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Overview

Current Role of Radiotherapy in Non-melanoma Skin Cancer

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Abstract

Non-melanoma skin cancer (NMSC) represents the most frequently diagnosed malignancy worldwide, most being cutaneous basal cell and squamous cell carcinoma**.** The global incidence of NMSC continues to increase as the global population ages. Numerous treatment options are available for NMSC patients, with radiotherapy an efficacious and tissue-preserving non-surgical option. External beam radiotherapy and brachytherapy are modalities with specific indications and advantages in treating NMSC. Where excision is not an option (medically/technically inoperable) or considered less ideal (e.g. cosmetic or functional outcome), radiotherapy offers an excellent alternative. Inoperable elderly and/or co-morbid patients of poor performance status can benefit from short-course hypofractionated radiotherapy, with very acceptable toxicity. Adjuvant radiotherapy in patients with unfavourable pathology can decrease the risk of local and regional recurrence and associated morbidity and mortality. Radiotherapy has advantages and disadvantages and it is important for clinicians to understand these. Managing patients with NMSC is carried out by clinicians from multiple disciplines but it is imperative that they are all aware of the role of radiotherapy in their patients in various clinical settings. Here we aim to discuss the role and indications for recommending radiotherapy in patients with NMSC.

Key words: Basal cell carcinoma; brachytherapy; external beam radiotherapy; non-melanoma skin cancer; radiotherapy; squamous cell carcinoma

Statement of Search Strategies Used and Sources of Information

PubMed, Medline, EMBASE and Cochrane Library were queried for ‘non-melanoma skin cancer’, ‘radiotherapy’, ‘radiation therapy’, ‘brachytherapy’, ‘squamous cell carcinoma’, ‘basal cell carcinoma’ and ‘hypofractionation’. All relevant articles were reviewed and incorporated as appropriate.

Introduction

Non-melanoma skin cancer (NMSC) represents the most frequently diagnosed malignancy worldwide, most being cutaneous basal cell and squamous cell carcinoma (BCC and SCC). White populations residing in countries of high ultraviolet exposure have a high risk of developing NMSC, especially of the sun exposed head and neck. In countries such as Australia, the incidence of NMSC is considered an epidemic and increasing despite primary prevention programmes [1]. Similarly, in the UK and Europe there is an increasing incidence of NMSC as the population ages and a recognition that NMSC can have an impact on a patient’s quality of life with associated local morbidity and mortality.

With an aging world population, the incidence of NMSC is increasing markedly [2] with an Australian study

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documenting an incidence of over 12 000 BCCs per 100 000 person-years in >80 year olds [3]. Elderly patients must be carefully considered following a diagnosis of NMSC. When deciding on treatment, consideration must be made of a patient's co-morbidities, life expectancy, cognitive capacity, preferences (including the family) and potential impact of any proposed treatment [4].

There is an increasing burden placed on global health care services and providers and a need to provide adequate resources, including radiotherapy centres, to treat NMSC. Surgery is usually the treatment for most NMSC, yet radiotherapy is an efficacious non-surgical option in the definitive, adjuvant and palliative settings and is a tissue-preserving modality that may offer a better cosmetic and functional outcome in comparison with surgery. It is a well-tolerated treatment with specific acute and late toxicities and with documented advantages and disadvantages compared with surgery [5] (Table 1).

Modern radiotherapy is a versatile modality delivered as either external beam (externally to the patient) or via the direct application of brachytherapy. External beam radiotherapy is delivered via photon or electron beams and can be superficial or deeply penetrating using different energy megavoltage electrons and photons [6]. Radiotherapy can be delivered to any field size, ranging from a small nasal tip BCC up to a large complex whole scalp treatment. Highly conformal radiotherapy, such as tomotherapy or volumetric modulated arc therapy, allows the delivery of relatively superficial radiotherapy to large complex and often curved structures, but also limit the radiotherapy dose to nearby organs at risk [7,8].

