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Radiotherapy for early non-melanoma skin cancer

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ABSTRACT

This article reviews the important role of radiotherapy in the management of early non-melanoma skin cancer, in the definitive and adjuvant settings. Therapeutic considerations and appropriate patient selection will be discussed, as well as evidence for efficacy and potential side-effects. Additionally, we present some recent advances which may improve accessibility and quality of radiotherapy, such as more convenient dose-fractionation, wide-field treatments, electronic brachytherapy and 3D printed bolus.

Radiotherapy in definitive management of early NMSC

There are a variety of treatment modalities available for early non-melanoma skin cancer (NMSC). Surgical excision alone is appropriate and curative for the majority of lesions, and some may be amenable to local ablative procedures such as curettage and electrodessication, photodynamic therapy or cryotherapy. The decision to use RT in the definitive management of NMSC requires consideration of patient factors, tumour location, long-term cosmesis and function. Commonly, definitive RT may be selected for patients with significant contra-indications to surgery (e.g. bleeding disorders), or who have cancers in areas where excision and reconstruction may result in poor cosmetic or functional outcome (e.g. nose or lip). Due to selection bias, comparative evidence on long-term efficacy and cosmetic outcomes between surgery, radiotherapy and other treatment modalities are limited (see Table 1).

Basal cell carcinoma

A systematic review of treatment options for basal cell carcinoma [1] identified only one randomized controlled trial which has directly compared surgery with RT in definitive management of BCCs. Avril et al. [2] conducted a study of 347 patients with facial BCCs under 4 cm in maximal dimension, randomized to surgery or RT. Frozen section margin was used in 91% of the surgical group of patients; a variety of modalities including brachytherapy, hypofractioned and conventionally fractionated 'contact' and superficial x-ray therapy were used in the RT group. At 4 years, high local control was observed in both arms, but favoured the surgical group (99.3 vs 92.5%, p = 0.003). Of note, the high local control of over 90% for definitive RT is consistent with other series in the literature [3,4], and may be acceptable for patients in whom surgery is a less preferred option for the reasons outlined above. However, caution must be exercised in patients with more advanced tumours, with larger size and bone or cartilage invasion associated with higher rates of local failure following definitive RT [3].

The authors of the randomized trial [2] also conducted an analysis of cosmesis using patient self-reported outcomes and standardized photographs rated by independent observers. In this report [5], cosmesis also favoured the surgical group. However, this result may not be widely generalizable as brachytherapy and hypofractionated low-energy x-rays were extensively used (together accounting for over 80% of the RT group). These techniques are particularly associated with significant dose inhomogeneity and an adverse radiobiological profile for late events. Modern departments would now tend to use more conventionally fractionated RT techniques, and modern treatment planning and delivery systems to improve dose homogeneity and reduce the risk of adverse late effects.

Squamous cell carcinoma

Current guidelines, for example the National Comprehensive Cancer Network [6] recommend definitive surgery as the treatment of choice

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Table 1
Selected studies of local control following definitive radiotherapy for non-melanoma skin cancer.

Study	Design	Epoch	Modality	Follow-up	Histology and inclusion criteria	n	Local control
Avril [2]	Randomized trial (RT vs surgery)	1982–1988	Interstitial brachytherapy (55%), superficial x-rays (33%), electrons	4 years	BCC < 4 cm	173	92.5%
Kwan [10]	Retrospective case series	1994–1998	Orthovoltage, electrons, megavoltage photons	4 years	BCC ≥ 2 cm or deeply invasive SCC ≥ 2 cm, deeply invasive and/or node-positive	61 121	86% 58%
Locke [3]	Retrospective case series	1966–1997	Superficial x-rays (60%), electrons, (19%), combined superficial and electrons (20%), megavoltage photons (< 2%)	≥ 2 years	BCC SCC	389 143	Previously untreated 92%, Recurrent 86% Previously untreated 80%, recurrent 68%
Tsao [8]	Retrospective case series	1982–1993	Orthovoltage x-rays (80%), electrons and Co-60	5 years	SCC, nasal skin	100	85%
Barysch [11]	Retrospective case series	1960–2004	Superficial x-rays	10 years	SCC, advanced	180	80.4%

Fig. 1. In-situ and superficially-invasive squamous cell carcinoma extensively involving the scalp in a middle-aged male patient with history of heavy sun exposure. Patient is being planned for wide-field radiotherapy to the area marked by the wire.

for cutaneous SCC, either by way of standard excision or margin-controlled microsurgery. No randomised trials have reported a comparison of surgery to RT, however a number of series report high local control of 90% or greater at 5 years [7] from definitive RT, particularly in early stage disease.

