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Author

Professor Michael Veness MBBS, MMed, MD(UNSW), MD(USyd), FRANZCR

Department of Radiation Oncology, Westmead Cancer Centre, Westmead hospital, Westmead, Sydney, University of Sydney

Corresponding author

Clinical Professor Michael J Veness

Radiation Oncologist, Senior Staff Specialist, Department of Radiation Oncology, Westmead Cancer Centre, University of Sydney

Westmead Hospital, Westmead, NSW, 2145, Sydney.

Tel: 02 98455200

Fax: 02 98915814

Email: michael.veness@health.nsw.gov.au

I deny any conflict of interest in regards to this research

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Professor Michael Veness MBBS, MMed, MD(UNSW), MD(USyd), FRANZCR

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Clinical Professor Michael J Veness

Radiation Oncologist, Senior Staff Specialist, Department of Radiation Oncology, Westmead
Cancer Centre, University of Sydney

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Email: michael.veness@health.nsw.gov.au

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PROF. MICHAEL JOHN VENESS (Orcid ID : 0000-0003-0106-8325)

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Point of View

The most frequent cancer worldwide is skin cancer, occurring at epidemic rates in countries exposed to high levels of chronic ultraviolet radiation such as Australia and New Zealand (ANZ). Australia has the highest incidence of non-melanoma skin cancer (NMSC) in the world. NMSC is predominantly a cancer of the middle aged or elderly and accounts for considerable consulting and treatment time in most radiation oncology departments. Many patients also suffer from medical co-morbidity, an important factor in any treatment decision.

Radiation oncologists (ROs) within ANZ manage patients with NMSC in the definitive, adjuvant or palliative settings. Many treatments are localised and relatively superficial (primary site) but also can involve regional (usually adjuvant) and occasionally non-cutaneous palliative sites. No other cancer is so effectively treated utilising such a variety of techniques using ionising radiotherapy (RT), delivered by either external beam

(superficial/megavoltage photons or electrons) or brachytherapy [(BT) low dose, high dose, electronic brachytherapy].¹

Whatever modality is utilised NMSC is radioresponsive and in most clinical scenarios patients treated with definitive RT (whatever technique) can expect local control rates of > 90-95%. Younger patients of good performance status (< 70 years old) have often been treated with longer course RT utilising smaller doses per fraction (e.g. 55-50 Gy in 2-2.5 Gy) aiming to achieve the best local control and minimise late cutaneous side effects (e.g. in-field hypopigmentation, epidermal atrophy, telangiectasia).

In older patients (70-80 years old) the late effects are less concerning with the aim to decrease the duration of treatment utilising fraction sizes of 3-4 Gy over 2-3 weeks (e.g. 40-45 Gy in 10-15 fractions). Most ROs would consider delivering fraction sizes ≥ 3 Gy as hypofractionation with published ranges of 3-20 Gy fraction sizes associated with a concomitant decrease in total dose as dose/fraction increases. Despite these variations in many cases a similar biological effective dose (BED), assuming an $\alpha/\beta = 10$, is delivered.

In elderly (> 80 years old) and/or poor performance patients extended course treatment is often inappropriate. Many have advanced and inoperable NMSC that if left untreated experience local morbidity. In these patients shorter course hypofractionated RT, delivered second daily or once weekly is a highly effective modality with acceptable and self-limiting treatment related toxicity.²

The COVID-19 global pandemic has presented an unprecedented challenge in the way we manage cancer patients. In an attempt to limit contact between staff and patients radiation oncology departments have identified low-risk patients, such as those with ductal *in situ* breast cancer (DCIS), basal cell carcinomas (BCC) or low risk squamous cell carcinomas (SCC), that could potentially have their RT safely deferred for a number of months (2-3 months). Organisations such as hospitals and specialist Colleges/Societies have released guidelines and recommendations to aid clinicians in decision making.