There is a well-documented global underutilisation of radiotherapy in cancer care and an acceptance that many patients with evidence-based indications for receiving radiotherapy do not do so, with the reasons being multifactorial. In many cancers (e.g. breast cancer), the impact of not undergoing radiotherapy may be measured in survival shortfall and disability-adjusted life years [9]. In NMSC, with sparse high-level evidence to guide clinicians, the extent of radiotherapy underutilisation is unclear and not well studied. Consensus-based guidelines often recommend indications for radiotherapy. However, based on data from other cancers, many patients with NMSC are not being referred for an opinion on radiotherapy [10,11]. Her we aim to discuss the role and indications for recommending radiotherapy in patients with NMSC.

Radiotherapy in Non-melanoma Skin Cancer

NMSC is a radioresponsive carcinoma and patients treated with definitive radiotherapy can expect excellent local control rates exceeding 90–95%, irrespective of the radiotherapy dose or dose per fraction. In a large study of patients with NMSC of the head and neck undergoing superficial energy radiotherapy and receiving 50–60 Gy, the authors documented an excellent local control rate at 5 years of 92% for SCC and 96% for BCC [12].

There are multiple dose fractionation schedules, but most younger (<50–70 years old) patients are prescribed radiotherapy fraction sizes of 2–2.5 Gy delivered over 4–5 weeks, aiming to achieve the best long-term outcome (cure and cosmesis) [13] (Table 2). In older (70–80 years old) patients, late effects are less of a concern, with consideration placed on decreasing the total duration of treatment, using daily radiotherapy fraction sizes of 3–4 Gy over 2–3 weeks (40–45 Gy in 10–15 fractions). In elderly patients (>80 years old) less frequent (one to three times per week), larger fraction sizes are recommended, such as 5–7 Gy in five to six fractions [14]. Chronological age must also be considered, together with a patient's medical co-morbidity, performance status and preference, when deciding on the number of fractions to prescribe for an appropriate course of radiotherapy.

Patients with SCC and BCC share the same aim of achieving optimal form and function. In SCC, wider radiotherapy field margins are used because of the increased risk and consequences of undertreating subclinical extension. Field margins of 5–10 mm are considered adequate for most well-defined BCC, but radiotherapy field margins of 10–15 mm for SCC are recommended, with wider margins for poorly differentiated/large (2 cm) SCC [15].

Table 1
Advantages and disadvantages of skin radiotherapy

Advantages	Disadvantages
Tissue-preserving modality	Clinical margin required to treat subclinical spread
No hospitalisation, surgical scars, grafts or flaps, postoperative complications	Limited pathological information available
Outpatient treatment (10–15 min)	Extended treatment (1–6 weeks)
	Hypofractionation an option in selected patients
Efficacious (90–95% local control)	Late cosmetic outcome not always optimal (e.g. hypopigmentation)
Well tolerated (self-limiting acute reactions)	Salvage surgery may result in poor wound healing
Reactions are site specific	
Predictable late reactions	Precludes further radiotherapy (or nearby within 5–10 mm)
Continue with anticoagulation	Poor wound healing in poorly vascularised tissues (e.g. lower limb)
Ability to treat large area	
Maintains form and function	

Table 2
Commonly used dose fractionation regimens for non-melanoma skin cancer

Intent	Total dose (Gy)*	Dose per fraction (Gy)†	Fractionation	Frequency
Definitive	50–66	2–2.5	20–33	Daily
	50	3.1–3.3	15–16	Daily
	40–45	3–4	10–15	Daily
	35*	7	5	Daily
	30–35	5–7	5–7	Alternate days or Weekly
	42	6	7	Weekly
Adjuvant	50–66	2–2.5	20–33	Daily
Palliative	24	8	3	Weekly

* Higher total dose may be used for squamous cell carcinoma versus basal cell carcinoma for comparable tumour size.
† Consider lower dose per fraction regimens for larger tumours and for better cosmesis.

