Modern radiation therapy for keratinocyte cancer: What the general practitioner needs to know

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Background
Keratinocyte cancer (KC) in Australia poses a unique healthcare challenge due to its high prevalence and the requirement for multidisciplinary management of many cases. Advances in radiation therapy (RT) have increased its use in treating different keratinocyte cancer presentations. Understanding the indications for RT and the role that general practitioners (GPs) play in the treatment pathway are imperative to ensure best patient outcomes.

Objective
This review examined the efficacy, advances and treatment considerations of RT for the management of keratinocyte cancer, and role of the GP in the treatment pathway.

Discussion
Radiation therapy offers effective alternatives to, or adjuvants for, surgery in existing keratinocyte cancer treatments in appropriate cases. The evolving RT landscape necessitates GPs to be well-informed for effective case identification, referral and management. This includes understanding RT advances, protocols, treatment reactions and managing patient expectations. Continuing education in this space is important for GPs to understand the suitability of RT for their patients.

THE PREVALENCE OF KERATINOCYTE CANCER in Australia presents a unique and significant healthcare challenge by global standards. Approximately 70% of Australians are expected to have at least one basal cell carcinoma (BCC) or cutaneous squamous cell carcinoma (cSCC) excised in their lifetime.[1] This figure also reflects long life expectancies and the strong correlation of keratinocyte cancer with advancing age.[2,3] With over one million Medicare Benefits Schedule (MBS) procedures, costing the healthcare system approximately $1.4 billion annually,[4] prevention strategies, early detection and treatment, as well as consistent follow-up, are essential. In addition, the availability of effective non-invasive treatments, such as radiation therapy (RT), continue to be important for suitable patients to help reduce treatment burden.

Role of radiation therapy in the management of keratinocyte cancer

Although surgery remains the gold standard treatment when viewed through the lens of efficacy, ablative techniques such as cryotherapy and curettage are important for the cost-effective and rapid management of lower risk lesions, particularly those on the limbs or trunk.[5] And although RT has been used to successfully treat skin cancer for over 100 years,[6] treatment guidelines recommend its first line use only for a minority of lesions:[5]

- In the adjuvant setting: following surgery on high-risk indications such as deep or large lesions and/or a combination of poor differentiation or other high-risk histological features, recurrent lesions, positive margins and/or multifocal, peri-neural invasion (PNI; Table 1).[5]
- In the definitive or palliative setting: RT is recommended for patients with surgical cautions that include poor performance status and/or lesions in a location where surgery would leave them with suboptimal functional or cosmetic outcomes (Table 1).[5]

Given the strong association of age, comorbidities and skin cancer risk, determining patient suitability for RT can be challenging. Indeed, some surgical cautions are also RT cautions, so decisions are often made in coordination with multiple specialists. Some flexibility can be incorporated into the RT course plan for local keratinocyte cancer lesions to ensure optimal treatment tolerability, compliance and efficacy for patients. Historical, long-term cure rates range from 80 to 96%[7] depending on lesion location, RT modality and planning, with recent studies of different modalities demonstrating ~95% complete responses at the four- to five-year follow-up,[8–11] which is suggestive of improved lesion mapping, treatment planning and dose delivery. In line with improved efficacy, recent studies report lower incidences of severe chronic

radiation-induced skin toxicities, such as non-healing wounds, fibrosis and/or necrosis.[12,13]

Rationale for dose fractionation

Treatment-emergent toxicities from RT can be associated with treatment location and size, as well as the dose administered.[14] Current treatment protocols are designed to reduce toxicity without compromising efficacy. Fractionation is a strategy used to divide the total prescribed dose into smaller daily sessions delivered over several weeks. Reducing the dose per fraction helps to mitigate the toxicity that would be induced by delivering the entire prescribed dose in a single session. The biologically effective dose (BED), often 2 Gray per fraction, exploits the heightened radiosensitivity of tumour cells over healthy cells.[15] The intent is to treat within a therapeutic window that maximises efficacy, while minimising toxicity in healthy tissue, such as hypopigmentation, telangiectasia and fibrosis, although several factors can influence outcomes.[14] For particularly frail patients or those unable to manage extended courses of fractionated RT, the treatment intent might be palliative to relieve symptoms caused by keratinocyte cancer; however, most patients can expect to have good outcomes.[16] Patient-specific discussions between the general practitioner (GP) and radiation oncologist are integral to managing clinical expectations and determining the most appropriate treatment course.

