. Rural GP with special interest in skin cancer. Maffra, Victoria
- Dr. Alexander Nirenberg. Dermatopathologist, Dorevitch Labs, Melbourne, Victoria
- Dr. Sama K Carley. Dermatology resident physician. University of California Irvine, USA.

The following are consensus positions of our team:

1. The document is perhaps too long and without key points and summary tables. Given the majority of skin cancer in Australia is managed by GPs, they should be considered the target audience. The document needs to be in a format where information can be accessed rapidly in a typically time-pressured general practice consultation, otherwise it is likely to be ignored.

2. Some sections are very dated and in substantial need of more current evidence-based study data.

3. For the section on photodynamic therapy (PDT), of 20 references, 19 are over ten years old. Our understanding on PDT has very significantly increased since that time. Considerable published data now suggest that the lower comparative cure rates and higher morbidity associated with PDT for KC preclude its use as a first or even second line treatment. Indeed, there are studies that report high cure rates when their cure rates are poor compared to other treatment modalities. These evidenced-based studies, including randomized controlled trials (RCT)s, demonstrate:
   a. Substantially lower efficacy in curing KC compared to other established therapies.
   b. Increased procedural pain and post procedural pain compared to other modalities.
   c. Substantially increased 5-year recurrence rates after short-term clinical clearance.
   d. Loss of number and function of Langerhans cells following PDT resulting in significant long-term cutaneous immune suppression.
   e. The lack of evidence of cancer preventative benefits after PDT for actinic keratoses (AKs).

The chapter on PDT needs a comprehensive revision to include this new data and a recommendation that PDT is not a first or second line treatment for KC. It should only be considered when all other management options are deemed inappropriate or declined by the patient. This would be an unusual circumstance.

4. The section on radiation therapy also needs a significant update with incorporation of more recent data. Current evidence strongly suggests that radiation therapy, including brachytherapy, should not be considered in managing AKs, superficial basal cell carcinoma (sBCC) or squamous cell carcinoma (SCC) in situ. The suggestion of any role of radiation therapy in the treatment of AKs is particularly concerning.

5. The section on curettage with ablation, either cryotherapy (C&C) or electrodessication (C&D), lacks current evidence-based data. The option of curettage followed by topical chemotherapy merits inclusion. The role of these approaches in managing sBCC and SCC in situ had been recently reviewed and published by our team.

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6. We would be concerned if clinicians accepted clearance rates managing KC of less than 90% in 2019. There may be exceptions with some patients considering age and other health issues. Our team agree that with currently available regimens, cure rates for KC below 95%, let alone 90%, would be unacceptable. Numerous applicable references of C&C, C&D and curettage followed by topical treatment for sBCC and SCC in situ are missing.8, 34-39

7. Given the length of the guidelines and the several available treatments, our team suggests inclusion of tables outlining expected clearance and cure rates for currently accepted beneficial modalities. This would allow readers to clearly see comparative efficacy of available treatments. More importantly, it would make clear the poorer results achieved with non-surgical treatments for KC extending into the dermis, (beyond that typically seen in sBCC and SCCis).

8. For the same reasons, the guide would significantly benefit from an algorithmic approach. This would guide clinician’s diagnostic and therapeutic decisions when managing intraepidermal KC versus indolent histologic variants (e.g. nBCC) versus more aggressive histologic sub-types and invasive KC. This National Comprehensive Care Network Cancer Guidelines routinely use this approach.40

9. Early feedback suggests that many (probably most) GPs are not familiar with term KC. The terms BCC and SCC are well understood, and we consider these terms preferable. Note that both SCCs and BCCs are distinct recognized entities that are internationally understood and accepted.

10. Whether keratoacanthoma (KA) is a variant of SCC or is a separate entity has been the subject of debate for many years. This is primarily due to its natural history of rapid growth often followed by regression. Furthermore, diagnosis of KA versus SCC varies widely, with the ratio of SCC/KA being diagnosed varying from 2.5: 1 to 139: 1.41 Pathological diagnosis of KA depends on a combination of clinical history and microscopic appearance. KAs and SCCs can have significant overlapping histologic features, which at least partly accounts for the variation in pathological diagnosis. It is well documented that there are KAs with SCC components, KA-like SCCs, and KAs with malignant transformation.42 From a genetic perspective, recent studies have shown that the MAP3K8 (TPL2) oncogene may be a driver to the development of both KA and SCC.43 Taking all current evidence together, the editors of the WHO classification of skin tumours 2018 consider KA to be a variant of SCC, rather than a separate entity.44

11. The draft guide suggests that topical imiquimod can be used alone as an option for managing nodular BCC (nBCC). The TGA does has never listed treating nBCC as an indication for imiquimod. The efficacy of managing nBCC with imiquimod is known to be poor. In the Bath-Hextall RCT45, 82% was the 3-year cure rate with imiquimod for nBCC. In this same trial, the nBCC randomized to surgical excision had 99% 3-year cure rate. There was a 17.1% difference. The cure rate difference in same study for sBCC was 12.9%. The more recent SINS trial report demonstrated similar data46. We recommend that the draft guidelines should be adjusted to advise that imiquimod is neither a first or second line choice when managing nBCC and is outside TGA indications. Similarly, the TGA guidelines do not approve usage of imiquimod to manage SCC in situ. Recommending a medication for non TGA approved indications is at best dangerous. There are also legal implications.

As it stands, ACCO would be advising our members to not consider these guidelines, as they are inaccurate and at times dangerous. Some recommendations regarding radiation and PDT amount to suggesting potentially negligent practice.

The ACCO team is available to assist if requested to advance these guidelines to a current level of understanding of an evaluation of when and where to use the various therapeutic options in managing SCCs and BCCs.

Yours,

Anthony Dixon, Howard Steinman, Alexander Nirenberg,
Sama Carley, Christopher Zachary, Stuart Anderson
References

29. Steinman HK, Clever H, Dixon A. The characteristics of Mohs surgery performed by dermatologists who learned the procedure during residency training or through postgraduate courses and observational preceptorships. Proc (Bayl Univ Med Cent) 2016;29:119-23.