Basal Cell Carcinoma

Definitive Radiotherapy

BCCs are rarely fatal but have the potential to be locally morbid. In patients with midface BCC, radiotherapy is an excellent tissue-sparing option. Achieving a margin-negative excision with primary closure in sites such as the tip of the nose or ala nasi can be difficult. Definitive radiotherapy is therefore an option, with reported local control rates of 80–100% and a 'good or excellent' aesthetic outcome in most [16]. Radiotherapy may be a better option for certain patients with midface BCC located on the medial canthus, lower eyelid or nose.

One advantage of radiotherapy is the ability to encompass microscopic extension by applying a wide field margin beyond the clinical lesion. This field margin incorporates set-up variation and dose drop-off at the edge of the field (penumbra). In a study of patients with an 'aggressive' head and neck BCC (>10 mm, multiply recurrent, extracutaneous extension), treated with either conformal megavoltage radiotherapy or electrons with a 20 mm field margin, the authors reported an 85% locoregional control rate at 3 years [17].

Adjuvant Radiotherapy

Adjuvant radiotherapy may decrease the risk of local recurrence after incomplete excision. A close or positive margin increases the risk of local recurrence, with rates of 7–40% reported [18–20]. Other risk factors for recurrence include histology, size and location. After reconstruction, deep recurrence may be difficult to detect and adjuvant radiotherapy should be considered [18,19]. Determining an individual's risk of recurrence can only be estimated and in many cases simple re-excision is not always possible and adjuvant radiotherapy may be considered an option to at least discuss with the patient. An observation policy is also an option, noting with BCC that any recurrence may occur a number of years after surgery and occasionally recurrences are not always surgically salvageable.

Squamous Cell Carcinoma

Definitive Radiotherapy

Low-risk SCC patients have an excellent prognosis after treatment, with only a minority of all SCC patients at risk of developing locoregional and occasionally distant relapse (i.e. referred to as high-risk SCC). The difference between SCC versus BCC is therefore the increased risk of morbidity and mortality in high-risk SCC patients [21]. Surgery aims to achieve negative margins, with the advantages of obtaining margin assessment, pathology review and is usually a 'one-step' procedure. Disadvantages include the possibility of hospitalisation, general anaesthesia, further surgery for margin positivity and the impact on function and cosmesis in sensitive areas (lip, eyelid, nose).

When surgery is not feasible (e.g. poor performance patient), or could result in unacceptable functional morbidity, radiotherapy is an option. Radiotherapy to lower lip SCC is associated with excellent maintenance of oral function and high rates of cure (90–95% 5-year relapse-free survival) and is an alternative, especially if complex flap reconstruction is required [22]. In a study of 180 patients with large SCC (mean size 3.5 cm) treated with definitive radiotherapy, an excellent relapse-free survival at 2 and 5 years of 95.8% and 80.4%, respectively, was achieved [23].

Adjuvant Radiotherapy

Following incomplete excision, where re-excision is not considered, adjuvant radiotherapy should be considered. Margin status is a well-documented risk factor for patients developing local relapse, with data that local adjuvant radiotherapy can decrease the risk of local recurrence. Other factors, such as the presence of perineural invasion (PNI) or in the recurrent setting, further increase this risk.

Adjuvant radiotherapy significantly lowered the risk of developing recurrence (hazard ratio 0.08, 95% confidence interval 0.03–0.26; $P < 0.001$) in a study of patients with extremity and head and neck SCC [24]. Local adjuvant radiotherapy also significantly improved relapse-free survival ($P = 0.008$) in a series of T1/T2 lip SCC patients, with

more patients relapsing after undergoing surgery alone in the setting of a close/positive margin (57%) compared with only 9% of those receiving adjuvant radiotherapy [25]. In a series of patients with advanced SCC receiving adjuvant radiotherapy, when compared with not undergoing radiotherapy, there was an improved overall survival (hazard ratio 0.59, 95% confidence interval 0.38–0.90) [26]. Close observation and expectant treatment, as an option, in patients with a close or positive margin need to be considered carefully, as although many will not develop local recurrence, those who do so are at increased risk of regional recurrence.