The high local control outcomes and acceptable toxicity from RT for early SCC are emphasized in a series of patients treated for nasal skin SCCs [8]. Cutaneous malignancy in this location can be difficult to manage surgically due to difficulty with reconstruction and late cosmetic deficits. In the series by Tsao et al. [8], patients were treated with definitive RT, and 5-year local control of 85% and cause-specific survival of 96%, with low levels of acute toxicity. There are also emerging data regarding the use of RT, particularly modern inverse-planned techniques as will be discussed subsequently, for wide-field treatment of extensive pre-invasive change and superficial SCC [9], another scenario where surgical management can be challenging (Figs. 1 and 2).

However, as with BCCs, caution should be exercised in using definitive RT to treat more advanced disease. Kwan et al. [10] reported a series of advanced SCCs (defined by size criterion, T2 and greater and/or node positive) treated with definitive RT, with a four-year locoregional control of only 58%, and a significant proportion of patients experiencing locoregional recurrence dying from uncontrolled malignancy. Therefore, for more advanced disease, oncologic and survival outcomes favour surgery, particularly margin-controlled excision [7,11], or surgery and adjuvant RT [12].

In the setting of SCCs recurrent after previous treatment, poorer local control outcomes are also observed with salvage RT alone. In a large series, local control at a median of 5 years was only 68% in patients receiving upfront RT for recurrent SCC [3]. Similar to more advanced disease, surgery including consideration of postoperative RT may be preferable in this setting [13].

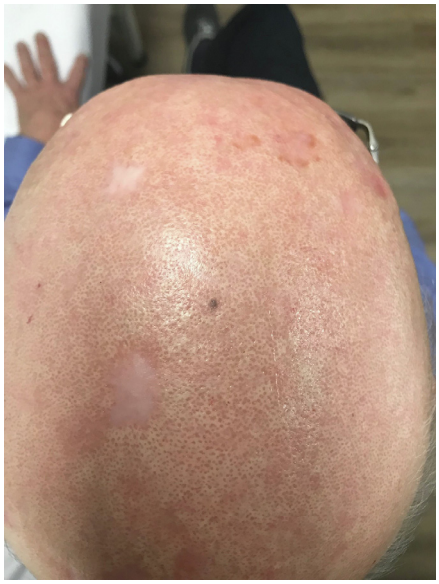

Fig. 2. Patient's scalp three months after completion of radiotherapy, 45 Gy in 25 daily fractions.

Radiotherapy in adjuvant management of early NMSC

Indications of adjuvant RT for excised cutaneous squamous cell carcinoma (SCC) are widely debated due to the lack of prospective randomised clinical trial data. For localised SCC without lymph node involvement, the National Comprehensive Cancer Network (NCCN) panel recommends RT for extensive pathological/small nerve perineural infiltration (PNI), large nerve PNI, and/or positive margins [14–19]. RT in the adjuvant setting is likely to improve local control and disease-free survival but may not confer an overall survival benefit.

It should be noted that recurrent cutaneous NMSC can be challenging to manage as it often requires salvage surgery and RT, resulting in poor functional and cosmetic outcome. If recurrent disease is unresectable, salvage RT alone is associated with higher rates of locoregional failure [3,13]. Therefore optimisation of local control in the *de novo* setting for patients with high-risk pathological features should be strongly considered, including adjuvant RT where appropriate.

The NCCN panel recommends adjuvant radiotherapy for any BCC that shows evidence of substantial perineural involvement (more than just a few small sensory nerve branches or large nerve involvement) [18]. Adjuvant RT should also be considered if tissue margins are positive after Micrographic Moh's surgery or excision with complete circumferential peripheral and deep margin assessment.

Pathological PNI infiltration as a risk factor

PNI is a phenomenon whereby NMSC extends along the perineurium of a nerve. PNI has been classified into two groups: the first group comprising pathological PNI detected solely on microscopic examination with no clinical or radiologic abnormalities; and a second group in which there are also clinical and/or radiologic findings of PNI. Patients with clinical PNI have an independently worse prognosis than the pathological PNI-only group [20,21]. This review will focus on the importance of pathological PNI as a risk factor.