Strategies for patients with NMSC include delaying consults and/or commencing RT, or considering alternative options e.g. excision. Unfortunately, the COVID-19 impact on other specialties (e.g. dermatology) is similarly profound and in many cases there are no easily accessible alternative treatments available as these specialties are also prioritising

resources. To compound this, many patients, especially those that are older, are self-isolating or finding difficulty in arranging consultations are thereby possibly delaying an early diagnosis (i.e. biopsy) and treatment (i.e. simple excision). Elderly nursing home patients are often in complete lockdown and in many cases are unable to be accessed or be sent for medical review.

During the COVID-19 crisis many departments have favoured the use of hypofractionated schedules for select cancers, e.g. 5 fraction short course RT in neoadjuvant rectal cancer and 15 fraction schedules in adjuvant breast cancer, to protect precious linear accelerator (LA) time and limit patient/staff exposure. In these clinical scenarios hypofractionated regimes are supported by published evidence as is the case for recommending hypofractionation in NMSC.³ The Royal College of Radiologists (UK) has recommended modestly decreasing the number of fractions for treating NMSC, for example, 40 Gy in 8 fractions instead of 10 and 50 Gy in 15 fractions instead of 55 Gy in 20 fractions.

In the months ahead post COVID-19 we are likely to witness an unprecedented surge in referral of patients, including those with NMSC, for consideration of RT. Despite the long established role of RT in NMSC the quality of evidence is low, predominantly observational cohort studies with very few randomised controlled studies. In settings such as adjuvant RT there is genuine debate regarding the indicated settings and benefits from RT. Similarly, the wide-ranging use of varied dose fractionation schedules is sparsely supported by evidence. Despite this the literature documents an excellent local control rate ranging between 90-100% when using hypofractionated RT in NMSC.³ Many hypofractionation schedules utilise 5-8 Gy fractions, or even higher, delivered either daily, on alternative days or weekly (Figs 1, 2).

In a systematic review of 40 publications involving over 12,000 NMSC (median lesion size 1-5 cm) treated with hypofractionation the authors reported a mean RT dose delivered of 38 Gy, using 8 Gy per fraction and delivered 3 times per week. Despite significant heterogeneity in the patients, RT (external beam vs BT) and follow-up, local recurrence rates did not exceed 8% in nearly all studies. Twenty-nine publications documented a local control rate > 90%.³

Evidence of a dose-response relationship in NMSC is weak or similarly whether BCC or SCC respond differently. Many studies report summary results for differing histopathology (BCC vs SCC), subsites (head and neck vs other) and settings (definitive vs adjuvant) with dose fractionation schedules independent of these differences.

Large single fractions are an extreme form of hypofractionation for treating patients with NMSC with concerns raised regarding late toxicity such as skin/soft tissue or cartilage necrosis. However in a UK study of 1005 BCC/SCC (95% 1.5-3 cm in size, mean age 68 yrs) treated with one single fraction (either 18 Gy, 20 Gy or 22.5 Gy) the incidence of late skin necrosis (at 10 years) was 6% with most cases healing spontaneously. Local recurrence rates were 4% and subsequently a fraction size > 20 Gy was not recommended because of an increasing risk of skin necrosis.⁴ It would not be unreasonable to consider a single fraction of 15-18 Gy as a reasonable option in many older unwell patients with a NMSC, accepting the extra time needed to deliver this larger fraction.

Beyond the role of definitive RT is that of adjuvant RT often in the setting of a positive/close margin or perineural invasion. There is an acknowledged lack of consensus on the clear indications and benefits of adjuvant RT in many settings. The literature suggests that many patients with close or margin positive NMSC (especially BCC) undergoing re-excision do not harbour residual NMSC, or will recur without further treatment, and consequently many patients with incompletely excised BCC, and even low risk SCC, could safely be observed and offered treatment if local recurrence occurs. Many will experience the competing risk of medical co-morbidity which is an important consideration in any management decision, perhaps more so in the adjuvant setting where there is no symptomatic disease present. If adjuvant RT is recommended the effectiveness of hypofractionation is likely to be similar to that of definitive RT and should be considered an option.