Regional Nodes/Intra-parotid Nodes

The incidence of SCC metastasising to regional nodes is low (2–3%) and accurately identifying patients who may develop metastatic nodal metastases is difficult [27]. In 20–30% of patients presenting with nodal disease, no obvious primary SCC is ever identified, although patients may have undergone excision of numerous low-risk SCC in the past. This risk does, however, increase in high-risk patients, such as those immunosuppressed or with unfavourable pathology (e.g. recurrent, poorly differentiated, size >2 cm, PNI present), although most of these will still not develop nodal metastases [28]. Patients with operable metastases are managed with appropriate surgery and adjuvant radiotherapy, which is considered best practice. Unfavourable pathological features, such as multiple positive lymph nodes, extranodal spread, large node >3 cm, close surgical margins or the presence of PNI, increase the risk of regional recurrence without further treatment in the form of adjuvant regional radiotherapy [29]. The TROG 05.01 randomised phase III trial compared concurrent chemoradiotherapy with radiotherapy as postoperative treatment in patients with high-risk cutaneous SCC. The trial results concluded that although surgery and postoperative radiotherapy provided excellent freedom from locoregional relapse, there was no observed benefit with the addition of weekly carboplatin [30].

Perineural Invasion

PNI is infrequent in SCC (5–10% of cases) or BCC (2–3% of cases) and a clear role for adjuvant radiotherapy is not well defined [31]. Patients with asymptomatic multifocal microscopic PNI may benefit from local adjuvant radiotherapy over a wide field (e.g. supraorbital forehead) but not necessarily require treatment to the entire course of the relevant cranial nerve. Patients with symptomatic and/or radiological PNI need to be discussed in a multidisciplinary setting. In select cases, skull base surgery and volumetric modulated arc therapy adjuvant radiotherapy may be recommended [32]. Modern conformal radiotherapy allows a more accurate and safer delivery of high dose (54–66 Gy) radiotherapy while limiting the dose to organs at risk (e.g. brainstem, optic nerve) [33]. Radiotherapy can also palliate debilitating neuropathic pain that may be difficult to manage pharmacologically. Pre-auricular and periorbital located NMSC with PNI on pathology are of most concern, noting the potential access pathways along branches of cranial nerve VII (facial nerve) and cranial nerve V (trigeminal nerve), respectively.

Elderly and/or Frail Patients

For the optimal management plan, a baseline assessment of older radiotherapy patients should ideally include some form of frailty assessment. Chronological age alone is a poor surrogate for biological age and should not solely be used for estimation in treatment options and outcome [34,35]. Other factors that should be used in the decision-making process include performance status, co-morbidities, current medications and symptoms, physical and mental fitness, life expectancy, and quality of life and patient's wishes [36,37]. When considering radical versus palliative intent, it should be stressed that older patients are underrepresented in clinical trials, which significantly limits evidence-based radiotherapy in this demographic.

Many patients seen in skin cancer radiotherapy clinics are elderly and frail, with multiple co-morbidities, and often present with NMSC not amendable to surgery. External beam radiotherapy offers an effective and non-invasive treatment, but may require multiple daily visits when delivered in radical settings. Frail patients with NMSC can be offered treatment with hypofractionated radiotherapy when long-term cosmesis is not as important, with the expectation of achieving excellent durable local control. The use of brachytherapy as an alternative to external beam radiotherapy in centres with the expertise and equipment is also an excellent option in this population.