Several published series of PNI in non-melanoma skin cancers of the head and neck without clinical and/or radiologic features have examined the treatment outcomes after RT [18,20–23]. Studies from University of Florida analyzed the combined outcome for both BCC and SCC and reported 5-year local control rates ranging from 78% to 87% after surgery and adjuvant RT [18]. Lin et al. [24] reported the outcome of 222 Australian patients (133 SCC, 89 BCC) with 5-year relapse free survival of 91% for BCC and 78% for SCC. Of note, recurrent SCC with PNI had higher rate of local overall relapse and nodal recurrence than *de novo* presentation (40% local relapse at 5 years for the recurrent group vs 19% for *de novo*; and 21% nodal relapse for the recurrent group at 5 years vs 95% for *de novo*).

The involvement of larger nerves, more than 0.1 mm in diameter, has been reported to negatively affect oncologic outcomes in patients with pathological PNI [25,26], and this is now recognised in the American Joint Committee on Cancer 8th edition staging system for cutaneous SCC of the head & neck [27]. However, SCCs with pathological PNI of any calibre with other risk factors (moderate or poor differentiation, tumour diameter of ≥ 2 cm, or deep invasion beyond subcutaneous fat) are likely to have greater risk of poor outcomes and should also be considered for adjuvant RT.

With more awareness of the treatment and prognostic implications of PNI, pathologists are providing more anatomical details including the extent (single or multi-focal) and location (intra- or extra-tumoural) of PNI in relation to the primary skin lesion. In the future it is hoped that a consistent method of reporting PNI will provide more reliable data collection to further address the significance of pathological PNI.

Indication of adjuvant RT for non-melanoma skin cancer with PNI

The potential benefit for adjuvant RT in improving outcomes for patients with pathological PNI remains debateable due to the lack of high-level evidence and the retrospective nature of published studies. Furthermore, heterogeneity of treatment and pathological reporting in different published series have confounded the interpretation of risk factors and outcomes.

An Australian review article advised adjuvant radiotherapy for head and neck cutaneous SCC with extra-tumoural PNI, larger calibre nerves (≥ 0.1 mm), invasion beyond dermis, recurrent tumour, diffuse intratumoural PNI, immune-supressed patient, size of tumour ≥ 2 cm, and poor differentiation [28]. In the context of cutaneous BCC with PNI, adjuvant RT is recommended if there is extratumoural PNI, involvement of larger calibre nerves (≥ 0.1 mm), invasion beyond dermis, recurrent tumour, and diffuse intra-tumoural PNI. Additional consideration should be given if patient is immunosupressed, and for aggressive histological subtype of BCC (infiltrative, morphoeic, sclerosing, and micronodular variants).

The issue of regional relapse in cutaneous SCC linked to PNI has been noted in previous series. Garcia-Serra et al. [20] reported 19% regional failure in SCC with PNI and thus advocated elective nodal RT. Other authors suggested addressing regional lymph node electively with nodal dissections for SCC with PNI [20,29,30]. In a large Australian series, nodal relapse (including parotid lymph nodes) occurred predominantly in the group with recurrent SCC (29%). Therefore in patients with recurrent cutaneous SCC found to have PNI, it is appropriate to consider elective nodal treatment [24].

Radiotherapy considerations for the elderly patient with NMSC

RT is prescribed in units referred to as Gray (Gy) and delivered as fractions (each treatment) to achieve a total dose (i.e. the sum of the fractions). By doing so, irradiated but non-involved normal tissue has the ability to repair sub-lethal cellular damage and minimise the late effects from RT which tend to increase as fraction sizes increase. Fractionation exploits the limited capacity of malignant cells to repair RT induced cellular damage compared to normal tissue. However, the relatively small areas treated in NMSC and the older patient population means late effects, such as in-field hypopigmentation and epidermal atrophy, are usually not a major concern.