Advances in radiation therapy

There are over 1.3 million MBS-funded RT doses administered annually across the entire cancer spectrum in Australia.[17] Although granular tumour-specific data are not publicly available, RT use has increased by up to 5% year-on-year for the past five years, particularly for the higher complexity cases.[17] This might be as a result of the effect of improved technology, protocols, treatment outcomes and a renewed understanding for the role of RT in the management of many cancers. Treatments with superficial RT modalities have decreased, which are primarily used for skin cancer, although these have likely been supplanted by more sophisticated, targeted RT modalities. In the case of keratinocyte cancer, technological advances in planning, delivery and validation have increased the use for definitive, adjuvant and palliative applications.[18]

The advent of modern RT techniques such as volumetric modulated arc therapy (VMAT) have revolutionised treatment, helping to enhance precision targeting with the goal of maximising efficacy while minimising collateral tissue damage.[18,19] VMAT works by rotating around the patient to deliver radiation in a continuous arc with the dose shaped and modulated in real time by multileaf collimators to achieve unmatched precision.[19] The precision of VMAT is particularly useful for lesions in complex locations where cosmetic and functional outcomes of surgical management might present concerns.[18] VMAT is also an effective treatment for patients with extensive skin field cancerisation (ESFC), which is characterised by widespread actinic keratoses often with multiple in-field invasive cancers, achieving stable >96% field clearance and complete lesion response rates at the 24-month follow-up.[20] Advanced imaging and planning software can shape and modify the dose to heterogenous areas of precancerous and invasive disease as required. For ESFC, VMAT is generally used if a patient has exhausted other treatment options.[20]

Image-guided radiation therapy (IGRT) is an advance that allows for real-time treatment adjustment to minimise variations in target dosing. Retrospective efficacy analysis of keratinocyte cancer cases treated with image-guided superficial radiation therapy demonstrated a 12-month control rate of 99.3%.[21]

The most recent radiation-based Australian Register of Therapeutic Goods (ARTG)-registered treatment for certain BCC and SCC indications is the OncoBeta epidermal radioisotope therapy using the beta-emitting Rhenium-188 radioisotope. Applied as a paste containing the beta-emitting radioisotope, Rhenium-188, the composition allows conformity to complex surfaces, minimising exposure to surrounding healthy tissue. Recent studies indicate >95% 12- and 24-month complete response rates from a single session.[22,23] This treatment might be an option for certain patients with surgical cautions, who are unable to attend multiple sessions of a fractionated RT course. Central to this technique is the collaboration between the referring skin specialist and the treating physician. This includes accurate lesion demarcation and area determination, as well as histological assessment including depth determination. As with all

Table 1. Keratinocyte cancer indications for radiation therapy

Definitive or palliative	Adjuvant
• Surgical contraindication and/or comorbidities • Risk of functional or cosmetic impairment	One or a combination of the following high-risk indications: • rapidly growing • deep invasion (beyond subcutaneous fat, bone, >6 mm) • significant PNI (>0.1 mm diameter nerve and/or multifocal PNI) • lymphovascular invasion • large (>2 cm diameter) • high-risk anatomical sites (eg nose, lips, eyes) • poor differentiation • in-transit metastasis or nodal involvement • aggressive BCC subtypes (infiltrative, sclerosing [morphoeic], basosquamous, micronodular) • aggressive cSCC subtypes (desmoplastic, spindle cell, adenosquamous, originating in scar) • recurrent lesion following prior excision with clear margins • positive margins where further surgery is not possible (or declined).

BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; PNI, peri-neural invasion.

radiation-based procedures, it is expected that the patient is returned to the care of their primary skin physician for ongoing management and surveillance, as necessary. As Medicare reimbursement is currently unavailable for this treatment, patients incur the full fee of several thousand dollars, which will be another consideration when selecting an appropriate treatment option.

In addition to the promising advances in this space, traditional RT techniques such as electrons, superficial and early megavoltage photon modalities continue to be invaluable for the management of many local keratinocyte cancer lesions requiring radiation, particularly those on areas that might not require complex planning.