Hypofractionation

Hypofractionated radiotherapy delivered two to three times a week or once weekly is a highly effective option with tolerable treatment-related toxicity. Two recent systematic reviews of hypofractionated radiotherapy reported durable local control rates of over 90% and acceptable side-effects [38,39]. In a systematic review comprising 40 relevant publications (external beam radiotherapy and brachytherapy included) of over 12 000 NMSC (24% SCC), local recurrence rates did not exceed 7.9%. The authors concluded that hypofractionated radiotherapy is an option that confers no obvious disadvantage in local control when compared with traditional more protracted radiotherapy schedules [38]. A meta-analysis of hypofractionated radiotherapy for NMSC involving 9729 patients reported median local recurrence rates of 2% at 1 year and 14% at 5 years, with good physician-assessed cosmesis in 92% [39]. Lansbury *et al.* [40] conducted a systematic review of all interventions for SCC and reported a local recurrence rate of 6.4% in 761 patients treated with external beam radiotherapy to the skin and 5.2% in 88 treated with brachytherapy. A systematic review of high dose rate brachytherapy of 1977 NMSC lesions, of which 23.5% were SCC, concluded that high dose

rate brachytherapy was an effective treatment with high local control rates and good/excellent cosmetic results, including in elderly patients. More data from large-scale randomised controlled trials and longer follow-up are needed to assess the efficacy and safety of brachytherapy [41].

With no prospective studies comparing skin brachytherapy with external beam radiotherapy, a recent SCRiBE meta-analysis compared the outcome of over 10 000 patients with T1/2 NMSC and treated with either brachytherapy ($n = 553$) or external beam radiotherapy ($n = 9965$) from 24 studies. Despite heterogeneity in patients, techniques and dose/fractionation schedules, the local recurrence rate at 1 year for either modality was <7% irrespective of any fractionation schedule. There was, however, a suggestion that cosmesis using brachytherapy may be better, although many brachytherapy studies had short follow-up times reported. Therefore, brachytherapy can be considered an efficacious option that may offer specific site-related advantages in select circumstances (e.g. lower limb, elderly patients) [42]. There is no one optimal dose fractionation schedule with data indicating that patients receiving five to seven fractions of 5–6 Gy per fractions two to three times a week can expect a good or excellent outcome. In a study of weekly radiotherapy of 6 Gy in seven fractions in frail and elderly patients (mean age 89 years), with large BCCs (mean size 4.2 cm), the treatment was well tolerated, with a 95% local control rate [43].

Chan *et al.* [44], in a UK study of 806 patients, suggested that a single large radiotherapy fraction of 20 Gy is an acceptable treatment for small superficial NMSC of the head and neck in patients who have difficulty attending multiple hospital visits, as long as the field size is no greater than 3 cm in diameter. Local recurrence rates were 4%, but a fraction size >20 Gy was not recommended because of an increasing risk of skin necrosis. Patients were treated with either 45 or 110 kVp superficial energy photons [44]. Small field electron radiotherapy may be an alternative in some centres, but with disadvantages including requiring a minimum field size of 4 cm, skin sparing and wide penumbra.

Brachytherapy in Poor Performance Patients

Brachytherapy is a particularly useful modality in the elderly, infirm and/or those with poor compliance, as it delivers larger doses per fraction over a shorter period of time (e.g. twice a day over 4 days) or less frequently than standard daily treatments (e.g. weekly, twice or three times a week) (Table 3). Skin brachytherapy is also associated with low recurrence rates, low toxicity and excellent cosmesis across all ages [45,46]. There are equivalent treatment outcomes published in the elderly population [47]. The fact that a radiation source is placed directly on the skin (applicator) or inserted directly into the tumour (interstitial) can improve patient compliance, as any movement (e.g. in patients with dementia or Parkinson's disease) during such treatment is not as concerning as it would be during external beam radiotherapy. In selected cases, skin brachytherapy with a personalised mould may often be the only viable alternative in elderly and/or frail patients with symptomatic skin cancers in whom their performance status and co-morbidities precluded any other active treatment options and they would otherwise have been referred for best supportive care [48].