Dose fractionation schedules vary with younger patients prescribed RT fraction sizes of 2–2.5 Gy delivered over 4–5 weeks aiming to achieve the best long term outcomes in terms of cure and cosmesis. In older patients, late effects are less of a concern with consideration

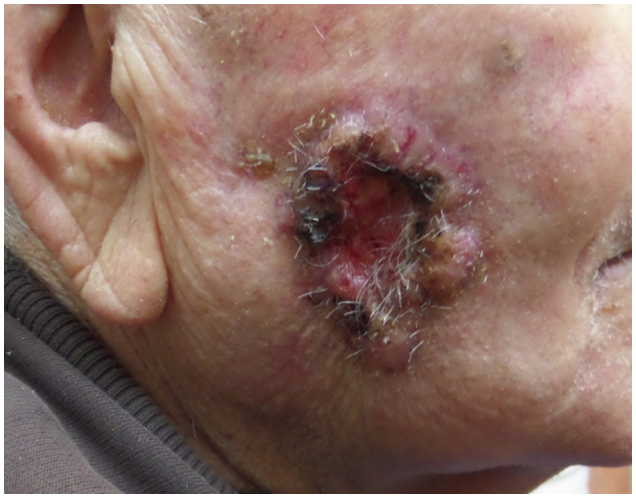

Fig. 3. 93 year severely demented nursing home patient with a rapidly growing deeply invasive bleeding right cheek squamous cell carcinoma. He was not an operative candidate and was recommended a course of hypofractionated radiotherapy.

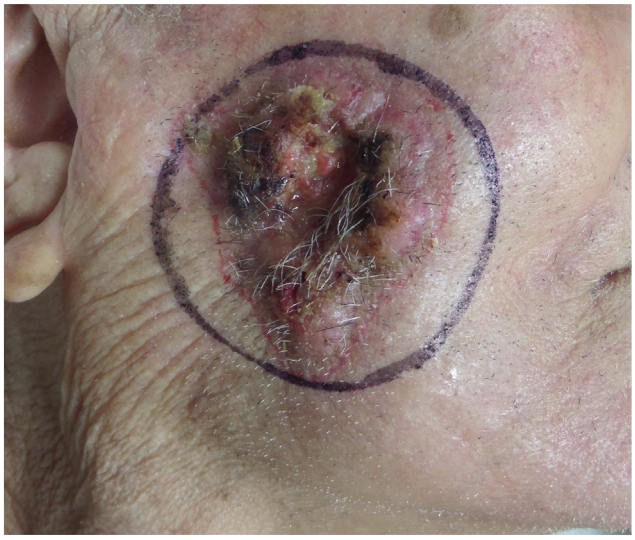

Fig. 4. A narrow radiotherapy field margin was applied to limit side effects and he received 36 Gy in total dose delivered in 6 Gy fractions twice per week using orthovoltage energy photons and tolerated this treatment well.

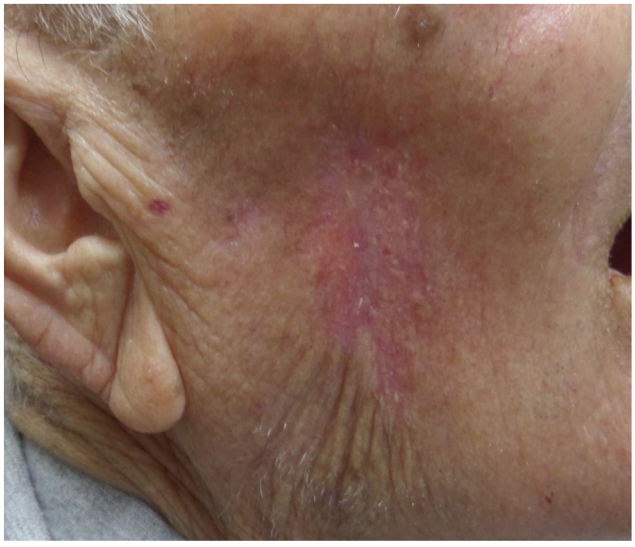

Fig. 5. At 6 weeks post completion of treatment he has experienced almost complete clinical regression of this lesion with resolving in-field desquamation which will resolve in the next 2 weeks.

placed on decreasing the total duration of treatment and often utilising daily fraction sizes of 3–4 Gy over 2–3 weeks. In elderly patients less frequent larger fraction sizes are recommended, such as 5–7 Gy in 5–6 fractions, referred to as hypofractionation [31]. The superficial location of NMSC and relatively limited fields treated with RT means even unwell patients can tolerate RT with limited degree of acute side effects, such as in-field desquamation.