A recent (pre-COVID-19) ASTRO evidence based clinical practice guideline recommended hypofractionation (2.1-5 Gy fraction sizes using 8-20 fractions) schedules, as options, in both the definitive and postoperative settings for NMSC, acknowledging the low level of published evidence.⁵ The evidence to support an excellent local control rate and in-field

cosmetic result with hypofractionation in NMSC is there. The late effects of primary cutaneous RT rarely, if ever, carry the potentially debilitating late consequences in other cancers, such as xerostomia and dysphagia in head and neck cancer or late CNS toxicity in cerebral RT.

Can RO's therefore justify prescribing 15-30 fractions for a primary NMSC if waiting times to be seen and treated are many months? Should hypofractionation RT (definitive or adjuvant) involving ≤ 15 be considered for most patients? In patients over 80 and/or those of poor performance status (ECOG 2/3) should not 1-4 fractions be the default schedule? And should not many adjuvant patients be observed and treated expectantly (Table 1)?

There will always be exceptions, for example larger RT fields/target volumes that encompass sensitive neural structures when treating patients with perineural invasion, or high-risk lower lip SCC where the aim is curative and to achieve the best long term function (oral competence), in which cases 20 or 25 fractions may be justified, but for many referrals this should not be the case.

Each RO will always remain the advocate for their patients but with possible lengthy waiting times ahead this may be challenging. More so than ever the proven role of hypofractionation in NMSC (and in many other cancers) in an era of post COVID-19 limited resources is increasingly relevant. This approach should not be seen as delivering a less optimal treatment.

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Figures

Fig. 1. 88 year old male with a recurrent dermal based squamous cell carcinoma following recent excision of left temple squamous cell carcinoma (superior wound) with a positive deep margin. He was recommended a hypofractionated course of radiotherapy treating the post op site and the recurrent lesion utilising orthovoltage energy photons to a dose of 28 Gy in 4 fractions delivered twice per week.

Fig. 2. Six months post radiotherapy the patient has achieved an excellent outcome with no clinical evidence of residual squamous cell carcinoma or recurrence. He has a degree of in-field hypopigmentation and epidermal atrophy.

Table 1 Suggested dose fractionation schedules in the post COVID-19 era for localised NMSC