Skin Radiotherapy Planning and Novel Medical Imaging

Computed tomography-based planning is the primary treatment planning modality in a modern radiotherapy department. Computed tomography scans are used to define treatment targets and organs at risk in photon and electron delivered treatment. Radiotherapy outcomes depend on accurate coverage of a target volume with appropriate margins. Margins that are too narrow may lead to local failure and margins that are too wide can increase radiotherapy-related morbidity. Delineating a target volume is challenging, particularly in superficial and small skin NMSC, where computed tomography spatial resolution limits visualisation of any skin lesion [15,49].

Table 3
Summary of commonly used dose fractionation regimens for non-melanoma with a high dose rate superficial brachytherapy technique

Definitive/adjuvant					Palliative			
Dose (Gy)		Dose/fraction	Fractions	Frequency	Dose (Gy)	Dose/fraction	Fractions	Frequency
*Superficial brachytherapy	45–54	3	17–18	3×/week	30–40	5–6	6–8	1–2×/week
	40–48	4	10–12	3×/week	20	5	4	2×/week
	50–60	5	10–12	2×/week	12	6	2	2×/week
	40	5	8	Daily				
	40–50	5	8–10	2×/week				
†Interstitial brachytherapy	24–30	3	8–10	2×/day	10–30	5	2–6	2×/day
	32	4	8	2×/day				
	40–45	4–4.5	10	2×/day				
	51	3	17	2×/day				

* Superficial brachytherapy is indicated for superficial lesions with a maximum depth of 4–5 mm.
† Interstitial brachytherapy is an invasive technique used for the treatment of lesions with a thickness more than 5 mm and/or in tumours on curved surfaces, as in the face.

In skin radiotherapy, the use of computed tomography-based planning is limited to cases of larger and deeply invading NMSC, nodal basin radiotherapy, skin brachytherapy planning and in select palliative settings. In planning for small and superficial NMSC, clinicians need to rely on a clinical examination to obtain essential information, such as lesion dimensions and borders (assessed via visual inspection with a bright light and a magnifying glass) and the depth of infiltration (assessed by applying tension to the skin). The lesion borders are marked with a fine felt-tip marker followed by the application of adequate peripheral field margins on the skin. Information on the depth of infiltration together with the required margin beneath the infiltration is crucial in deciding on the radiation energy required. The size of such additional margins depends on the lesion pathology and the intended radiotherapy technique.

The manual planning process in NMSC radiotherapy may lead to radiotherapy delivery inaccuracies and increased risk of recurrence. Recently there has been an increased interest in the use of various imaging concepts that may assist with improving target definition in NMSC radiotherapy, such as fluorescent and targeted contrast agents, radiofrequency, Raman and elastic scattering spectroscopy, optical coherence tomography (OCT), high frequency and contrast-enhanced ultrasonography, and optoacoustic microscopy and confocal microscopy [50].

High frequency ultrasound (HFUS) is a concept that has moved into clinical practice and is used not only to improve lesion delineation, but to evaluate more accurately the thickness of any NMSC, and in monitoring the post-treatment response to radiotherapy (Figure 1). There are also reports of HFUS in identifying pathological subtypes of BCCs, following specific ultrasound patterns that such subtypes exhibit [51]. Currently, clinicians undertake clinical mark-up on a patient after a visual inspection and usually add a 1 cm radiotherapy field margin depending on the pathology. HFUS, if available, can be used to aid delineation as sometimes >1 cm field margins are required, e.g. in morphoeic/infiltrating BCC or high-risk SCC. Visual inspection still remains the gold standard in clinical skin mark-up, but HFUS may help to better delineate certain high-risk lesions. It is expected that the combination of visual inspection/clinical examination and skin HFUS could reduce the risk of geographical miss and underdosage at the subclinical borders of a poorly defined NMSC.