Chronological age must also be considered along with a patient's medical co-morbidity and performance status when deciding on the number of fractions to prescribe. In elderly, poor performance status patients, sequential week day treatment may be inappropriate. Patients often present with medically or technically inoperable NMSC and experience local morbidity from the tumour such as bleeding, ulceration or itch which impacts on their quality of life. Hypofractionated RT can be delivered on alternative days or once weekly and is highly effective with tolerable treatment related toxicity. There is evidence documenting the efficacy of hypofractionated RT with recent systematic reviews reporting durable local control rates of over 90% and acceptable side effects [4,32]. Patients prescribed 5–7 fractions of 5–6 Gy, 2–3 times per week can expect an excellent tumour control outcome (Figs. 3–5). Patients may also be recommended extremely hypofractionated treatments, 1–3 fractions in select circumstances. If required, mild oral sedation can also be administered to improve patient co-operation and immobilisation. An Australian study treated patients with 25 Gy in 5 daily fractions and delayed any further RT for 8 weeks to be delivered only if visible NMSC was present. The authors documented 50% of patients achieving complete response after the first course and not requiring further RT with an overall 85% complete response rate [33].

New technologies in RT for early NMSC

Mold brachytherapy

Surface applicator brachytherapy (BT) has been in use for over a century. Surface mold BT is used to treat superficial, < 5mm, but extensive areas of skin [34]. Custom molds ideally have catheters placed up to 10 mm apart, with dwell points at distances between 2 and 5 mm from skin. Molds are manually constructed and may be personalised for each patient, but the variation in separation between catheters and between mold and skin needs to be monitored [35]. Despite the versatility of HDR molds, several studies have shown increased dose homogeneity and reduced dose to organs at risk with intensity modulated radiotherapy (IMRT) plans [36–38].

Electronic brachytherapy (EBT)

The emergence of remote after-loaders and high dose rate (HDR) radionuclide BT in the 1960s led to renewed interest in BT for skin cancers. The 21st century Valencia surface applicator brought improved dose profile and penumbra to HDR BT by incorporating a flattening filter [35]. This applicator can treat planning target volumes up to 5 cm in diameter [39].

EBT is a newer treatment modality for early NMSC that delivers HDR BT from a low energy (50–69.9 kV) x-ray source (Fig. 6). The low energy enables treatment in an unshielded room and also permits essential medical staff to remain in close proximity to patients. EBT systems provide a dose distribution at skin surface similar to radionuclide BT and applicator sizes range from 10 to 60 mm [35]. EBT may deposit significantly more dose in bone than radionuclide BT or electron beams,

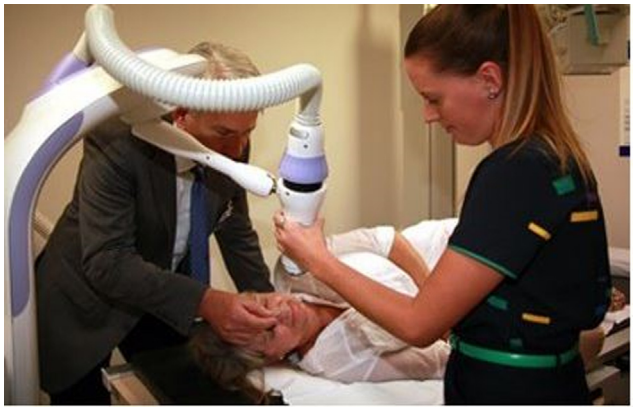

Fig. 6. Simulation using electronic brachytherapy unit, template based clinical mark-up with applicator on a flexible arm.

due to photoelectric effect [40]. For this reason, EBT is relatively contraindicated for lesions immediately overlying bone.

HDR radionuclide and EBT offer similar dose distributions for small, superficial NMSCs [35]. The favourable penumbra and rapid falloff with dose allow the use of hypofractionation: often 5–8, but up to 22 Gy per fraction [41], given weekly to second daily. These fractionation schedules deliver biologically equivalent doses often exceeding 60–70 Gy, providing patient convenience and high levels of local control with largely good to excellent cosmesis [35]. Conversely, more moderately hypofractionated regimens treating to 36 Gy in daily 3 Gy fractions have shown excellent local control of 95% or greater with acceptably low toxicity [42]. Using the Valencia applicator, a study by Tormo [43] reported 98% local control at a median follow up of 47 months, with no severe toxicity, using 42 Gy in 6 to 7 Gy fractions. Studies using EBT have achieved similar local control and toxicity rates using fraction sizes of 5 Gy or more. However, being a newer treatment modality, median patient follow-up in these studies is significantly lower, with most current studies offering 4–16 months median follow-up [44,45]. Despite the paucity of longer term follow-up, there is no physical or biological reason to believe that EBT will prove significantly inferior to radionuclide BT in tumor control or cosmesis.