Role of general practitioners in the RT pathway for the management of keratinocyte cancer

GPs continue to be pivotal in the ever-evolving keratinocyte cancer treatment landscape, being the linchpin of coordinated long-term surveillance, treatment or referral, post-treatment follow-up and aftercare. For these reasons, understanding the nuances of new and existing treatments and their indications is essential to identifying suitable patients, providing informed guidance where appropriate, and collaborating with specialists. This is particularly important in rural and remote areas.

For radiation-based treatments, GPs continue to monitor patients, often in communication with the radiation oncologists, if deemed necessary. As with all skin cancer management, this focuses on ensuring appropriate treatment reaction resolution and monitoring of recurrence or new lesions locally or elsewhere on the patient, as prior diagnoses dramatically increase the risk of future keratinocyte cancer.

GPs should understand the expected and well-documented acute skin reaction profile associated with treatment, such as radiodermatitis, erythema, desquamation and pruritis. Understanding the expected onset and duration ensures to the appropriate provision of supportive care to patients, including wound care, pain management (if necessary) and understanding when, where and how to escalate care in the unlikely event of severe and or chronic reactions.

Understanding and managing acute radiation-induced toxicities

Radiation-induced dermatitis is an expected treatment reaction and is graded from one to four as severity increases. The expected range is generally grade 1–2, which includes erythema, pruritis and dry desquamation. Grade 3 reflects moist desquamation and grade 4 reflects a more serious reaction with bleeding and/or requiring further intervention. For patients, these are often described as ‘mild-to-severe sunburn’. GPs and their clinic nurses who are adept at wound care can manage all radiation reactions very well. In some circumstances, radiation departments will liaise with local wound clinics in the community or hospital for advice. The principles of wound care are to keep the wound moist, avoid trauma and infection and minimise sun exposure. Mild reactions can be managed with over-the-counter, non-perfumed emollients. More intense reactions (higher than grade 2) can be managed with silver or zinc-based creams including hydroactive colloid gel, zinc with castor oil or silver sulfadiazine, which also possess antiseptic properties. In principle, reactions that represent moist desquamation with bleeding should be referred back into the radiation department for review, but others can be managed conservatively in clinic as they will most commonly heal over two to four weeks. The treating department will be able to provide advice for referring clinicians if there is any uncertainty.

When to consider referral of keratinocyte cancer for RT

Surgery and ablative techniques continue to be the primary treatment options for keratinocyte cancer; however, indications where a GP might consider a referral for RT include:

- persistent or recurrent lesions
- positive margins following surgery (adjuvant)
- PNI of multiple nerves, or a single nerve >0.1 mm (adjuvant)
- immunocompromised patients (adjuvant)
- comorbidities that preclude surgery
- patients who refuse surgery
- concerns about cosmetic or functional outcomes from surgery
- extensive skin field cancerisation that has failed prior interventions.

Conclusion

The advanced age of some keratinocyte cancer patients and propensity to develop multiple lesions over a protracted period presents a unique disease and treatment burden for clinicians to consider. The ever-increasing keratinocyte cancer incidence in Australia reinforces the need for GPs to be well-versed in all treatment options, including managing patient expectations and aftercare protocols. Although most presentations can be managed within the primary care clinic, collaboration with specialists, including radiation oncologists, might be necessary in the management of many keratinocyte cancer patients at some point in their lives. The key focus of continuing advances in radiation-based treatments for skin cancer is to expand indications, improve efficacy, reduce treatment times and minimise side effects. Continuing education opportunities are essential to stay abreast of the latest technology, treatment protocols, efficacy, safety and patient suitability, thereby ensuring GPs remain at the forefront of comprehensive care for keratinocyte cancer patients.

Key points

- RT is suitable as a first-line therapy for a minority of lesions.
- RT can be used to treat keratinocyte cancer in the definitive, adjuvant or palliative setting, or treatment-refractory extensive skin field cancerisation.
- Dose fractionation can be modulated based on the modality, the patient and treatment intent.
- Advances in RT technology allows for the improved tailoring of treatment to disease presentation.
- It is essential for GPs to understand appropriate patient/lesion selection, and how to manage radiation-induced skin reactions to ensure successful outcomes.

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