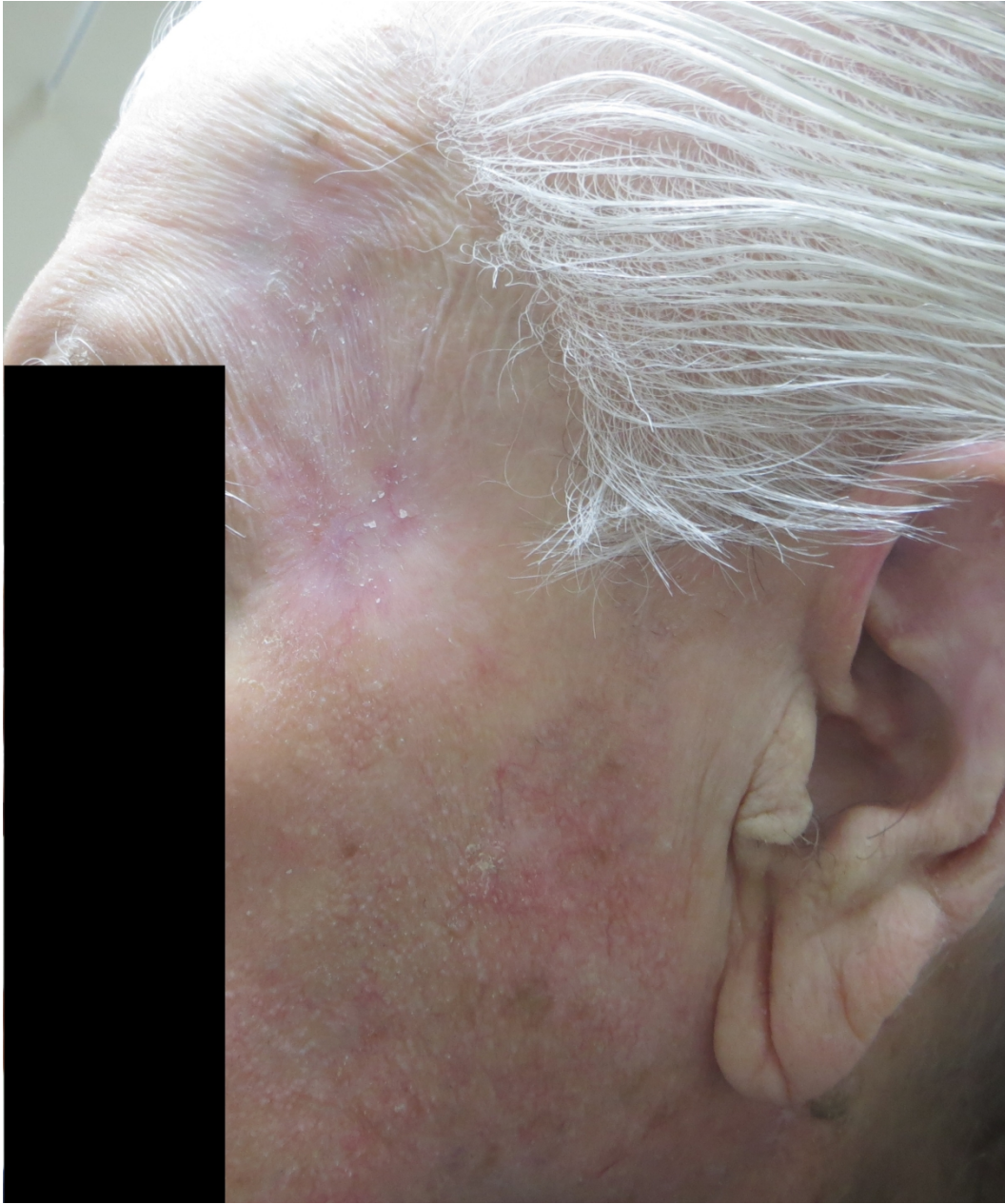
Setting	<70 yrs ECOG 0/1	70-80 yrs ECOG 0/1	≥80 yrs or ECOG 2/3	ECOG 3/4
BCC				
definitive	30-45Gy in 5-15#s	30-40Gy in 5-10#s	15-28Gy in 1-4#s	15-18Gy single#
adjuvant	30-45Gy in 5-15#s	30-40Gy in 5-10#s	15-28Gy in 1-4#s†	no RT
adjuvant high risk site (perioral/orbital)	45-50Gy in 15-20#s	40-45Gy in 10-15#s	30-36Gy in 5-6#s†	no RT
SCC				
definitive	30-45Gy in 5-15#s	30-40Gy in 5-10#s	15-28Gy in 1-4#s	15-18Gy single#
definitive high risk site (perioral/orbital)	45-50Gy in 15-20#s	40-45Gy in 10-15#s	15-28Gy in 1-4#s	15-18Gy single#
adjuvant	30-40Gy in 5-10#s	30-40Gy in 5-10#s	15-28Gy in 1-4#s†	no RT
adjuvant high risk site (perioral/orbital)	45Gy in 15#s	40-45Gy in 5-10#s	30-36Gy in 5-6#s†	no RT

BCC, basal cell carcinoma; SCC, squamous cell carcinoma

† consider need for adjuvant radiotherapy vs observation in most BCCs and low risk SCCs



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