BT remains useful for treating skin lesions up to 4–5 mm in depth, beyond this surface doses become excessively high. For deeper and more extensive lesions, interstitial BT using implanted applicators can be employed [35], however this has largely been supplanted by external beam RT.

3D printed bolus for electron beam therapy

Electron external beam RT is particularly useful in treating skin lesions as it delivers a relatively high dose to the skin with rapid drop-off at depth, accepting a trade-off of greater lateral penumbra which must be accounted for, particularly adjacent to sensitive organs at risk. Tissue equivalent bolus material is essential electron RT to ensure acceptably high surface dose and minimise the impact of surface curvature on dose heterogeneity. The latter occurs due to uneven electron scattering with altering distance between the source and surface. Bolus preparation has been innovated by the advent of 3D printing. 3D printed bolus (Fig. 7) is time efficient and has shown improved reproducibility and dose distribution over manual bolus [46,47]. These benefits may be particularly useful in anatomic areas of curvature and near organs at risk [47].

Volumetric modulated arc therapy (VMAT)

Volumetric modulated arc therapy (VMAT) is a form of intensity-modulated radiotherapy (IMRT) that incorporates a moving gantry with dynamic modulation of the beam by multi-leaf collimators during treatment delivery. Coplanar and non-coplanar delivery is feasible and plan quality is comparable to static-field IMRT, with shorter delivery times [48]. VMAT provides superior target volume coverage with less dose to underlying organs than electrons [38] or mold brachytherapy [34] for convex surfaces such as the scalp and lower limb. In irradiating extensive skin fields, for example in situations of extensive superficial disease, VMAT is a particularly useful technique [9]. In high-risk NMSC, VMAT can also be useful in providing coverage for the primary skin tumor while simultaneously treating elective at-risk lymphatics, dermis, or neural pathways [49,50].

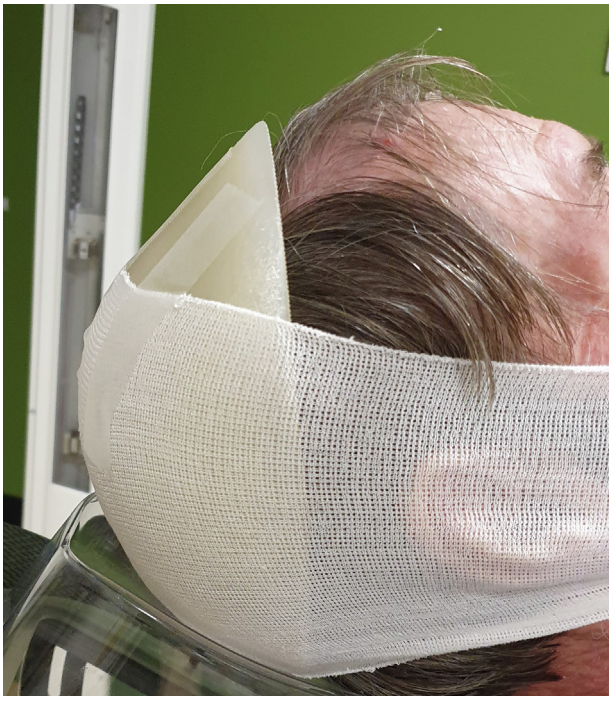

Fig. 7. CT simulation with the use of custom 3D bolus which matches the contour of his scalp and minimises air gaps.

While VMAT is often used for extreme hypofractionation, for example in stereotactic ablative radiotherapy, its surface dose profile is less suitable for skin hypofractionation than BT. Due to the megavoltage x-rays used with VMAT, the dose fall-off at depth cannot compare with radionuclide or EBT. Therefore VMAT is most useful for more extensive areas of skin, and conventional to moderately hypofractionated daily doses of between 2 and 3 Gy per fraction are commonly prescribed.

Summary

RT is a well established modality for management of NMSC. In the definitive setting, treatment of early BCC and SCC is associated with high rates of local control although caution should be exercised in larger or recurrent tumours. In the adjuvant setting, RT plays a vital role in improving locoregional control after surgery for high-risk lesions. In the elderly patient with NMSC, modified dose and fractionation regimes have been developed to improve convenience and tolerability of RT, and are associated with high rates of local control comparable to more fractionated RT. New RT technologies such as electronic brachytherapy, 3D printed bolus and VMAT have been developed to improve quality and patient outcomes.

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