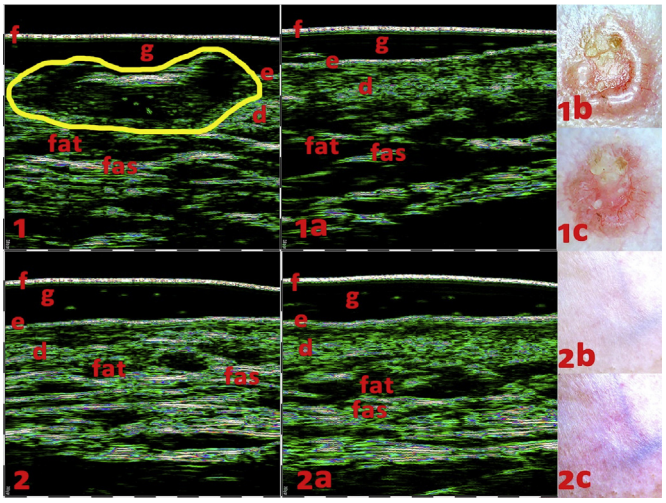

Fig 1. Nodular basal cell carcinoma (1) before and (2) after radiotherapy. Skin cancer is delineated in yellow. (1a, 2a) Surrounding but intact skin for comparison, (1b, 2b) videodermoscopic image, (1c, 2c) polarised videodermoscopic image, before and after radiotherapy, respectively. g, gel; e, epidermis; d, dermis; fat, subcutaneous fat; fas, superficial fascia.

The resolution of HFUS ranges from 80 to 16 μm and the depth of penetration into the skin in the range of 20–100 MHz, equalling the depth of penetration from 2 to 12 mm. Such resolution is sufficient for the study of the epidermis, dermis and subcutaneous fat [52]. Ballester-Sanchez *et al.* [53] compared the depth of skin lesions assessed by 18 MHz ultrasound and by punch biopsy [53]. The results confirmed expected significant discrepancies in depth determination, with 18 MHz ultrasound being less accurate at very shallow depths for treatment purposes. Other studies showed that the accuracy of HFUS in determining the dimensions and thickness of NMSC before surgery is comparable with postsurgical histopathology used as a reference standard [54]. Goyal *et al.* [55] reported the feasibility of using HFUS during follow-up for superficial NMSC after electronic brachytherapy.

In summary, HFUS is a feasible and non-invasive imaging modality that can be used in skin radiotherapy planning and for post-radiotherapy follow-up. It can help clinicians to objectively evaluate the treatment response and identify early recurrence before being diagnosed clinically. There is also a potential use for identifying patients with a poor response to radiotherapy who may require earlier and more frequent follow-up.

There are, however, limitations to HFUS, as it is operator dependent and requires a specific ultrasound unit, adequate training and experience. Another potential issue with the use of HFUS includes detecting possible early clinical recurrence not visible and/or palpable and whether this would require immediate salvage treatment.

Photodynamic therapy involves the application of a topical prodrug, δ-aminolevulinic acid or methyl-aminolevulinic acid, which is taken up preferentially by malignant cells and converted to protoporphyrin IX. Application of blue light results in red fluorescence and visualisation of a tumour. Protoporphyrin IX fluorescence for photodelineation of NMSC borders has been examined in patients undergoing Mohs micrographic surgery with mixed results in improving surgical efficacy [56]. The application of protoporphyrin IX fluorescence in radiotherapy planning has been explored in a prospective series of 33 patients, which reported significantly larger clinical target volume margins (15 mm) than would have conventionally been used (10 mm) for poorly defined tumours ($P = 0.03$) [57].

OCT uses reflection of infrared light to generate a three-dimensional image with micrometre resolution (10–15 μm). This non-invasive imaging technique can be used to

examine the micromorphology of the skin and to assess changes in tissue architecture characteristic of malignancy. Advantages of OCT include rapid image acquisition using a hand-held device; disadvantages include the shallow depth of penetration (2 mm) and limited field-of-view. Work has been carried out on the clinical application of OCT as an 'optical biopsy', providing a rapid, non-invasive technique for the characterisation of skin lesions during an initial assessment and follow-up [58]. OCT has also been used for presurgical margin assessment in NMSC [59,60]. There is ongoing research investigating the role of OCT, fluorescence imaging and micro-ultrasound in personalising the margins required to prove tumour coverage for patients [61,62].

Brachytherapy

Brachytherapy has been in use since the discovery of radioactivity in 1896 [63]. With the development of better surgical techniques its application in skin cancer significantly decreased over the years, but with the introduction of the high dose rate afterloading technique and electronic brachytherapy there has been a renewed interest in the role of brachytherapy in NMSC. Compared with external beam radiotherapy, high dose rate brachytherapy has certain advantages, such as delivering a high radiation dose into the clinical target volume/planning target volume, rapid dose fall-off at the target periphery, optimal sparing of normal tissues in sensitive structures, a shorter treatment time and the use of a hypofractionated course. Skin brachytherapy is advantageous particularly in curved surfaces and should be considered instead of external beam radiotherapy (if surgical excision is not possible) in areas of poor vascularisation, such as the dorsum of the hands or feet or lower legs.

Skin brachytherapy can be delivered using a superficial or an interstitial technique. Superficial application with, most commonly, ^{192}iridium requires skin applicators such as surface flap applicators, a custom-made mould or the Leipzig or Valencia applicator [64]. Interstitial brachytherapy is an invasive approach to deliver high dose rate brachytherapy in thicker (above 5 mm) skin lesions and requires catheters to be inserted under anaesthesia directly into the lesion or surgical bed in the adjuvant setting [65].

Electronic brachytherapy is a new technique of radiotherapy based on a miniaturised X-ray source that allows it to treat small and flat surfaced NMSC, mainly BCC [66,67]. With the development of new devices compatible for use with the equipment of electronic brachytherapy (such as Xoft® Axxent®, Zeiss® INTRABEAM® and Elekta® Esteya®) electronic brachytherapy has attracted considerable interest in recent years in the management of NMSC [68]. Although the preliminary data on the use of electronic brachytherapy in NMSC are promising, there is a lack of direct comparison with external beam radiotherapy or radionuclide brachytherapy, as well as a lack of long-term follow-up data. The American Brachytherapy Society consensus statement does not recommend the use of electronic brachytherapy outside of prospective clinical trials [69].

Future Directions

With a dearth of published high-level evidence on many aspects of managing NMSC, exploring the benefits of radiotherapy in various clinical scenarios should be encouraged. The utilisation of modern conformal radiotherapy, novel medical imaging, newer radiotherapy modalities, such as electronic brachytherapy, and the emerging role of immunotherapies are all potential avenues for future research.

Conclusions

Managing patients with NMSC is carried out by clinicians from multiple disciplines but it is imperative that they are all aware of the role of radiotherapy in their patients in various clinical settings. Many patients are treated without the need for radiotherapy, but it is an efficacious option to consider in selected NMSC patients and can be associated with an improved outcome and decreased morbidity and mortality.

Key Points

- With the increasing incidence of NMSC worldwide, there is a rising unmet need for the utilisation of radiotherapy in NMSC management.
- Surgery may be the preferred option for most operable NMSC, but radiotherapy can be considered an excellent and versatile non-surgical option in the definitive, adjuvant and palliative settings.
- Hypofractionation should be considered in elderly and less compliant patients.
- In the absence of surgical options, brachytherapy may be considered in NMSC on curved surfaces and in locations of poor vascularisation, such as lower limbs, dorsum of the hands and feet.
- Studies conducted in skin radiotherapy have been small, heterogeneous, non-randomised and often retrospective.
- Guidelines to aid the use of skin radiotherapy in primary and metastatic nodal NMSC need to be supported by data from prospective trials.
- As such, the opportunity exists to conduct prospective studies to develop standards of care in NMSC.

Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.08.004.

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